New Generation ENaC Inhibitors Detach Cystic Fibrosis Airway Mucus Bundles via Sodium/Hydrogen Exchanger Inhibition

Melania Giorgetti[1], Nikolai Klymiuk[2], Andrea Bähr[3], Martin Hemmerling[4], Lisa Jinton[4], Robert Tarran[5], Anna Malmgren[4], Annika ° Astrand[4], Gunnar Hansson[1], and Anna Ermund[1]

[1]Goteborg University Institutes of Biomedicine
[2]Technische Universität München Fakultät für Medizin
[3]Technische Universität München
[4]AstraZeneca R&D Gothenburg
[5]UNC-Chapel Hill

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Abstract

Background and Purpose: Cystic fibrosis (CF) is a recessive inherited disease caused by mutations affecting anion transport by the epithelial ion channel cystic fibrosis transmembrane conductance regulator (CFTR). The disease is characterized by mucus accumulation in the airways and intestine, but the major cause of mortality in CF is airway mucus accumulation, leading to bacterial colonization, inflammation and respiratory failure. One of the drug targets under evaluation to alleviate airway mucus obstruction in CF is the epithelial sodium channel, ENaC. Experimental Approach: To explore effects of ENaC inhibitors on mucus properties, we used two model systems to investigate mucus characteristics, mucus attachment in mouse ileum and mucus bundle transport in piglet airways. We quantified mucus attachment in explants from CFTR null (CF) mice and tracheobronchial explants from newborn CFTR null (CF) piglets to evaluate effects of ENaC or sodium/hydrogen exchange (NHE) inhibitors on mucus attachment. Key Results: ENaC inhibitors detached mucus in the CF mouse ileum, although the ileum lacks ENaC expression. This effect was mimicked by two sodium/proton exchange (NHE) inhibitors. Airway mucus bundles were immobile in untreated newborn CFTR null (CF) piglets but were detached by the therapeutic drug candidate AZD5634. Conclusion and Implications: These results suggest that the ENaC inhibitor AZD5634 causes detachment of CF mucus in the ileum and airway via NHE inhibition and that drug design should focus on NHE instead of ENaC inhibition.

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