Pulmonary $\text{Na}^+$ transport induced by lung edema fluid

R. E. Olver and S. M. Wilson

Lung Membrane Transport Group, Division of Maternal and Child Health Sciences, University of Dundee, Dundee, Scotland, United Kingdom

THE EPITHELIAL CELLS that line both the conductive airways and gas-exchanging regions of the lung actively absorb water from the overlying film of surface liquid, a process that is driven by electrogenic $\text{Na}^+$ transport. The capacity to absorb water develops during the very last stages of gestation (3), enabling the perinatal removal of fetal lung liquid. This process is essential for the efficient establishment of air breathing, and its failure in premature infants contributes to the development of respiratory distress syndrome (RDS) in the newborn (12). It is clear that the lung’s capacity to absorb $\text{Na}^+$ is retained throughout adult life and is tightly regulated to prevent liquid accumulation in the gas-exchanging regions of the lung (15). However, in patients with pulmonary edema, the volume of liquid entering the air spaces may overwhelm this absorptive capacity. Although this life-threatening condition has many possible causes, including congestive heart failure, acute injury, and septic or hemorrhagic shock, its eventual resolution is dependent on lung epithelial $\text{Na}^+$ absorption (11, 15).

Pulmonary $\text{Na}^+$ transport thus plays an important role in protecting lung function, and this process is dependent, at least in part, on the expression of epithelial $\text{Na}^+$ channels (ENaC). These transport proteins are composed of three subunits ($\alpha$-, $\beta$-, and $\gamma$-ENaC) that together form a highly selective $\text{Na}^+$ channel (4). In newborn mice, deletion of $\alpha$-ENaC disrupts the physiological perinatal absorption of lung liquid and causes death within ~48 h of birth (8). Moreover, although heterologous expression of a rat $\alpha$-ENaC transgene can rescue this lethal phenotype, functional studies of these chimeric animals have shown that the respiratory epithelia display an abnormally low rate of $\text{Na}^+$ transport and that in vivo, the mice are abnormally sensitive to experimentally induced pulmonary edema (5). These and other studies (10) thus suggest that ENaC is an important determinant of pulmonary $\text{Na}^+$ transport throughout life. However, it is equally clear that amiloride, a drug that blocks ENaC at concentrations below 1 $\mu$M, does not entirely abolish $\text{Na}^+$ transport in the adult lung (14). Despite much work, the channels underlying this amiloride-insensitive $\text{Na}^+$ absorption have yet to be identified, and their role in pulmonary $\text{Na}^+$ transport is only now beginning to be understood.

A series of three papers from Hugh O’Brodovich’s group in Toronto, one of which is an article in focus in this issue (6), has given unexpected insights into the process of $\text{Na}^+$ transport in pulmonary edema. The first of these papers (13) showed that edema fluid harvested from the lungs of adult rats with experimentally induced heart failure contained a factor, or factors, that almost doubled the rate of $\text{Na}^+$ transport when applied to adult distal lung epithelial cells in monolayer culture. This fluid also hyperpolarized the transepithelial potential difference in explanted fetal mouse trachea, and, since this hyperpolarization persisted in the presence of bumetanide, the observation provided evidence that edema fluid could stimulate $\text{Na}^+$ absorption. Further support for this interpretation came from studies of lung tissues explanted from fetal mice. It is well established that such explants normally expand into fluid-filled cysts when maintained in primary culture and that this expansion reflects the active secretion of liquid into the explant lumen (2). However, when treated with edema fluid, the explants displayed a net reduction in volume, indicating that the fluid had induced an absorptive phenotype.

Perhaps the most surprising outcome of these studies of Rafii and colleagues (13) was that this stimulatory effect of edema fluid was resistant to amiloride, suggesting that it was not dependent on ENaC. Further evidence supporting this conclusion came from the observation that the absorptive effect of edema fluid on fetal distal lung cysts persisted in tissues removed from $\alpha$-ENaC knockout mice. Although $\alpha$-ENaC is clearly important for the clearance of liquid from the neonatal lung (8), these results appear to show that edema fluid can induce an absorptive phenotype independently of this channel subunit. The identity of the cation channel involved in this response was not determined, but cyclic nucleotide-gated cation channels do not appear to be involved since inhibitors of these channels, which have also been implicated in lung liquid clearance (9), have only a very weak effect on the response to edema fluid.

In the second of the papers examining the effect of edema fluid on pulmonary $\text{Na}^+$ and fluid transport, Elias and colleagues (6) have shed new light on the mechanisms underlying the response to edema fluid by making direct measurements of fluid transport across fetal distal lung epithelial cells in monolayer culture. Although the response to edema fluid was not absolutely identical to that described in the earlier study, these experiments clearly confirm that: 1) at high concentrations (i.e., undiluted), pulmonary edema fluid stimulates fluid absorption that persists in the presence of a concentration of amiloride that would be expected to completely block ENaC and 2) the net absorption of liquid from the lumen induced by edema fluid persists in tissues removed from $\alpha$-ENaC knockout mice. However, the most intriguing result to emerge from this study is that the transition from net secretion to net absorption induced by edema fluid is substantially reduced in fetal lung tissues isolated from both $\beta$- and $\gamma$-ENaC knockout mice. It therefore appears that the absorptive response to edema fluid is dependent on these channel subunits but independent of $\alpha$-ENaC.

This result is surprising since it is widely accepted that the $\alpha$-subunit is the only subunit able to form a $\text{Na}^+$-permeable channel in isolation and that the role of $\beta$- and/or $\gamma$-ENaC is to modify the magnitude and conductive properties of this $\alpha$-ENaC-dependent conductance (4). It is therefore interesting that while $\beta$- and $\gamma$-ENaC knockout mice can clear fluid from
their lungs during the perinatal period, although at an abnormally low rate, the most severe consequence of deleting these genes is a profound dysfunction of renal ion transport (1). These new data, in contrast, indicate that β- and γ-ENaC are both involved in the absorptive response to pulmonary edema and therefore suggest that these subunits might, in some unknown way, contribute to amiloride-resistant Na⁺ transport.

In the most recent paper in the series, Gandhi et al. (7), using primary cultures of rat alveolar type II (ATII) cells and in situ (lung slice) and in vivo experimental models, provide additional evidence that edema fluid stimulates Na⁺ transport in the adult lung, and, furthermore, that a factor responsible for the amiloride-insensitive component of the response resides in the globulin fraction of cardiogenic edema fluid. Since plasma from rats with congestive heart failure did not alter Na⁺ transport in cultured ATII cells, it is assumed that activation of the responsible factor(s) occurs during transudation from the circulation or within the air spaces. If the signaling pathways underlying the Na⁺ transport response to edema fluid can be determined, then this may open up new and potentially important therapeutic avenues to treat pulmonary disorders characterized by fluid accumulation in the newborn and adult lung, as in newborn and adult RDS.

REFERENCES