Mechanisms of pulmonary edema clearance

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Mutlu, Gökhan M., and Jacob I. Sznajder. Mechanisms of pulmonary edema clearance. Am J Physiol Lung Cell Mol Physiol 289: L685–L695, 2005; 10.1152/ajplung.00247.2005.—The mechanisms of pulmonary edema resolution are different from those regulating edema formation. Absorption of excess alveolar fluid is an active process that involves vectorial transport of Na⁺ out of alveolar air spaces with water following the Na⁺ osmotic gradient. Active Na⁺ transport across the alveolar epithelium is regulated via apical Na⁺ and chloride channels and basolateral Na-K-ATPase in normal and injured lungs. During lung injury, mechanisms regulating alveolar fluid reabsorption are inhibited by yet unclear pathways and can be upregulated by pharmacological means. Better understanding of the mechanisms that regulate edema clearance may lead to therapeutic interventions to improve the ability of lungs to clear fluid, which is of clinical significance.

acute lung injury; acute respiratory distress syndrome; alveolar epithelium; alveoli

WHEREAS MECHANISMS REGULATING the formation of pulmonary edema have been well established, our understanding of how edema is cleared from the alveoli is the focus of significant research. Earlier experimental studies conducted at room temperature in dogs (which have very low fluid clearance rates) led to misconceptions that persisted until ~20 years ago when it was proposed that alveolar fluid clearance is an active process linked to active Na⁺ transport (15, 115, 177, 186). Lung edema clearance is affected by active Na⁺ transport where Na⁺ moves vectorially across the alveolo-capillary barrier mostly via apical Na⁺ channels and basolaterally located Na-K-ATPase with water following isosmotically the Na⁺ gradient (111) (Fig. 1).

ALVEOLAR EPITHELIUM

The alveolar epithelium comprises 99% of the surface area of the lung and is the primary site for the removal of excess alveolar fluid. The alveolar epithelial monolayer is thin, consisting of squamous type I cells (AT1) and cuboidal type 2 cells (AT2) (178, 200). Although similar numbers of AT1 and AT2 cells populate the alveolar epithelium, AT1 cells comprise >90% of the alveolar surface (200). They are squamous cells with a diameter ranging from 50 to 100 μm. The AT2 cells are cuboidal with a diameter of ~10 μm.

Under normal conditions, the alveolo-capillary barrier has a very low permeability to solutes (69, 186). Tight junctions are critical for the alveolar epithelial barrier function as they connect adjacent epithelial cells and modulate dynamic permeability via distinct ion-selective channels and pores (73, 168). The diffusion of solutes across the alveolar epithelium is much slower than through the intercellular junctions of the adjacent lung capillaries (75, 167, 170, 177). Radii of the pores for small solute movement across the alveolar epithelium and pulmonary capillary endothelium have been estimated to be 0.6–1.0 and 4–5.8 nm, respectively (43, 44). As such, most of the resistance to albumin flux across the alveolo-capillary barrier is due to alveolar epithelium, which has a higher reflection coefficient for proteins than the capillary endothelium (69, 167, 186).

Transepithelial osmotic gradient created by the active Na⁺ transport represents the major driving force for water reabsorption. Sodium enters the alveolar epithelial cell via amiloride-sensitive and -insensitive channels in the apical surface, and then it is “pumped out” via the basolateral surface into the lung interstitium and the pulmonary circulation by the Na-K-ATPase.

Among two types of epithelial cells, the AT2 cell has been better studied. Previously, it was thought that the AT2 cell is responsible for the majority of the vectorial transport of Na⁺ across the alveolar epithelial barrier (56, 68, 109, 110, 114, 123, 154). However, recently, an important role for AT1 cell in vectorial Na⁺ transport has been demonstrated, and it appears that the α2 Na-K-ATPase isozyme expressed mostly in AT1 cells is responsible for ~60% of Na⁺ transport (23, 89, 154, 155). Freshly isolated AT1 cells have the highest osmotic permeability to water of any mammalian cell, possibly contributed by aquaporin (AQP)-5 (46). Similar to Na-K-ATPase, there is evidence for the presence of all three subunits of epithelial Na⁺ channel (ENaC) in AT1 cells (22). This new evidence strongly supports the role of the AT1 cells in vectorial ion transport.

In addition to alveolar epithelial cells, distal airway epithelium may also contribute to fluid clearance (2, 7, 25, 26, 82, 202). Supporting evidence for the contribution of distal airways includes active Na⁺ absorption by Clara cells and regulation by cystic fibrosis transmembrane conductance regulator (CFTR) (190, 191), but because of their smaller surface area, distal airways probably contribute to a smaller degree to the overall fluid reabsorption (2, 7, 25, 26, 82).

Apical Sodium Channels

Transepithelial Na⁺ transport at the apical surface of alveolar epithelial cells is mediated predominantly by amiloride-sensitive Na⁺ channels (ENaC) and also in part by other, less well-characterized cationic channels (16). The ENaC consists
of three subunits, α-, β-, and γ-ENaC (31, 119) and is widely distributed in epithelia such as lung, kidney, and colon. The ENaCs are expressed along the respiratory tract epithelia as well as in the apical surface of alveolar epithelial cells (28, 52, 113, 150) usually as a tetramer made of two α-, one β-, and one γ-subunit or a much larger complex made of nine subunits (3 from each subunit) (58, 96, 176). In Xenopus oocyte studies, amiloride-sensitive sodium transport was detected when only α-ENaC was injected; however, maximal transport required the presence of all three subunits (32, 122). Whereas highly selective channels (HSCs) are composed of α-, β-, and γ-subunits, nonselective channels (NSCs) are composed of α-subunit alone and moderately selective channels are some combination of α-subunit with β and γ (83, 84). The HSC has a high Na+/K+ selectivity (Na+/K+ permeability ratio >40), is insensitive to Ca2+, and has a conductance of 4–6 pS. The NSC has equal permeability for both Na+ and K+ (Na+/K+ ~1.5) with a conductance of 21–28 pS. It is voltage dependent, Ca2+ activated (at high doses), and completely inhibited by 1 μM amiloride (53).

The importance of ENaC in fluid transport is supported by studies in transgenic mice with targeted deletions of ENaC subunits. In both animal and human lungs, the expression of α-ENaC is greater than that of β- and γ-subunits (35, 38, 41, 83, 111, 117, 123, 137, 166, 185, 187). Mice with targeted deletion of α-ENaC die with pulmonary edema within 40 h of birth (78). Mice lacking β- or γ-ENaC are able to clear fluid out of alveolar space, albeit at a lower rate compared with wild

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phosphate bonds and has the catalytic site for the exchange of intracellular Na\(^+\) for extracellular K\(^+\) (172). The \(\beta\)-subunit is a smaller glycosylated transmembrane protein that appears to control the heterodimer assembly and insertion into the plasma membrane (120). Both subunits are required for a functional Na-K-ATPase (39, 120). Interestingly, overexpression of the \(\beta_1\) or the \(\alpha_2\)-subunit increases Na-K-ATPase expression and thus alveolar fluid clearance in adult rats and fetal alveolar epithelial cells (50, 152, 154, 188). The short-term regulation of Na-K-ATPase activity is regulated by the changes in Na-K-ATPases at the plasma membrane via recruitment of the Na\(^+\) pump proteins from intracellular compartments via dephosphorylation and phosphorylation events involving protein phosphatase 2A PKC and Rho-associated kinase (18–20, 39, 100, 101, 153). Long-term regulation of the Na-K-ATPase is elicited by stimulation of dopaminergic (D\(_2\)\_A) and \(\beta_2\)ARs via transcription and translational mechanisms (71, 72, 144, 145).

**Aquaporins**

Transcellular water channels or AQPs have been localized to the lung (193). In mice and rats, AQP-1 is expressed in both the apical and basolateral membrane of endothelial cells and fibroblasts (95), and AQP-3, AQP-4, and AQP-5 are found on both apical and basolateral membranes at different locations of respiratory tract epithelium (94). In the human respiratory system, AQP-5 is expressed in the apical surface of alveolar AT1 cells and in the nasopharyngeal epithelium, and AQP-3 is expressed at the apical membrane of columnar epithelial, basal, and AT2 cells (97).

Studies in transgenic mice with targeted deletions of AQPs have suggested that AQPs are not essential for alveolar fluid clearance (193). A limitation of these and other transgenic mice studies is that while absence of AQPs did not limit the rate of fluid clearance from the alveoli, compensatory mechanisms could have taken place. It is also possible that AQPs may be important in regulation of cell volume, especially of alveolar AT1 cell (77) and of fluid secretion from mucus-secreting cells (104).

**REGULATION OF ALVEOLAR FLUID ABSORPTION**

Although active Na\(^+\) transport appears to be the primary mechanism by which catecholamines regulate lung edema clearance across alveolar epithelium, stimulation of Cl\(^-\) uptake may also contribute to alveolar fluid clearance (87, 88, 114, 139).

**\(\beta\)-Adrenergic Receptor-Mediated Regulation**

Both endogenous and exogenous catecholamines stimulate alveolar fluid reabsorption in newborn and adult animals via activation of \(\beta\)-adrenergic receptors (\(\beta\)ARs) (17, 27, 33, 37, 57, 85, 107, 136, 146, 156, 161). Similar to catecholamines, both nonspecific \(\beta\)AR agonists and those specific for \(\beta_2\)AR, such as salmeterol and terbutaline, increase fluid reabsorption of rat (85), dog (15), guinea pig (135), mice (62, 65, 80), and human lungs (156, 157). Interestingly, \(\beta\)AR stimulation does not increase alveolar fluid clearance in rabbits and hamsters (174).

Both \(\beta_1\)ARs and \(\beta_2\)ARs are present in the membrane of AT2 cells (11, 49). The \(\beta\)AR-mediated increase in alveolar fluid clearance is due to the upregulation of ENaC, chloride channel, and Na-K-ATPase (20, 67, 85, 111, 130, 135, 146, 180) (Fig. 2). The cAMP serves as the second messenger for the stimulatory effects of \(\beta_2\)AR agonists (14), regulating ENaC open-state probability (108, 110, 180) and increasing protein abundance of ENaC and Na-K-ATPases at the plasma membrane (21, 29, 54, 88, 175), which leads to increased Na\(^+\) transport across the alveolar epithelial cells (6, 10, 17–20, 39, 48, 159, 163). These effects can occur within 1 min via highly regulated translocation of Na\(^+\) pump proteins due to phosphorylation of the intermediary cytoskeletal proteins and RhoA kinase (20, 34, 100). Interestingly, activation of \(\beta\)ARs also increases Na-K-ATPase long term (>24 h) (145) via increased translation of the Na-K-ATPase (144) and ENaC (40) via PKA- and PKC-induced phosphorylation of cAMP-responsive elements and posttranscriptional regulation via MAPK/ERK and rapamycin-sensitive pathways (144, 145). Overexpression of \(\beta_2\)AR increases alveolar fluid clearance in transgenic mice (121) and in mice and rats with adenosine-mediated overexpression of \(\beta_2\)AR (48, 130).

Recent studies have proposed a role of Cl\(^-\) channel for catecholamine-mediated regulation of fluid transport in the lungs, where stimulation of \(\beta_2\)AR increased transepithelial chloride absorption leading to increased edema clearance (87, 93). Furthermore, the presence of CFTR is required for \(\beta_2\)AR-mediated upregulation of alveolar fluid clearance (129). It has also been suggested that the transepithelial \(\beta\)AR-mediated Na\(^+\)
transport occurs indirectly via activation of Cl− channels, which results in hyperpolarization to provide the driving force for Na+ influx through ENaC (139).

The β2AR-mediated upregulation of active alveolar Na+ transport makes exogenous β2-agonist use a promising therapeutic option for management of pulmonary edema (131). However, receptor desensitization remains a well-known limitation of this therapy (131). Desensitization includes loss of signaling upon subsequent engagement by agonists (homologous desensitization), downregulation of membrane-bound receptors, and inhibition/alteration of downstream effector pathways (heterologous desensitization).

Although these processes have been extensively studied in myocytes and airway smooth muscle cells, recently, more data regarding desensitization of alveolar β2AR became available. Morgan and colleagues (127, 128) have reported that sustained infusion of high-dose isoproterenol (400 μg·kg−1·h−1) impairs β2-agonist-induced alveolar active Na+ transport in rats; however, other groups using albuterol have noted downregulation of receptor number but not loss of effect on alveolar active Na+ transport (165). More interestingly, Morgan and colleagues have shown that sustained, high-dose albuterol infusion diminishes adenyl cyclase and PKA activity, providing the first evidence of heterologous receptor desensitization in the alveolar epithelium (128).

Other Mechanisms of Edema Clearance Regulation

There are several βAR-independent mechanisms that may contribute to fluid clearance in distal air spaces (Table 1). Catecholamines and α-adrenergic agonists may upregulate alveolar active Na+ transport and increase edema clearance independent of βAR stimulation (4). Among other βAR-independent mechanisms are dopamine, hormones such as glucocorticoids and mineralocorticoids, and cellular growth factors such as epidermal growth factor (EGF), transforming growth factor-α (TGF-α), fibroblast growth factor-10 (FGF-10), keratinocyte growth factor (KGF), hepatocyte growth factor, thyroid hormone, and leukotriene D4 (LTD4) (1, 9, 10, 12, 42, 47, 59, 81, 103, 112, 132, 150, 173, 184, 187, 189, 198, 199).

Dopamine. Dopamine increases alveolar fluid clearance in lungs (1, 9, 10) via short-term activation of D1 receptors in alveolar epithelial cells (10, 100, 162, 164) (Fig. 3). This action promotes recruitment of Na+ pumps from intracellular compartments into the cell basolateral membrane resulting in increased catalytic activity within minutes (100, 153). Both PKC (PKC-δ and PKC-ε) and protein phosphatase 2A regulate the dopamine-mediated exocytosis of Na-K-ATPase in the alveolar epithelial cells (100, 101, 153). Na-K-ATPase activity is also regulated long term (18–24 h) by D2 receptor activation and stimulation of MAPK/ERK pathway, resulting in increased transcription and translation of Na-K-ATPase via Ras, Raf-1 kinase, and PKC (71, 72).

Corticosteroids. Glucocorticoids regulate Na+ and fluid transport in both adult and fetal lungs (12, 81, 150, 187). Serum cortisol levels are important in maintenance of lung fluid balance and fluid clearance in distal air spaces. Corticosteroids increased mRNA levels and protein expression of ENaC in cultured, both fetal and adult, alveolar epithelial cells (40, 99, 134, 150, 187). Dexamethasone increased β1, but not α1, Na-K-ATPase mRNAs in rat AT2 cells (12, 40), which resulted in increased α1 and β1 Na-K-ATPase proteins with an increase in Na+ pump activity, suggesting also posttranscriptional regulation (12).

Lung epithelial cells express mineralocorticoid receptors as well as 11-β-hydroxysteroid dehydrogenase, an enzyme responsible for conversion of corticosterone into 11-dehydrocorticosterone. Similar to other epithelial cells, aldosterone increased the number of highly selective channels (84) and alveolar fluid clearance by increasing mRNA and α1 and β1 Na-K-ATPase proteins in AT2 cells (142).

Growth factors. Several growth factors including EGF, TGF-α, KGF, and FGF-10 have been reported to regulate alveolar fluid clearance. For example, EGF increased both α1 and β1 Na-K-ATPase mRNA and protein and increased lung liquid clearance (42, 184). EGF did not change in ENaC subunits but induced nonselective cation channels in cultured AT2 cells (42, 91). The TGF-α increased CAMP activity and alveolar fluid clearance via increased tyrosine kinase, which is stimulated by both EGF and TGF-α (59, 112, 132). KGF, a heparin-binding growth factor, has been shown to increase alveolar fluid clearance as a mitogen for AT2 cells (195). Pretreatment with KGF prevented ventilator-induced lung injury as well as hydrostatic pulmonary edema (198, 199). Although hyperplasia of AT2 cells appears to be the major mechanism of KGF-mediated increase in alveolar fluid clearance, it may also contribute to the increased expression of ENaC and Na-K-ATPase (3, 24). FGF-10 is also a potent mitogen of alveolar epithelial cells. It is structurally similar to KGF and has short-term (15 min) effects on alveolar epithelial cells by increasing Na-K-ATPase activity via Grb2-SOS/Ras/MAPK pathway (189).

Cysteine leukotriene levels are elevated during acute lung injury in animals and may play a role in upregulation of alveolar active Na+ transport. LTD4 increased alveolar fluid clearance by upregulating Na-K-ATPase activity (173). Last, exogenous thyroid hormone administration, particularly 3,3',5'-triiodo-L-thyronine, increases active Na+ transport by stimulation of Na-K-ATPase (103).

### INHIBITION OF ALVEOLAR FLUID REABSORPTION

In several models of lung injury, the ability of the lungs to clear alveolar fluid is impaired, which is particularly relevant to
clinical situations, as described by Ware and Matthay (197). Although the lung epithelium is relatively more resistant to injury than the endothelium (126), alveolar fluid clearance, which is a marker of alveolar epithelial cell function, is altered during both hydrostatic pulmonary edema (5, 160, 192) and various models of acute lung injury (61, 98, 102, 125, 179).

Hydrostatic Pulmonary Edema

Mechanisms of pulmonary edema clearance have been reported to be impaired in animal models of hydrostatic pulmonary edema independently of the mechanisms regulating edema formation (5, 160, 192). Elevation of left atrial pressure decreased alveolar fluid clearance via increased atrial natriuretic peptide (ANP) (30, 141). Lung serves as a target organ for ANP as well as a site of synthesis and has the highest tissue concentration of binding sites for ANP (74, 149). Some patients with cardiogenic pulmonary edema may have clearance rates $\leq 3\%$ per hour (192) due to elevated levels of catecholamines, which may mask the deleterious effects of ANP released in response to left atrial hypertension (30), the presence of circulatory ouabain-like substances (55), and regional hypoxia. In ex vivo lung models, acute elevation of left atrial pressure inhibits active $\text{Na}^+$ transport possibly by decreasing the number of Na-K-ATPase at the basolateral membrane of alveolar epithelial cells (5, 6, 160).

Acute Lung Injury

Alveolar fluid clearance mechanisms are inhibited in several models of lung injury even when the injury to the distal lung epithelium is not associated with gross disruption of the alveolo-capillary barrier (140, 183). Most patients with noncardiogenic pulmonary edema have impaired ability to clear alveolar fluid (197). However, those who clear edema rapidly (a minority of these patients) have better outcomes (116, 181, 182, 196, 197). However, in some models of lung injury, the lung’s capacity to clear fluid out of alveolar air spaces can be upregulated (146). The increase in alveolar fluid clearance is usually mediated by surges of endogenous catecholamines acting on $\beta$ARs as reported during hemorrhagic shock (124), bacterial pneumonia (151), and subacute models such as moderate hyperoxia (66, 183). Whereas increase in alveolar fluid clearance is mediated by $\beta$ARs during hemorrhagic shock, increase in $\text{Na}^+$ transport across alveolar epithelium during bacterial pneumonia appears to depend on tumor necrosis factor-$\alpha$, which may have a direct effect on ENaC (63, 151).

More severe lung injury is associated with decreased fluid clearance out of the alveoli. For example, the effects of bacterial sepsis on alveolar fluid clearance depend on the extent of the lung injury. Although alveolar fluid clearance is enhanced if the alveolar epithelium is intact, it is significantly reduced when injury is associated with alveolar flooding. Similar to bacterial sepsis models of lung injury, acid aspiration (125), smoke inhalation (98), ventilator-associated lung injury (61, 102), and reperfusion injury after lung transplantation (179) are also associated with decreased alveolar fluid clearance.

The effect of hyperoxia on alveolar fluid clearance depends on the duration and the degree of hyperoxia. In the model of
accompanies the osmotic gradient. Regulation of Na\(^+\)/H\(^+\) activity and clearance are decreased (143). In contrast to increased permeability, Na\(^+\)/H\(^+\) may represent an adaptive mechanism in response to increased permeability.

Hypoxia impairs active Na\(^+\) transport across the alveolar epithelium (36, 39, 106, 194) and inhibits ENaC and Na-K-ATPase activity (36, 39, 105, 106, 147, 148, 194, 203). Short-term severe hypoxia inhibits Na-K-ATPase activity by phosphorylating the Na\(^+\) pump, triggering it to endocytose via generation of mitochondrial reactive oxygen species activating atypical PKC-\(\zeta\) (39). Prolonged hypoxia promotes degradation of the Na\(^+\) pump via the ubiquitin/proteosome pathway (unpublished observations).

Persistence of lung edema in patients with lung injury is due to both increased permeability of the alveolo-capillary barrier and decreased ability of the alveolar epithelium to clear edema. Although some of the excess edema fluid is removed via the pleura and the lung lymphatic systems, active Na\(^+\) transport from the alveoli into the pulmonary circulation is the major pathway for removal of alveolar edema, which is cleared even in the absence of pulmonary blood flow in ex vivo models (70, 86, 158).

TGF-\(\beta\)1 directly increases the permeability of endothelial and epithelial cell monolayers (79, 201), which appears to be dose and time dependent. TGF-\(\beta\)1 at low concentrations (5- to 10-fold lower than what is required to increase alveolar epithelial permeability) has been shown to decrease alveolar epithelial fluid transport by inhibiting ENaC via MAPK, ERK1/2 pathway (60). However, these results contrast those from another study that showed an increase in alveolar Na\(^+\) transport in response to TGF-\(\beta\)1 (201). It is noteworthy that the increase in alveolar Na\(^+\) transport occurred after 72 h, suggesting that the increase in alveolar fluid clearance in response to TGF-\(\beta\)1 may represent an adaptive mechanism in response to increased permeability.

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PULMONARY EDEMA CLEARANCE


