

Rationale for Hypertonic Saline Therapy for Cystic Fibrosis Lung Disease

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ABSTRACT

Cystic fibrosis (CF) is caused by alterations in the CF transmembrane conductance regulator (*CFTCR*) gene. More than 1400 mutations in the *CFTCR* gene have been described, but the most common mutation (noted in 70% of CF chromosomes) is $\Delta F508$. Alterations in the *CFTCR* gene result in deranged sodium and chloride ion transport channels. This leads to failure of airway epithelia to hydrate their surfaces normally, particularly in response to infectious or toxic insults. Additional effects include mucus adhesion to airway surface, chronic inflammation, and infections. The concept that airway surface dehydration can cause CF-like lung disease is supported by in vitro data and in vivo animal models. Rehydrating airway surfaces may reduce or prevent lung injury and damage. Short- and longer term studies have shown that inhalation of hypertonic saline is well tolerated and improves lung function, reduces exacerbations, and improves quality of life in CF patients. This review discusses the importance of airway epithelial sodium and chloride channels in the pathogenesis of CF, and strategies (particularly the use of inhaled hypertonic saline) to reverse or minimize lung inflammation and injury in this disease.

KEYWORDS: Cystic fibrosis, cystic fibrosis transmembrane conductance regulator (*CFTCR*) gene, hypertonic saline, sodium and calcium channel, osmotic gradient

The syndrome of cystic fibrosis (CF) reflects a spectrum of more than 1400 mutations in the CF transmembrane conductance regulator (*CFTCR*) gene.¹ The *CFTCR* gene is large, ~ 250 kb, and resides on chromosome 7.^{2,3} The *CFTCR* protein encoded by the *CFTCR* gene is a 1480 amino acid protein that typically resides in the plasma membrane of epithelial cells.⁴ This protein appears to have many functions, but a unifying theme is that it acts at virtually all sites as a protein kinase C and cyclic adenosine monophosphate (cAMP)-regulated chloride (Cl^-) channel.^{5,6} Interestingly, in the sweat duct, *CFTCR* acts as a Cl^- absorptive channel; in the pancreas, it serves to secrete Cl^- , which is exchanged

for bicarbonate (HCO_3^-); and in the lung, it is involved in secretion of Cl^- . Importantly, in the lung, the *CFTCR* protein has a second function acting as a regulator of the epithelial sodium (Na^+) channel (ENaC) and hence Na^+ absorption.^{7,8}

There are five classes of mutations in the *CFTCR* gene that produce disease. The most common mutation, which occurs on 70% of all CF chromosomes, is a three-base-pair deletion that leads to a deletion of phenylalanine at position 508 of the *CFTCR* protein and is designated as $\Delta F508$. The molecular pathogenesis of this class of *CFTCR* mutations is relatively well understood. Typically, the absence of a phenylalanine at position 508

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leads to problems in intracellular protein folding and maturation that are part of the normal biosynthetic pathway of membrane proteins.^{9,10} Consequently, the $\Delta F508$ CFTCR protein is “edited” out of the cell by molecular chaperones and a variety of intracellular degradative pathways. Hence, the molecular pathogenesis of this most common form of *CFTCR* mutation reflects the absence of a functioning CFTCR polypeptide in the plasma membrane. Other mutations can produce a non-functioning CFTCR Cl^- channel at the apical membrane and/or a mutant CFTCR with abnormal ion permeation characteristics.

CYSTIC FIBROSIS LUNG DISEASE

CF lung disease fundamentally reflects a failure in the capacity of airway epithelia to normally hydrate their surfaces, particularly in response to infectious or toxic insults. Poor hydration of airway surfaces leads to reduced mucociliary clearance, adhesion of mucus to airway surfaces, and, ultimately, chronic bacterial infection of airway surfaces (Fig. 1).

Data from an *in vitro* well-differentiated cell culture model interfaced to a confocal microscope to measure airway surface liquid (ASL) volume were key in elucidating the importance of airway surface hydration in lung defense.^{11,12} The hydration of the normal airway surface (i.e., the volume of ASL), is determined in a highly water-permeable epithelium such as airway epithelia by ion transport processes that control the mass of salt (NaCl) on airway surfaces.¹³ Normal airway epithelia have the capacity to remove (absorb) NaCl from or add (secrete) NaCl to airway surfaces (Fig. 2A). The absorptive pathway reflects the capacity to actively absorb Na^+ ions, with Na^+ entering the cell from ASL through the

ENaC. Na^+ ions exit the cell via the activity of a basolateral Na^+-K^+ -adenosine triphosphate (ATP)ase. Chloride may be secreted from the cell by an apical membrane CFTCR Cl^- channel or a Ca^{2+} -activated Cl^- channel (CaCC), with Cl^- entering the cell principally via an $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ cotransporter. Regulation of the balance between absorption and secretion determines the net transport of ions across the epithelium and, hence, the mass of salt on an epithelial surface.

The processes that regulate the balance between Na^+ absorption and Cl^- secretion are beginning to be elucidated (Fig. 2A). Important signals that are contained within the ASL itself include the triphosphate adenine nucleotide, ATP, and the adenine nucleoside, adenosine (ADO).¹⁴ ATP, interacting with luminal P2Y_2 receptors, can slow the rate of Na^+ absorption and initiate/accelerate Cl^- secretion via PKC-mediated actions on CFTCR and Ca^{2+} -mediated actions on CaCC.¹⁵ Adenosine can initiate Cl^- secretion via cAMP-dependent activation of CFTCR and CFTCR-dependent inhibition of ENaC. Recent data have suggested that both systems are operative and important in regulating the balance of Na^+ absorption versus Cl^- secretion in normal airway epithelia.¹⁶ The quantities of ATP, and its metabolic product ADO, on airway surfaces are determined by the mechanical stresses imparted to airway epithelia during breathing that regulate the rate of ATP release from epithelial cells into ASL.¹⁷ A key concept is that the ATP signaling and the ADO signaling systems are redundant and, hence, ensure sufficient hydration under many conditions in the normal lung.

CF airway epithelia are vulnerable to dehydration because of the absence of the CFTCR protein in the plasma membrane (Fig. 2B). Specifically, the adenosine- A_{2b} receptor system is functional, cAMP-dependent activation of PKA is functional, but the absence of CFTCR protein in the membrane renders the Cl^- secretory and Na^+ inhibitory effects of ADO signaling ineffective. In contrast, the ATP- P2Y-R signaling system is effective in CF airway epithelia in inhibiting ENaC and initiating CaCC-mediated Cl^- secretion.¹⁵ *In vitro* studies demonstrate that, under conditions that reprise tidal breathing *in vivo*, CF airway epithelia are covered by sufficient ASL to mediate normal mucociliary clearance, but they are missing a liquid reserve observed on normal airway cells.¹⁶ Importantly, the CF hydration capacity collapses if the lung is confronted with circumstances that degrade the efficacy of the ATP signaling system. A relevant *in vitro* observation is that infection of CF airway epithelia with paramyxoviruses, such as respiratory syncytial virus (RSV), induces CF airway epithelia to upregulate extracellular ATPase expression.¹⁶ This increased ATPase activity is sufficient to degrade the ATP in ASL and diminish/abolish P2Y_2 inhibition of Na^+ absorption and stimulation of

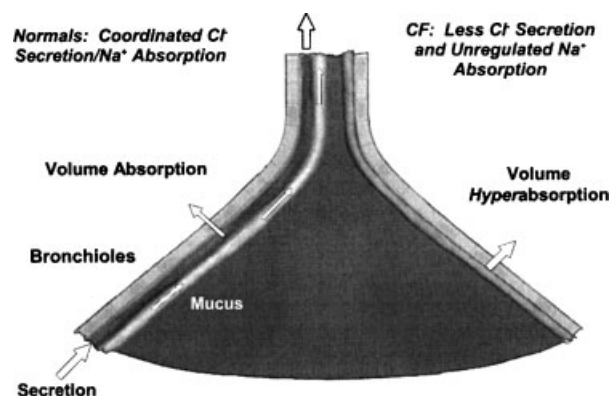


Figure 1 Schema depicting relationship of Na^+ and Cl^- transport to mucus clearance and lung defense. (L) In health, Na^+ absorption and Cl^- secretion are coordinated to optimize airway surface hydration and promote the clearance of mucus from airway surfaces. (R) In cystic fibrosis, unregulated Na^+ absorption and diminished Cl^- secretion produce a propensity for airway surface dehydration, mucus adhesion to airway surfaces, and, ultimately, chronic inflammation and infection.

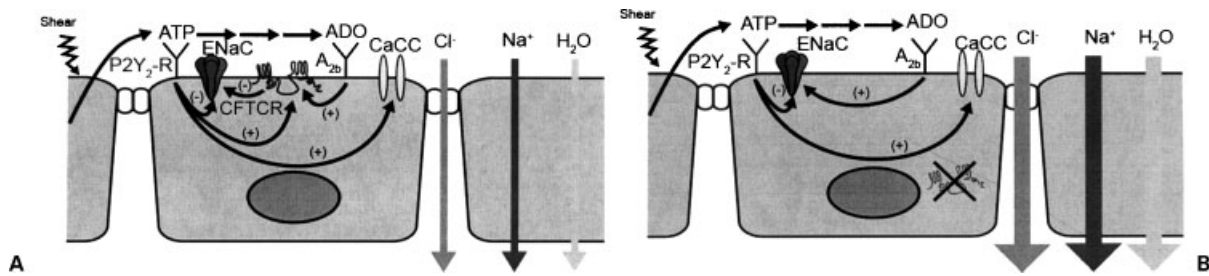


Figure 2 Constitutive and shear-dependent release of adenine triphosphate (ATP) into airway surface liquid (ASL), coupled with metabolic enzymes, produces levels of ATP and its metabolic product adenosine (ADO) that regulate the ion transport paths which control the mass of salt and ultimately water on airway surfaces. (A) In normal airways, ATP signaling through P2Y₂ receptors and ADO signaling through A_{2b} receptors provide redundant inhibition via the epithelial sodium channel (ENaC) (directly via P2Y₂-R and indirectly via A_{2b}-CFTCR mechanisms) and regulation of both CFTCR- and CaCC-mediated Cl⁻ secretion. The typical net result is a modest rate of NaCl and water absorption to remove ASL continually transported proximally from distal pulmonary regions. (B) In cystic fibrosis, the absence of CFTCR function at the apical membrane removes the ADO contribution to inhibition of ENaC and the CFTCR contribution to Cl⁻ secretion. Indeed, the ADO-A_{2b} regulation is redirected toward activation of ENaC. The ATP-P2Y₂-R system remains intact and is the sole system to inhibit ENaC and regulate CaCC-mediated Cl⁻ secretion. The net effect is a tendency for increased and inappropriate NaCl and water absorption. This residual form of regulation is vulnerable to any exogenous insults that perturb ASL ATP concentration.

CaCC-mediated Cl⁻ secretion. Under these conditions, unregulated salt and liquid absorption occurs, the CF airway surface becomes dehydrated, mucus transport is abolished, and mucus stasis ensues. It has been speculated that a similar event may occur in CF patients *in vivo* during viral infections, leading to sludging of dehydrated mucus in virus-infected areas of the lung and spread of bacterial infection from bronchiectatic areas to produce an acute exacerbation.^{18,19}

The concept that airway surface dehydration can produce CF-like lung disease was tested in an *in vivo* model to ascertain whether the *in vitro* observations cited here were pertinent to lung defense *in vivo*. As a test of this hypothesis, subunits of the epithelial Na⁺ channel were transgenically overexpressed in mice under the control of an airway-specific promoter in an attempt to tip the balance toward Na⁺ absorption over Cl⁻ secretion.²⁰ Analysis of the ion transport characteristics of mice overexpressing the β ENaC subunit revealed that Na⁺ absorption was increased threefold over controls, whereas the ability to generate Cl⁻ secretion in response to nucleotide-activated CaCC activity was not perturbed. The disturbance of the balance between absorption and secretion produced the predicted depletion of ASL volume, which resulted in mucus stasis, and death due to mucus obstruction in ~50% of transgenic animals. Unexpected but important findings were that the reduction in ASL volume also produced neutrophilic inflammation and goblet cell hyperplasia that are typical features of CF lung disease. Thus, these observations provided strong evidence that a disturbance of the balance between Na⁺ absorption and Cl⁻ secretion, in this case by transgenically raising Na⁺ transport rates without disturbing Cl⁻ secretion, could produce airway surface dehydration and a phenotype quite typical of CF-like lung disease.

Finally, data from human clinical studies are consistent with the notion that dehydration is a central

feature of CF lung disease.^{21–23} Clinical studies have also employed inhaled hypertonic saline (HS), which osmotically draws water from epithelial cells/interstitium into the airway lumen, to test whether this action restores mucus clearance and improves pulmonary function. Initial studies conducted approximately a decade ago suggested that short-term (~2 week) administration of HS to CF patients was associated with an improvement in lung function.^{24,25} More recently, a pair of papers revealed that the inhalation of HS (7%, delivered by a jet nebulizer) by CF patients over a 2-week period could increase the rates of mucociliary clearance and improve pulmonary function tests, and, over a 1-year interval, reduce exacerbations and improve quality of life.^{26,27} Importantly, the inhalation of HS for 1 year was not associated with any untoward events (e.g., increased airways inflammation or increased bacterial densities).²⁷ These studies have spurred intense interest in the possibility that HS and other “hydration therapies” may provide a new form of therapy that treats CF lung disease at its basic cause.

RATIONAL USE OF HYPERTONIC SALINE

There are many interesting and important concepts that underlie the use of HS in CF subjects. The first is to understand reasons why HS is more effective in CF patients than in normal subjects. Second, it is important to understand that HS probes the passive permeability properties of the epithelium, and its actions should not be confused with the functions of the epithelium under physiological active ion transport modes. Some of these important concepts can be evaluated in the context of Fig. 3.

Beginning with normal airway epithelia, under baseline conditions, when ASL Na⁺ and Cl⁻ concentrations are isotonic, Na⁺ is absorbed through ENaC in response to the apical membrane–cellular electrochemical

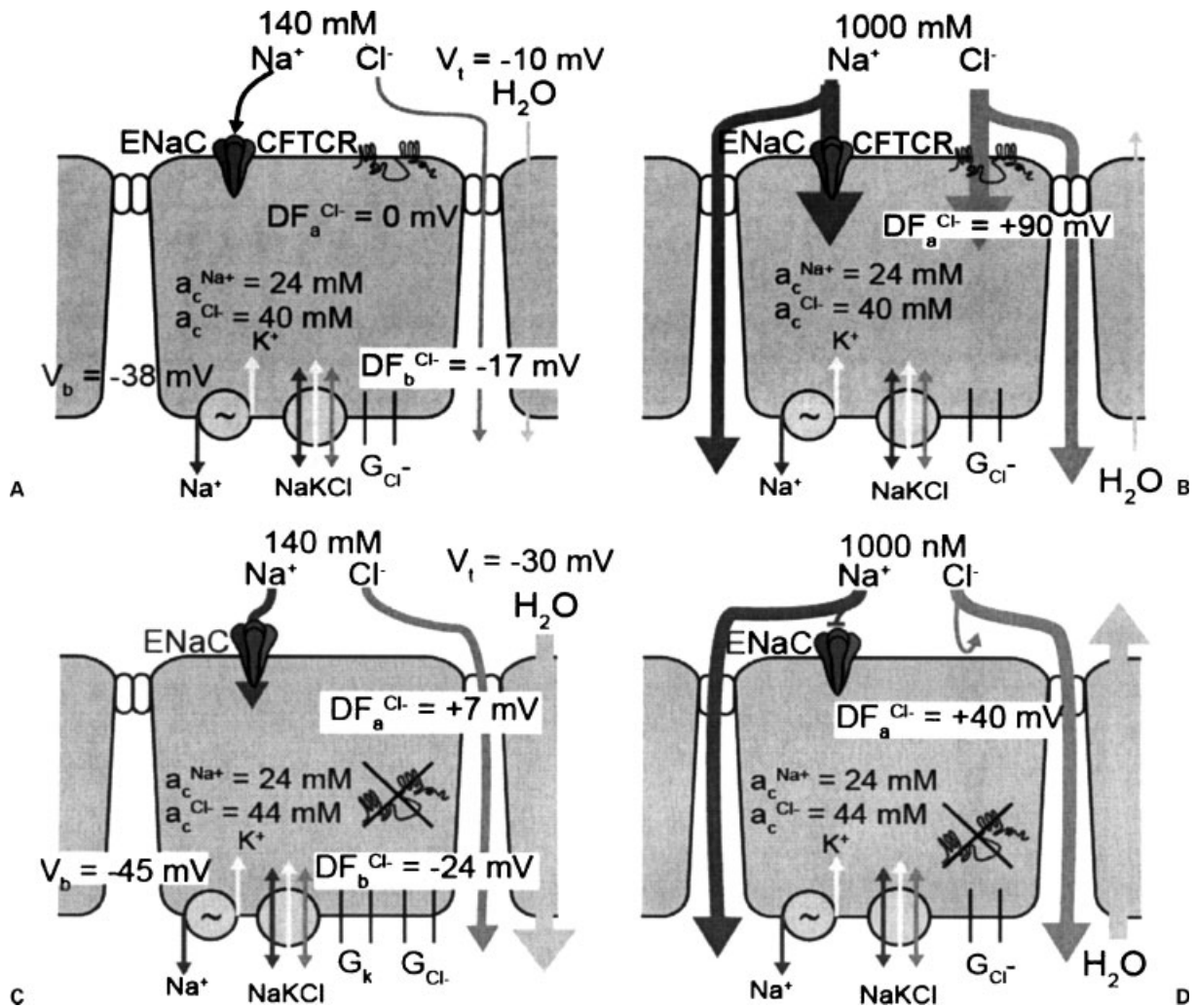


Figure 3 Ion and water transport under basal active ion transport conditions and after aerosol deposition of 7% NaCl on airway surfaces. (A) Normal active ion transport: The net rate of active ion transport is determined by the rate of active Na^+ transport, which is a product of the electrochemical gradient favoring Na^+ entry across the apical membrane ($DF_a^{\text{Na}^+} = +60 \text{ mV}$) and Na^+ extrusion across the basolateral membrane by the $\text{Na}^+\text{K}^+\text{ATPase}$ pump. Because there is no net driving force for Cl^- flow through the apical membrane CFTCR, Cl^- is absorbed paracellularly in response to the transepithelial electric potential difference (V_t) to preserve electroneutrality. Water accompanies NaCl transport through cellular and paracellular paths. Note, ASL is isotonic; that is, $[\text{NaCl}] = \sim 140 \text{ mM}$.^{39,40} (B) Normal airways after hypertonic saline (HS) deposition. Airway surface liquid (ASL) NaCl concentrations are acutely raised ($\sim 1000 \text{ mM}$ at 7% NaCl). The increased concentrations of Na^+ and Cl^- increase the chemical driving force component for Na^+ entry into the cell and generate a large gradient favoring cellular Cl^- entry (i.e., absorption). The Na^+ and Cl^- entering the cell exit the basolateral membrane via the pump (Na^+), cotransporters (Na^+ and Cl^-), and a basolateral Cl^- channel. In parallel, there is a relatively smaller increase in Na^+ and Cl^- absorption through the paracellular path, which is nonselective for ions, in response to the chemical gradients generated by HS deposition. Water moves in the opposite direction in response to the transient NaCl osmotic gradient generated by HS deposition. (C) Cystic fibrosis (CF) airway epithelial, active ion transport. The absence of CFTCR in the apical membrane removes a major inhibitor of the epithelial sodium channel (ENaC), producing higher basal rates of Na^+ transport and limiting the ability to regulate ENaC at low ASL volumes. The high rate of Na^+ transport generates a raised transepithelial potential difference (PD) (V_t), which provides the driving force for Cl^- absorption via the paracellular path to match Na^+ absorption. The raised net rate of NaCl absorption produces raised H_2O absorption and a tendency for ASL volume depletion (i.e., dehydration). (D) CF airway epithelia, post-HS deposition. Again, the concentration of NaCl is raised in CF ASL by this maneuver to $\sim 1000 \text{ mM}$. Despite a large chemical driving force favoring Cl^- entry into the cell from ASL, the absence of CFTCR in the membrane prevents entry of Cl^- into the cell. Despite the presence of a functioning ENaC, transcellular Na^+ absorption is limited by the block of cellular Cl^- entry. Therefore, virtually all the NaCl absorption occurs via the paracellular path. Because NaCl absorption following HS deposition is limited to the paracellular path, it is slower, allowing more time for water to flow into the lumen in response to the persistent NaCl osmotic gradient. Thus, the ASL volume response to a given quantity of HS deposition is greater in CF than in normal airways.

gradient favoring Na^+ entry^{28,29} (Fig. 3A). Despite the fact that there is a partially active CFTCR Cl^- channel in the apical membrane of the normal airway epithelium, Cl^- is not absorbed with Na^+ transcellularly, because

there is no electrochemical driving force for Cl^- movement across the cell membrane.³⁰⁻³² Thus, Cl^- is absorbed with Na^+ via the paracellular path, in response to the transepithelial electric potential difference (lumen

negative) generated by active Na^+ transport. Isotope flux and ion-selective electrode data suggest that the overall ion conductance of the cellular path is approximately twofold greater than through the paracellular path in normal airway epithelia.^{33,34} Recent data suggest that water is absorbed with the actively transported Na^+ and Cl^- ions via cellular aquaporin water channels.

For illustrative purposes, we will assume that the entire quantity of 7% HS is deposited undiluted on the airway surface (note, the argument will hold with any exogenously increased Na^+ or Cl^- concentration in ASL). It is important to note that the addition of NaCl to airway surfaces via inhalation of hypertonic NaCl is an artificial, unphysiological situation that produces an exogenously induced Na^+ and Cl^- chemical gradient across the epithelium. In the normal airway epithelium, the increase in Na^+ concentration increases the electrochemical driving force for Na^+ to enter the cell and generates the electrochemical driving force for Na^+ to move through the paracellular path (Fig. 3B). Importantly, the increase in the Cl^- concentration in ASL now generates an electrochemical driving force for Cl^- to enter the cell via an active CFTCR and/or CaCC Cl^- channel, with the residual Cl^- moving through the paracellular path. The Na^+ and Cl^- that enters the cell in response to the aerosolized HS-induced NaCl concentration gradient on the airway surface exits the cell through the basolateral Na^+ - K^+ -ATPase, a basolateral Cl^- channel, and likely through the Na^+ - K^+ - 2Cl^- cotransporter. Based on the estimates of the relative permeabilities of the cell and paracellular paths for Na^+ and Cl^- , it is estimated that approximately two thirds of the NaCl may move through the transcellular path in response to these imposed chemical gradients.^{33,34} Note that the aerosol-induced increase in NaCl concentration on airway surfaces produces a gradient for water to move through water channels in the opposite direction to that generated by active ion transport (i.e., there is osmotically induced water flow from the submucosa to the airway surface). Because NaCl is absorbed rapidly through the normal cell as well as the paracellular path after the imposition of the salt gradient, the osmotic gradient generated by NaCl on normal airway surfaces dissipates relatively rapidly, and only a modest amount of water moves to airway surfaces in response to this challenge (see Fig. 3B).

For CF airway epithelia, under baseline active ion transport conditions, the rate of Na^+ absorption is often accelerated due to the absence of CFTCR-mediated inhibition of ENaC (Fig. 3C). Interestingly, the absence of the CFTCR Cl^- conductance per se and the absence of CFTCR inhibition of ENaC actually produces an electrochemical driving force for Cl^- to be absorbed across the apical membrane of CF airway epithelia.^{31,32} However, because of the absence of the CFTCR Cl^- channel in this barrier, Cl^- must move through the paracellular

path to accompany the transcellular absorption of the Na^+ cation. The driving force that serves to match the rate of transepithelial Cl^- absorption with Na^+ absorption is the relatively high transepithelial potential difference (-30 mV, lumen negative) generated by a high rate of transcellular Na^+ absorption. The increase of Na^+ and Cl^- transport in CF airway epithelia compared with normal airway epithelia produces an increase in osmotically entrained water absorption from the airway lumen to the submucosa via airway epithelial water channels.

In the case where an aerosol of 7% HS has been used to increase the NaCl concentration on CF airway surfaces, the differences in the passive ion permeabilities of the CF airway epithelium versus normal airway epithelium are revealed. As for normal airway epithelia, when a high NaCl concentration in the ASL is generated by aerosol deposition of HS on ASL, an increase in the electrochemical gradient for Na^+ entry into the cell is developed (Fig. 3D). Despite the fact that an increased electrochemical gradient for cellular Cl^- entry is also generated, Cl^- cannot enter the cell due to the absence of the CFTCR Cl^- channel in the apical membrane. The only available path for cellular Cl^- to be absorbed across the CF airway epithelium, in response to the chemical gradients generated by the deposition of NaCl via aerosols in ASL, is the paracellular path.

Data from radioisotopic and electrophysiological techniques suggest that the paracellular path permeability to NaCl is not different in CF versus normal airway epithelial cells.^{7,30-32,35} Therefore, because CF airway epithelia can absorb the aerosol-deposited NaCl only via the paracellular path, the rate of absorption/dissipation of the salt gradient will be reduced by ~ 60 to 70% as compared with normal airway epithelia, reflecting the absence of a cellular route for Cl^- absorption in CF airway epithelia. The slower rate of NaCl absorption leads to a relative retention of NaCl on CF airway surfaces. Thus the osmotic gradient favoring water flow generated by the aerosolized NaCl persists for longer periods of time in CF than normal airway epithelia, leading to increased volumes of water on CF versus normal epithelial surfaces (see Fig. 3D). Interestingly, this inability to absorb Cl^- passively via an artificially imposed Cl^- gradient, producing increases in ASL volume, may be the only "break" CF patients get with respect to therapy of their lung disease.

Note, at the large NaCl concentration gradients (10s to 100s mM) generated by HS deposition on CF airway surfaces, the Cl^- conductance of the paracellular path is limiting for Na^+ and, hence, net NaCl absorption. Under baseline conditions where CF active ion transport determines ASL volume, active Na^+ transport generates μM salt gradients across CF airway epithelia. At physiologic transport rates, the Cl^- conductance of the paracellular path is not limiting, so the rate of active Na^+ transport determines ASL volume. These considerations

resolve the apparent paradox of the importance of the absent cellular CFTCR Cl^- conductance in the response of the CF airway to aerosolized HS versus the relative unimportance of the cellular Cl^- conductance in the abnormal NaCl absorptive states that are a feature of CF airways under basal conditions.

THE EFFECT OF AMILORIDE PRETREATMENT ON HYPERTONIC SALINE EFFICACY

An observation that led to some confusion and controversy pertaining to the paper of Donaldson et al²⁶ was the fact that amiloride blunted the responses of CF airway epithelia to HS³⁶ (see Fig. 4A). It had been predicted that by blocking the cellular path for Na^+

absorption, the amiloride-induced block of ENaC would slow the active epithelial absorption of Na^+ (and Cl^-) across the epithelium. This effect was predicted to promote a longer duration of the aerosolized HS deposited on airway surfaces that would subsequently be rendered isotonic via the osmotically driven movement of water.³⁷ Surprisingly, what was observed was that administration of amiloride blocked the initial volume response so that it was not possible to ascertain whether amiloride slowed the subsequent active absorption of ASL (Fig. 4A). Because it seemed implausible that amiloride would accelerate the absorption of Na^+ and Cl^- across the CF airways epithelium, studies were initiated to ascertain whether amiloride had a second action on airway epithelial salt and water transport (e.g., blocked epithelial water permeability). These studies

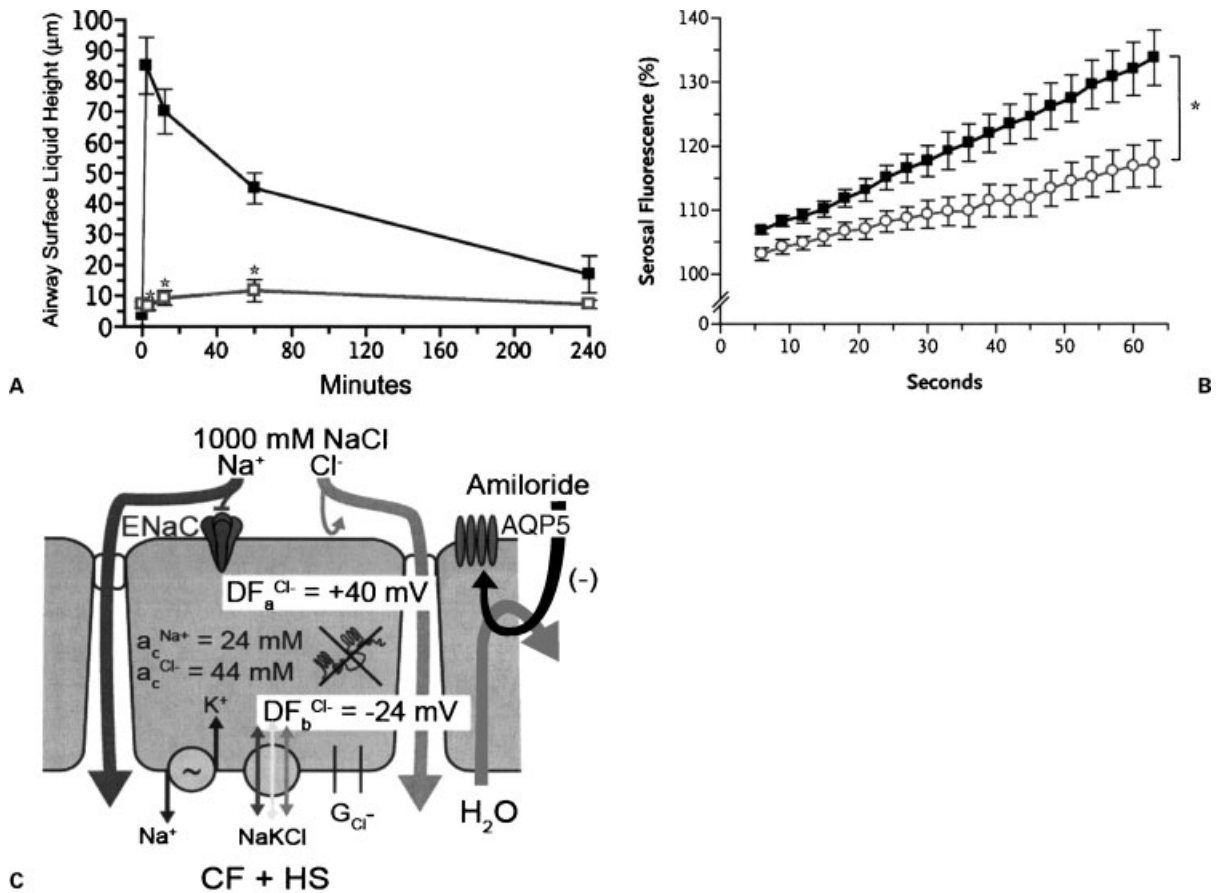


Figure 4 Effect of amiloride on hypertonic saline (HS)-induced airway surface liquid (ASL) volume responses. (A) Confocal measurements of ASL height/volume in cystic fibrosis (CF) airway epithelia in response to 7% HS without (■) and with (□) amiloride (3×10^{-4} M) pretreatment. *Different from HS alone ($p < .05$). (B) Effect of amiloride on osmotically induced water flow across CF airway epithelia. Cultured CF airway epithelia were placed on a confocal microscope with a fluorescent, impermeant probe in the basolateral bath. At $t=0$, hypertonic mannitol was placed in the luminal bath and the flow of water from the basolateral to the luminal bath measured from the increase in serosal bath fluorescence (i.e., concentration of the serosal bath probe increased as water moved into the luminal compartment). This assay was performed without (■) and with (○) amiloride (3×10^{-4} M) administration to the lumen 10 minute prior to osmotic challenge. *Different from without amiloride pretreatment ($p < 0.05$). (C) Speculated cellular action of amiloride on transepithelial water flow after HS administration. The deposited HS produces the increase in ASL [NaCl], as depicted in Fig. 3D. Again, the absence of a path for Cl^- absorption limits NaCl absorption to the paracellular path. It is speculated that amiloride slows water flow in response to the HS-generated NaCl gradient by inhibiting aquaporin 5 in the apical membrane. This action allows NaCl absorption to occur relatively more rapidly than water flow into the lumen, greatly decreasing the ASL volume expansion in response to HS administration.

revealed that amiloride at high concentrations blocked transepithelial water flows in response to osmotic gradients generated by added NaCl or a nonionic solute, mannitol (Fig. 4B). Although the precise mechanisms are not known, it appears from subsequent studies that amiloride may block the aquaporin 5 channel that is an important water channel in the apical membrane of normal and CF airway epithelia. Thus, as shown in Fig. 4C, a partial block of the apical membrane water channel slows water movement toward the lumen in response to the aerosol-imposed NaCl gradient, allowing the NaCl gradient to be dissipated through the paracellular path. Thus the “kinetic horse race” between the absorption of NaCl via the paracellular path versus the movement of water toward the lumen via the cellular path is tipped in favor of paracellular NaCl absorption via the actions of amiloride. The net effect is a reduced volume response to the aerosol-generated salt gradient.

Interestingly, amiloride might have been therapeutically useful if given after HS rather than as a pretreatment. That is, amiloride would have blocked the active absorption of Na⁺ (and Cl⁻). Because, as noted earlier, the gradients of NaCl across the epithelium generated by active Na⁺ (and Cl⁻) absorption are very low (μM) as compared with aerosol deposition of salt (mM), any amiloride block of water flow would have negligible effects on osmotic water flow coupled to active ion transport. However, the clinical utility of delivering amiloride after HS may be minimal because the half-life of amiloride on airway surfaces is short (~ 30 min).

THE FUTURE OF HYDRATION THERAPIES

A central question will be the position of HS within the spectrum of therapies available to CF patients. On one level, because HS may treat the initiating cause of CF lung disease, it may make sense to make HS the “base” therapy for CF patients. However, the current experience principally reflects administration of HS with pressure-driven nebulizers to adolescents and young adults. Studies are under way to transition the delivery of HS to more time-efficient devices (e.g., ultrasonic devices) that can also be more easily interfaced to infants. Thus important studies that will soon be initiated are ones designed to test whether inhaled HS in infants over a 1-year period can forestall the decrements in lung function and the abnormalities in CT (air trapping/bronchiectasis) that characterize this period. Similar studies are under way in 4- to 6-year-old cohorts to ascertain whether HS can arrest the decrement of lung function typically seen in this age group.

Because the initiating events of many acute exacerbations in CF are viral infections that may induce mucus sludging in airways that were previously “quasi-normally” hydrated via the actions of ATP (see earlier), it may make sense to study relationships between HS

therapy and exacerbations. Because this thesis has not been tested, it will be important to generate randomized trials to ascertain whether maximization of HS therapy at the time the CF patient clinically senses a “virus” will forestall an exacerbation. In parallel, studies may also be warranted to test whether maximization of HS-mediated hydration will shorten the interval of the exacerbation and improve the outcome of therapy for exacerbations.

Finally, HS does have limitations with respect to the therapy of CF lung disease. For example, HS at 7% can be irritating to some patients and cause bronchoconstriction. Similarly, particularly in children, the taste of HS is a detriment to chronic use of this agent. Perhaps most importantly, it is difficult to deliver HS efficiently to the very large surface area of the small airways/bronchioles that appear to be the site of initiation of CF lung disease.^{38–40} This phenomenon reflects the simple aerosol physics parameters of the modern nebulizer, which deposits approximately equal volumes of aerosol on the relatively small surface area of central airways compared with the relatively large surface area of small airways. Because the hydration effect of HS is a linear function of the amount of salt deposited on airway surfaces, the small airways will always be less well treated by HS. Thus, it may be advantageous in the future to utilize approaches that hydrate airway surfaces by inducing secretion of NaCl via receptor-mediated pathways that can be fully activated by potent ligands delivered to small airway surfaces, for example, stabilized nucleotide molecules (INS37217), or by the coadministration of new, potent, long-acting Na⁺ channel blockers that will retain all NaCl added to small airway surfaces to amplify the hydrating effects of HS in this region. It is likely that the requirement to effectively treat the bronchiole will be a central feature of any hydrating regimen to, in a most assured fashion, prevent and/or arrest the progression of lung disease in CF patients.

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