In this section we feature some of the latest and most striking new findings in physiology, interpreting the term “physiology” in its broadest sense. In each instance, an effort will be made to place the new findings in perspective.

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Altered NaCl Concentration of Airway Surface Liquid in Cystic Fibrosis

The major pathology in cystic fibrosis (CF) results from the colonization of the airways by the bacterium *Pseudomonas aeruginosa*. Indirect evidence suggests that this colonization occurs because the thin (10 µm) film of liquid that lines the airways (so-called airway surface liquid; Fig. 1) is saltier in CF patients than in healthy individuals and the endogenous antibiotics that are secreted by the respiratory epithelium are better able to kill bacteria in comparatively dilute medium (1).

If this view is indeed correct, it is of obvious importance to obtain direct measurements of Na and Cl concentrations in airway surface liquid. This task is made difficult, however, by the small volume of such liquid. The problem has been partially circumvented by a new approach (3) using human tracheal epithelium in culture, in which radioactive $^{22}\text{Na}$ and $^1\text{H}_2\text{O}$ (or radioactive $^{36}\text{Cl}$ and $^1\text{H}_2\text{O}$) are added to the medium bathing the basolateral side of these cultured cells. The isotopes take 1–2 days to equilibrate with the air-

![Diagram of airway epithelium](image-url)

**NORMAL**

- Lumen (apical)
- Air
- Airway surface liquid
- Epithelium
- Interstitium (basolateral)

$[\text{NaCl}] = 140 \text{ mM}$

**CYSTIC FIBROSIS**

- Na$^+$
- CFTR
- Cl$^-$

$[\text{NaCl}] = 100 \text{ mM}$

$[\text{NaCl}] = 140 \text{ mM}$

**FIGURE 1.** Schematic representation of airway epithelium during healthy conditions and during cystic fibrosis. The solid downward arrow denotes active Na transport. The two dashed arrows denote passive transport of Cl, with by far the larger portion being transcellular (heavy dashed arrow) and the minor portion being paracellular (lighter dashed arrow). In cystic fibrosis, the transcellular pathway for Cl is effectively absent, and absorption of Cl is reduced. The demands of electroneutrality result in an equivalent reduction in active absorption of Na.

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way surface liquid on the apical surface of the epithelium. After this time, the airway surface liquid is removed by flushing the apical surface with a large volume of saline. The ratio of counts from $^{22}\text{Na}$ (or $^{36}\text{Cl}$) to counts from $^3\text{H}_2\text{O}$ provides estimates of the Na (or Cl) concentrations of the surface liquid. It was found that the concentrations of Na and Cl were both ~50 mM in normal epithelium and both ~100 mM in epithelium from CF patients, in contrast to ~140 mM in the medium bathing the basolateral side.

To explain this striking change in CF, we must first ask how the NaCl concentration of airway surface liquid is normally held at values so much lower than those in the medium bathing the basolateral side (Fig. 1). The primary process that removes salt from the airway surface liquid is active absorption of Na. This creates a transepithelial potential difference of ~30 mV (lumen negative), which drives the passive movement of anions, mainly Cl, that accompany the Na and maintain electroneutrality. Why doesn’t water follow the absorbed NaCl down the resulting osmotic gradient? Or put differently, Why is the absorbate apparently so hypertonic? A low osmotic permeability of airway epithelium would provide the answer, but this does not seem to be the case. An untested possibility is that the absorption of NaCl is balanced by secretion (into the apical medium) of some unknown osmolyte. Another possibility is that when the film of airway surface liquid becomes sufficiently thin, the structures on the apical (airway) surface (cilia, microvilli, mucus gel) generate surface tension forces that prevent the osmotic flow of water.

The next question is, Why are the Na and Cl concentrations of airway surface liquid elevated in CF? The answer may lie in recent research indicating that a substantial fraction of the Cl that follows the actively absorbed Na passes through rather than between the cells (2), a route that involves the cystic fibrosis transmembrane conductance regulator (CFTR), which is defective in CF. Thus, in cultures of bovine tracheal epithelium, the use of microelectrodes revealed that the net electrochemical driving forces for Cl movement were inward across the apical membrane (i.e., from apical surface liquid into the cell) and outward across the basolateral membrane (i.e., from the cell into the interstitium). Patch-clamp studies showed that both the apical and basolateral cell membranes contained cAMP-activated Cl channels. In the apical membrane the predominant channel was CFTR, but the channel in the basolateral membrane had a biophysical signature quite distinct from CFTR. The following experiment illustrates that this transepithelial pathway can be activated physiologically. The apical surface of bovine cell sheets was bathed in a large volume of liquid. Under these circumstances (as opposed to when airway surface liquid is present as a thin film held in place by surface tension), the epithelium could absorb isotonic NaCl solution and opening of apical and basolateral Cl channels by elevation of intracellular cAMP resulted in a threefold increase in transepithelial fluid absorption.

In summary, in CF lack of functional CFTR in the apical membrane will block the transepithelial route for Cl absorption (indicated in Fig. 1 by the heavy dashed arrow). When CF tissues are bathed with a large volume of apical medium, this will result in lower than normal rates of isotonic saline absorption, as has recently been reported (3). When the airway surface liquid is present as a thin film of set volume, the reduced ability of Cl to pass through the cells will inhibit removal of NaCl from this film and promote the higher than normal levels of Na and Cl found in airway surface liquid in CF (3).

References


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