Small Molecule Ion Channels Increase Host Defenses in Cystic Fibrosis Airway Epithelia

Rajeev S. Chorghade and Martin D. Burke

In the classic paradigm of pharmacology, small molecules bind to and inhibit overactive proteins and thereby restore physiology in the case of diseases caused by excess protein function. Conversely, diseases caused by a deficiency of protein function are especially difficult to treat, and modern medicine currently lacks a general mechanistic strategy to address such diseases. We therefore set out to test the hypothesis that because living systems are robust, small molecules that can imperfectly replicate the function of missing or dysfunctional proteins may be sufficient to restore physiology. Specifically, cystic fibrosis (CF) is caused by loss-of-function mutations in the CFTR anion channel. Loss of CFTR-mediated bicarbonate secretion to the airway surface liquid (ASL) decreases pH and impairs host defenses. We found that the ion channel-forming small molecule natural product amphotericin B (AmB) permeabilizes differentiated human lung epithelia to bicarbonate, and thereby increases ASL pH. In genetically diverse CF primary human lung epithelia, AmB increased ASL pH, restored viscosity, and increased antibacterial activity, key components of host defenses. AmBisome, a clinically approved formulation that has been safely aerosolized to the lung to treat fungal infections, increased ASL pH in CFTR$^{-/-}$ pigs. In a small-scale clinical trial, AmB changed nasal potential difference (NPD), a key biomarker used to evaluate CFTR modulators, in 8 people with CF. Collectively, these results indicate that though AmB is an imperfect substitute for the CFTR anion channel, the robust network of endogenous pumps and channels in airway epithelia establish a setting in which a non-selective channel is sufficient to support net anion secretion, the fundamental defect in CF. Because networks of active pumps and passive transporters similarly underlie the movement of other ions in living systems, these findings further provide a mechanistic framework to address a range of diseases caused by a deficiency of protein function.