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Cystic Fibrosis Research News

Title:

Amphotericin B induces epithelial voltage responses in people with cystic fibrosis

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What was your research question?

Cystic fibrosis (CF) is caused by a loss of function of the CFTR channel. We previously discovered that a drug called amphotericin B (AmB), can act like a prosthesis (artificial replacement) on the molecular scale to substitute for the missing CFTR channel, restore secretion, and thereby restore airway host defenses in cultured epithelia from people with CF and in CF pigs. In this study we asked whether AmB in the nose (intranasal) could restore anion secretion and perform CFTR-like function in people with CF who were not taking CFTR modulators. It is hoped that this molecular prosthetics approach could provide benefit for people with CF.

Why is this important?

CFTR modulators, including ivacaftor, tezacaftor, and elexacaftor, partially improve the function of CFTR with certain mutations and have improved lung function and health-related quality of life for people with CF. However, approximately 10% of people with CF have mutations that result in little to no CFTR production, or they cannot tolerate CFTR modulators,

and therefore cannot benefit. Small molecule ion channels represent an alternative strategy to potentially improve lung function in people with CF who cannot benefit from modulators. Testing whether this strategy can impact channel function in people with CF could encourage additional studies to determine the clinical effectiveness of this approach.

What did you do?

In the lab we tested the capacity for AmB to cause electric changes consistent with anion secretion in cells from the airway lining (epithelia) from people with CF caused by two nonsense mutations of CFTR. In a clinical study we evaluated whether AmB could change nasal potential difference (NPD), a key clinical biomarker previously used to test the effectiveness of ivacaftor, in people with CF not on CFTR modulators.

What did you find?

We found that, independent of the CF genotype, AmB restored ion secretion in cells of CF large airways (bronchus) and airway lining epithelia of the nose. AmB also caused NPD to become more negative in 7 out of 8 people with CF not on modulators, suggesting the recovery of anion secretion in these people. This change was similar to the effects previously caused by ivacaftor in people with at least one *G551D* mutation. Further, we found that AmB forms ion channels in CF airway epithelia in the lab at concentrations which have previously been safely delivered to the airways to treat fungal infections.

What does this mean and reasons for caution?

Despite being an imperfect substitute for the CFTR ion channel, AmB can generate ion channels in people with CF. These results provide the first clinical evidence that small molecule ion channels may be able to benefit people with CF who cannot benefit from CFTR modulators.

This study has not yet determined whether inhaled AmB can improve lung function in people with CF. Additionally, delivery of small molecule channels via inhalation directly to the airways will not address CF disease in other organs, such as distal intestinal obstruction syndrome (DIOS) in the bowels.

What's next?

Given the encouraging safeness of AmB when delivered to the airways and the ability to form anion channels in CF airway epithelia at these concentrations, this study lays the foundation for additional clinical trials to determine whether inhaled AmB can improve lung function and

health-related quality of life in people with CF, including those who cannot benefit from CFTR modulators. This work also encourages further studies to determine whether AmB can increase ion secretion in CF intestinal epithelia and thereby benefit people with DIOS. More broadly, this study encourages additional research into molecular prosthetics for treating human diseases caused by missing or dysfunctional proteins.

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