European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title:

Pulmonary Surfactant Dysfunction in Pediatric Cystic Fibrosis: Mechanisms and Reversal with a Lipid-Sequestering Drug

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What was your research question?

To examine the role of oxidation and cholesterol in causing pulmonary surfactant dysfunction in infants and children with cystic fibrosis (CF). Surfactant is a mixture of certain fats (called phospholipids) and proteins; it lines the lung tissue and makes breathing easy. We also wanted to see the dysfunction could reversed using a methylated β-cyclodextrin (MβCD) drug.

Why is this important?

Pulmonary surfactant prevents airway collapse by maintaining a low surface tension in liquid in the airways which makes breathing easier. It also has anti-bacterial properties that prevents airway infection. Pulmonary surfactant is impaired in CF which is associated with a progressive decline in lung function. Understanding why surfactant does not function correctly should provide important insights into how to treat or repair dysfunctional surfactant.

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What did you do?

Diagnostic fluid (lung lavage), was collected from 26 infants and children with CF and 9 lung-healthy children and pulmonary surfactant was subsequently extracted from these samples were possible. We then measured the lipid content (fatty acids or their derivatives), inflammatory cells, different bacteria present and determined the CF genotype. Pulmonary surfactant function, as determined by surface tension, was investigated using a research instrument called a bubble surfactometer. We studied the effects of high cholesterol (which is genetically increased in CF), oxidized surfactant lipids and molecules that mediate lung inflammation in CF on pulmonary surfactant function. Finally samples with dysfunctional surfactant were re-tested in the presence of MβCD, a drug that can sequester lipids such as cholesterol (known to inhibit surfactant) and similarly shaped molecules that drive inflammation.

What did you find?

The 24/26 CF samples analysed were unable to maintain a low surface tension within the normal range. Lung cholesterol was much higher in children with CF than in lung-healthy children. MβCD treatment completely restored surfactant function for 14/16 CF samples. We showed that the mechanism of surfactant dysfunction involves a combination of increased cholesterol and free radical mediated degradation of surfactant phospholipids due to inflammation. All of these effects could be reversed with MβCD treatment in our laboratory experiments.

What does this mean and reasons for caution?

We confirm that nearly all children with CF have dysfunctional pulmonary surfactant. Other investigators have shown this dysfunction is a major contributor to worsening lung function. Most importantly, pulmonary surfactant function was restored in CF samples after treatment with MβCD regardless of genotype, type of infection or severity of the inflammation. These findings have implications for alleviating the harmful effects of the disease and improving lung function in people with CF on a long-term basis, offering hope for the long-term survival of those awaiting specific treatments such as genetic interventions or transplant.

Caution: although cyclodextrins (compounds made up of sugar molecules, including MβCD) have few side effects, are generally considered safe and have been approved as carriers (excipients) for many FDA approved drugs, it will be necessary to demonstrate their safety when delivered as an aerosol for long-term treatment in people with CF. Safety studies are

required. Preliminary studies at the University of Calgary indicate that inhaled MβCD is non-toxic and anti-inflammatory in a mouse model of lung injury.

What's next?

Current medications to manage airway disease (bronchodilators, antibiotics), and enhance mucus clearance (mucolytics) are effective in the short- to medium term but become less effective over time.

A therapy that targets and repairs pulmonary surfactant has potential to improve air flow and mucus clearance. While not a cure, it would complement existing therapies by improving lung function and reducing the harmful effects of infection and lung inflammation.

Original manuscript citation in PubMed

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