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Ursodeoxycholic acid inhibits ENaC and Na/K pump activity to restore airway surface liquid height in cystic fibrosis bronchial epithelial cells

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Abstract

Cystic fibrosis (CF) is a disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) that in the airways result in reduced Cl^- secretion and increased Na^+ absorption, airway surface liquid (ASL) dehydration, decreased mucociliary clearance, infection and inflammation leading to lung injury. Cystic fibrosis patients often present with bile acids in the lower airways, however the effects of bile acids on ASL and ion transport in CF airways are not known. Secondary bile acids, such as ursodeoxycholic acid (UDCA), have been shown to modulate immune responses and epithelial ion transport. Here we investigated the effects of UDCA in normal and CF airway epithelial cell models. NuLi-1 (normal genotype) and CuFi-1 (CF genotype, Δ508/Δ508) primary immortalized airway epithelial cells were grown under an air-liquid interface. Electrogenic transepithelial ion transport was measured by short-circuit current (Isc) across cell monolayers mounted in Ussing chambers. We observed that UDCA (500 μM, 60 min, bilateral) decreased the basal Isc and ENaC currents in both NuLi-1 and CuFi-1 cells. UDCA inhibited the amiloride-sensitive ENaC current by 44% in NulI-1 monolayers and by 30% in CuFi-1 cells. Interestingly, UDCA also inhibited currents through the basolateral Na/K pump in both Nuli-1 and CuFi-1 monolayers without alterting the expression of ENaC or Na^+/K^+-ATPase proteins. The airway surface liquid height is regulated by transpeithelial Na^+ absorption (ENaC) and Cl^- secretion (CFTR) in normal airway but mainly by ENaC activity in CF epithelia when Cl^- secretion is compromised by CFTR mutations. UDCA increased ASL height by 50% in Nuli-1 and by 40% in CUFI-1 monolayers. In conclusion, we demonstrate a previously unknown effect of UDCA to inhibit ENaC activity and increase ASL height in normal and CF human airway epithelial cells suggesting a therapeutic potential for UDCA in CF lung disease.

Keywords: Airway surface liquid; Bile acids; CFTR; Cystic fibrosis; ENaC; UDCA.

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