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Determining the Pharmacological Activity of in Cystic Fibrosis Sputum Ex Vivo: A Potential New Treatment for Mucus Stasis

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short report

Determining the Pharmacological Activity of in Cystic Fibrosis Sputum Ex Vivo: A Potential New Treatment for Mucus Stasis

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Abstract

Small airway mucus obstruction is characteristic of cystic fibrosis (CF). CF patients have a defect in the cystic fibrosis transmembrane receptor (CFTR) which leads to increased viscosity and elasticity of mucus in the lungs. This study investigates the most effective dosage of mucolytic to lower mucus viscosity and elasticity. Lower viscosity and elasticity of small airway mucus in CF patients can better allow airway clearance through mucociliary clearance and coughing. An effective mucolytic breaks up mucus in the lungs and allows CF patients to better expectorate their mucus. Spontaneously expectorated sputum was collected from CF patients and incubated with a novel mucolytic or vehicle control for 2 hours. Viscosity and elasticity were then measured using a TA instruments rheometer (DHR-II). The most effective mucolytic dose was found to be 0.003 mg/mL. These preliminary findings are an important indicator of proper dosage amount, which can be used in future experiments and clinical trials.

Introduction

Obstruction of small airways is characteristic in patients with cystic fibrosis and is associated with loss of lung function. CF causes mucus to become highly viscous and elastic mucus and accumulate in the small airways. Increased mucus in the lungs leads to infections, inflammation and ultimately end stage lung disease. Many of the problems with mucus in the lungs of cystic fibrosis patients result from a defect in the cystic fibrosis transmembrane receptor (CFTR), which hydrates the mucus. A mucolytic agent that lowers the viscosity and elasticity of CF small airway mucus would help reverse the pathogenesis of the disease.

Methods

Spontaneously expectorated sputum was collected from cystic fibrosis patients. Samples were homogenized together ten times with a 5 mL syringe. The samples were aliquoted and the following concentrations of the mucolytic were added to each vial: 0.01 mg/mL, 0.003 mg/mL, 0.001 mg/mL, 0.0003 mg/mL, 0 mg/mL (Control). The aliquots were vortexed for 10 seconds each and then incubated at 37°C for 2 hrs. The samples were then vortexed for another ten seconds and run on the TA Instruments rheometer with either a 20 mm geometry plate or a 40 mm geometry plate based on the sample size.

Results

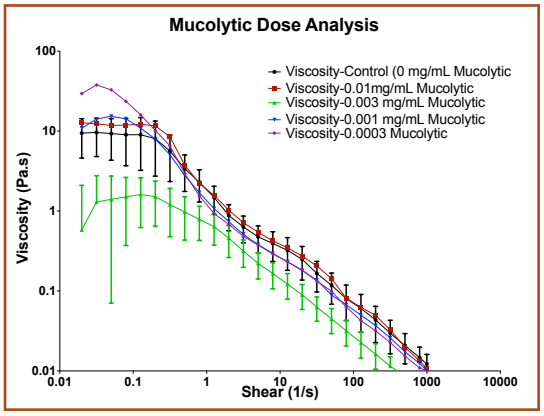

Figure 1. The effect of a novel mucolytic on sputum viscosity. Controlled stress rheometric measures of viscosity in freshly expectorated CF sputum (n=5) treated with varying doses of mucolytic ex vivo. A reduction in viscosity at low shear stress is thought to significantly improve the transportability of CF mucus.

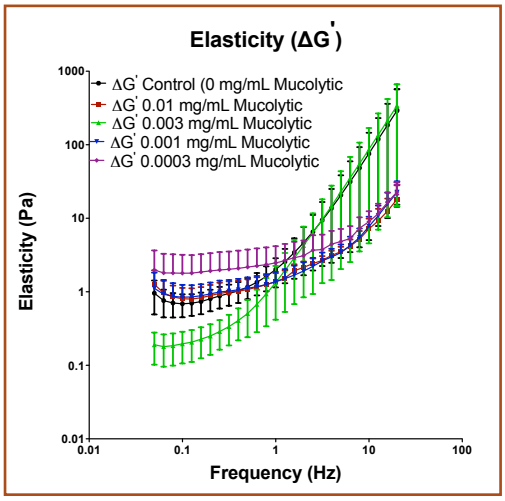

Figure 2. The elasticity of cystic fibrosis patient sputum treated with varying concentrations of mucolytic. The novel mucolytic reduces sputum elasticity in dose-dependent fashion. Low frequency elasticity is the clinically relevant parameter since the structure of the sputum breaks around a frequency of 1 Hz.

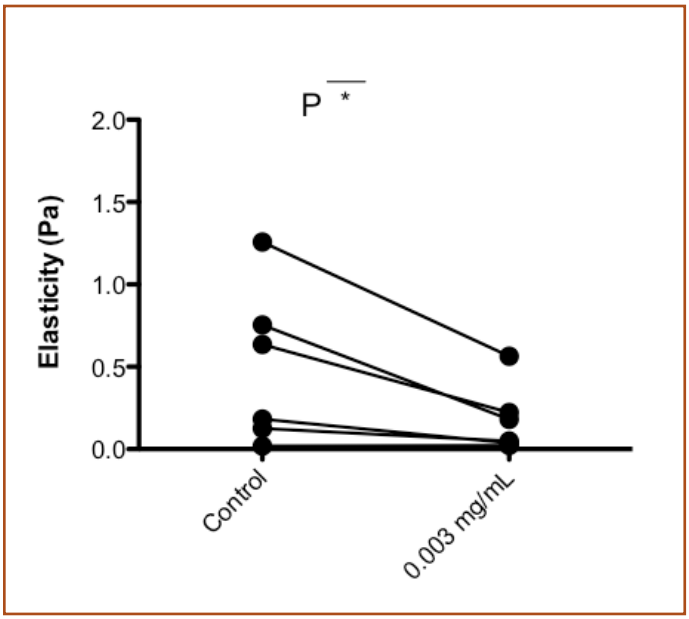

*Figure 3. Dose response of the novel mucolytic on sputum elasticity. The elasticity of sputum from CF patients (n=6) at a shear of 0.063 Hz is lowest at the 0.003 mg/mL concentration of the mucolytic. *P < 0.05.*

Conclusions

When 0.003 mg/mL mucolytic is added to the sputum from CF patients, the viscosity and elasticity are significantly decreased compared to the control sample. A dose response was observed for these parameters, which will be used to select doses to be advanced in further studies.

Future Directions

Further research in the Rowe laboratory will include varying molecular weights of the mucolytic along with varying incubation times to identify the maximum efficacy of this mucolytic as a potential treatment for CF patients. Additional experiments will examine the effect of mucolytic on mucus transportability. The promising results of decreased viscosity and elasticity from this study support the effectiveness of this mucolytic and provide a strong rationale for *in vivo* testing.