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Alveolar Edema Fluid Clearance and Acute Lung Injury

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Abstract

Although lung-protective ventilation strategies have substantially reduced mortality of acute lung injury patients there is still a need for new therapies that can further decrease mortality in patients with acute lung injury. Studies of epithelial ion and fluid transport across the distal pulmonary epithelia have provided important new concepts regarding potential new therapies for acute lung injury. Overall, there is convincing evidence that the alveolar epithelium is not only a tight epithelial barrier that resists the movement of edema fluid into the alveoli, but it is also actively involved in the transport of ions and solutes, a process that is essential for edema fluid clearance and the resolution of acute lung injury. The objective of this article is to consider some areas of recent progress in the field of alveolar fluid transport under normal and pathologic conditions. Vectorial ion transport across the alveolar and distal airway epithelia is the primary determinant of alveolar fluid clearance. The general paradigm is that active Na^+ and Cl^- transport drives net alveolar fluid clearance, as demonstrated in several different species, including the human lung. Although these transport processes can be impaired in severe lung injury, multiple experimental studies suggest that upregulation of Na^+ and Cl^- transport might be an effective therapy in acute lung injury. We will review mechanisms involved in pharmacological modulation of ion transport in lung injury with a special focus on the use of β -adrenergic agonists which has generated considerable interest and is a promising therapy for clinical acute lung injury.

1. Cellular mechanisms involved in edema clearance

The alveolar epithelium plays a primary role in the process of edema fluid clearance. In fact, the alveolar epithelium is not only a tight epithelial barrier that resists the movement of edema fluid into the alveoli, but it is also actively involved in the transport of ions and solutes, a process that is essential for edema fluid clearance (Berthiaume, Y. et al. 1999). Considerable experimental evidence indicates that active Na^+ transport is the dominant ion transport mechanism involved in alveolar liquid clearance. (Matthay, M. A. et al. 2002a). The results of several studies indicate that the primary site of edema fluid clearance is located in the alveolar epithelium, although distal airway epithelial cells can also actively reabsorb sodium (Matthay, M. A. et al. 1996; Berthiaume, Y. et al. 2002). The cellular and molecular mechanisms responsible for the vectorial transport of Na^+ from the alveoli to the interstitium has been reasonably well defined. Na^+ enters the cell by the amiloride-sensitive Na^+ channel (ENaC) or by other cationic channels located at the apical surface, and is extruded by $\text{Na}^+-\text{K}^+-\text{ATPase}$

located at the basolateral surface (Matthay, M. A. et al. 1996; Matthay, M. A. et al. 2002b) (Figure 1).

Recent experimental data have made it possible to better characterise the structure and function of the major system involved in this transepithelial transport. ENaC is the first constituent of the Na⁺ transport system. It has been cloned and is made up of three subunits, α , β and γ ENaC, which are able to reconstitute a functional channel (Berthiaume, Y. et al. 1999; Matalon, S. et al. 2002). This channel is expressed in both alveolar type II and type I cells (Guidot, D. M. et al. 2006). The physiological role of α ENaC in the lungs has been demonstrated in the mouse in which the α ENaC gene was deleted by targeting a transgene by homologous recombination (Hummler, E. et al. 1996). Unable to clear liquid from their lungs, these mice die shortly after birth (Hummler, E. et al. 1996). Furthermore, another animal model with reduced α ENaC expression was shown recently to have a delayed resolution of pulmonary edema following thiourea induced lung injury (Egli, M. et al. 2004). In the same animal model there was an increase in the wet-to-dry ratio after hyperoxia induced lung injury in the mice with a reduced α ENaC expression (Egli, M. et al. 2004). This increase in the wet-to-dry ratio after hyperoxia could be related to a decrease in edema clearance although these animals could be more susceptible to edema formation. Na⁺-K⁺-ATPase, which is made up of two subunits, is another major component of the transepithelial Na⁺ transport system (Figure 1). The α subunit is the catalytic component of the complex and is involved in Na⁺ extrusion, K⁺ intrusion and ATPase activity (Sznajder, J. I. et al. 2002). The β subunit is a highly glycosylated protein whose role is not well understood; it seems to be an important regulatory component of the sodium pump. Na⁺-K⁺-ATPase inhibition with ouabain reduces the short circuit current across alveolar type II cells (Berthiaume, Y. et al. 1999), and markedly decreases solute and fluid transport in alveoli (Sznajder, J. I. et al. 2002).

ENaC activity and expression are regulated by a complex control system (Figure 2). ENaC function is dependent on direct modulation of channel activity (Matalon, S. et al. 2002), by channel degradation, and by membrane trafficking (Kamynina, E. et al. 2002). ENaC channel activity can be modulated by a number of different mechanisms. For example, cAMP increases channel activity either by increasing its open probability or by increasing the number of channels at the apical membrane (Eaton, Douglas C. et al. 2004). More recently it has been shown that intracellular as well as extracellular protease can affect the activity of the channel potentially by modulating the Na⁺ self inhibition of the channel (Planes, C. et al. 2005; Kleymann, T. R. et al. 2006). Trafficking of the channels to the membrane, which involves a complex system of ubiquitination, is also an important system that modulates ENaC activity (Snyder, P. M. 2005). Na⁺ transport can also be regulated by increased gene expression (Figure 2). The two major hormones that modulate ENaC expression in the lung are catecholamines (Berthiaume, Y. et al. 1999) and glucocorticoids (Dagenais, A. et al. 2001). Like ENaC, modulation of Na⁺-K⁺-ATPase activity is complex and also involves the modulation of the trafficking of the protein to the membrane (Sznajder, J. I. et al. 2002). Changes in intracellular Na⁺ concentration and hormones like mineralocorticoids, adrenergic agonists and thyroid hormones modulate Na⁺-K⁺-ATPase activity (Ingbar, D. H. et al. 1998) (Figure 2). Furthermore, as with ENaC, heightened Na⁺-K⁺-ATPase expression could also be an important mechanism to augment transepithelial Na⁺ transport. Many major hormonal systems, like the thyroid, mineralocorticoid and glucocorticoid systems (Ingbar, D. H. et al. 1998), have been reported to modulate Na⁺-K⁺-ATPase expression. The β adrenergic stimulation upregulates Na⁺-K⁺-ATPase expression in alveolar epithelial cells (Berthiaume, Y. et al. 1999).

Other channels or transporters are also likely essential for transepithelial Na⁺ transport. Recently it has been shown that K⁺ channels are expressed in alveolar type II (Leroy, C. et al. 2004) and type I cells (Guidot, D. M. et al. 2006). Furthermore, these channels can participate not only in transepithelial Na⁺ and Cl⁻ exchange (Leroy, C. et al. 2006), but also in alveolar

fluid clearance (Sakuma, T. et al. 1998). Less is known about the role of specific chloride channels in regulating transepithelial fluid transport. Under basal conditions, active fluid transport is mainly driven by ENaC, although Cl^- must follow for electroneutrality through an as yet unidentified pathway, possibly another chloride channel (Fang, X. et al. 2006). However, when alveolar fluid clearance is stimulated with cAMP, both Na^+ and Cl^- absorption are increased (Fang, X. et al. 2006). There is now evidence that CFTR might be the chloride channel involved in this process (Matthay, M. A. et al. 2002b). CFTR is expressed in rat alveolar type II cells (Brochiero, E. et al. 2004) and in human alveolar type II cells (Fang, X. et al. 2006) as well as in alveolar epithelial type I cells (Johnson, M. D. et al. 2006). Based on *in vivo* studies, the absence of CFTR or inhibition of CFTR activity (Folkesson, H. G. et al. 2006) leads to an inhibition of the stimulation of alveolar liquid clearance by beta adrenergic agonist (Fang, X. et al. 2002; Mutlu, G. M. et al. 2005) as well as more lung edema in the presence of a hydrostatic stress (Fang, X. et al. 2002). Furthermore, CFTR inhibition also prevents cAMP mediated fluid clearance in the human lung (Sakuma, T. et al. 2006).

Until recently, it was generally accepted that liquid movement across the alveolar epithelium was an intercellular process secondary to the osmotic gradient generated by transepithelial Na^+ transport across the alveolar epithelium. However, many laboratories have now demonstrated the presence of specialized water-transporting proteins (aquaporins) in the lungs. Water movement may occur through both paracellular pathways and transcellular pathways (Figure 1). Although four different family members of aquaporins are expressed in lung tissue, aquaporin 5 is the predominant form in the apical surface of alveolar type I cells (Borok, Z. et al. 2002), the site where much of alveolar edema fluid is cleared. Since this cell type has one of the highest cellular permeability coefficients for water, it could be postulated that some water movement across the alveolar epithelium goes across type I cells (Dobbs, PNAS, 1998). However, the data available from transgenic mouse models of aquaporin deletion suggest that alveolar liquid clearance in the neonatal and adult lung is not affected by aquaporin deletion (Borok, Z. et al. 2002). The lack of apparent functional importance for aquaporins in edema clearance does not eliminate the possibility that they play a role under conditions of stress or injury.

2. Clinical relevance of alveolar liquid clearance

Although there is convincing experimental evidence demonstrating that Na^+ transport is involved in this process, what is the clinical significance of alveolar liquid clearance? To explore this question the investigators had to identify a tool to estimate alveolar fluid clearance in the clinical environment. The method requires measurement of serial protein concentrations in pulmonary edema fluid. This approach is an adaptation of the experimental method used routinely to quantify alveolar fluid clearance in animal models (Berthiaume, Y. et al. 1987; Berthiaume, Y. et al. 1988; Pittet, J. F. et al. 1994; Charron, P. D. et al. 1999). Although there are potential limitations to this technique it can correctly estimate net alveolar fluid clearance in the majority of patients (Ware, L. B. et al. 2001). Using this method investigators have demonstrated a relationship between the prognosis of lung injury and alveolar liquid clearance (Matthay, M. A. et al. 1990; Ware, L. B. et al. 2001). In the most recent study, 56% of patients with lung injury had impaired alveolar liquid clearance, and only 13% of them had a maximal alveolar liquid clearance rate. In contrast, 75% of patients with hydrostatic edema had submaximal to maximal alveolar liquid clearance (Verghese, G. M. et al. 1999). Interestingly, the survival of patients with pulmonary edema from acute lung injury and a maximal alveolar clearance rate was higher compared to patients with an abnormal clearance rate. Furthermore, there was also a decrease in the number of days of mechanical ventilation in patients with better alveolar edema clearance. A similar observation was also made in post-lung transplant patients where those patients with the best alveolar liquid clearance had the best clinical outcomes (Ware, L. B. et al. 1999). Patients with hydrostatic pulmonary edema

and altered alveolar liquid clearance capacity also have decreased arterial pH, suggesting that systemic hypoperfusion and systemic factors might have an important regulatory influence on alveolar liquid clearance (Verghese, G. M. et al. 1999). Recently, it has even been shown that the manipulation of the sodium-driven alveolar fluid clearance could represent an appropriate target for therapy (Sartori, C. et al. 2002). In this study the investigators reported that subjects who are susceptible to high-altitude pulmonary edema, prophylactic inhalation of salmeterol, a beta-2 agonist decreased the incidence of high altitude pulmonary edema by more than 50%. One of the explanations proposed by the authors to understand this protective effect was that salmeterol would enhance the clearance of alveolar fluid since beta-adrenergic agonists up-regulate the clearance of alveolar fluid by stimulating transepithelial sodium transport. This hypothesis is also supported by the fact that the level of sodium transport in the respiratory epithelium is lower in patients prone to high altitude pulmonary edema (Sartori, C. et al. 2002; Sartori, C. et al. 2004). However the experimental design of this study did not exclude the possibility that beta-2 agonist could have modulated vascular permeability or the hemodynamic response associated with hypoxia and high altitude pulmonary edema (Hultgren, H. N. 1996). Overall, there is physiological and clinical evidence that active ion transport system in the distal pulmonary epithelium is important in the pathophysiology of lung injury especially in its recovery phase.

3. Strategies to increase alveolar fluid clearance in the lung

Since patients with maximal alveolar fluid clearance have a lower mortality (Ware, L. B. et al. 2001), increasing alveolar liquid clearance could potentially enhance the evolution of lung injury. Multiple pharmacological or molecular tools could be used to stimulate alveolar fluid clearance (Figure 2).

The best studied agents are cAMP agonists, i.e., β -adrenergic receptor agonists. β -adrenergic agonist therapy enhances alveolar fluid clearance in multiple models of lung injury, including hyperoxic lung injury, ventilator-induced lung injury, and beta agonists can even stimulate alveolar fluid clearance when administered as an aerosol (Folkesson, H. G. et al. 2006). More recently, it has also been shown that aerosolized salmeterol, a lipid-soluble β -2 agonist, can stimulate lung liquid clearance at a clinically-relevant dose (McAuley, D. F. et al. 2004). Furthermore, as already discussed, β -adrenergic agonists have been proposed as prophylactic agents in high-altitude pulmonary edema (Sartori, C. et al. 2002). Although it has been suggested that prolonged stimulation of the β -adrenergic receptors could lead to a desensitization of the receptors or a decrease in their density and could prevent effective stimulation by exogenous catecholamines (Folkesson, H. G. et al. 2006), more recent data showed that this downregulation of the β -adrenergic receptor will recover, even in the continuous presence of the β -adrenergic agonists (Folkesson, H. G. et al. 2006). The importance of β -adrenergic stimulation in edema resolution has also been demonstrated in experimental models where there is an overexpression of the β -adrenergic receptor. Overexpression of the β -adrenergic receptor leads to enhanced edema clearance (Dumasius, V. et al. 2001) and can even protect against lung injury (Mutlu, G. M. et al. 2004a). The mechanism leading to this improvement is not completely known but it is suggested that it could be secondary to an increased expression of Na^+ transport protein (Dumasius, V. et al. 2001). Also, decreased expression of both the alpha-1 and alpha-2 NaKATPase in mice results in a submaximal response to cAMP stimulation in terms of alveolar fluid clearance (Looney, M. R. et al. 2005).

Vasoactive agents, such as dobutamine or dopamine, augment alveolar fluid clearance (Crandall, E. D. et al. 2001). Growth factors, such as epidermal growth factor (EGF), transforming growth factor- α (TGF α), and keratinocyte growth factor (KGF), can also stimulate vectorial sodium transport (Crandall, E. D. et al. 2001) (Figure 2). Since KGF has

been shown to stimulate alveolar fluid clearance and to have additive effects to β -adrenergic agonists with even protective action in some models of lung injury, it may be an alternative to β -adrenergic agonist therapy (Berthiaume, Y. et al. 1999; Berthiaume, Y. et al. 2002). However, it still remains to be shown if these agents can increase alveolar fluid clearance and decrease lung injury if they are administered after the insult in patients with acute lung injury. One recent randomized placebo controlled phase II trial of 40 patients with acute lung injury in the UK indicated that intravenous salbutamol, a beta-2 agonist, decreased lung water in the group treated with intravenous beta agonist therapy (Perkins, G. D. et al. 2006; Matthay, M. A. et al. 2006).

One final approach that could be used to upregulate alveolar fluid clearance is gene therapy. Overexpression of the Na^+ , K^+ -ATPase (Factor, P. et al. 1998) can stimulate alveolar fluid clearance and improve the survival of animals with hyperoxic lung injury (Factor, P. et al. 2000) or decrease edema formation in a model of thiourea-induced lung injury (Stern, M. et al. 2000).

4. Edema clearance in injured lungs

Although we have substantial evidence suggesting that Na^+ transport is essential for edema clearance and that it can be modulated pharmacologically *in vivo*, can this process be altered in injured lungs and can it be upregulated by pharmacological tools?

Interestingly, the alveolar and distal airway epithelia are remarkably resistant to injury, particularly in comparison to the adjacent lung endothelium (Berthiaume, Y. et al. 1999). When lung endothelial injury occurs, the alveolar epithelial barrier may retain its normal impermeability to proteins and its normal fluid transport capacity. For example, when intravenous or intra-alveolar endotoxin is used to produce lung endothelial injury, permeability to proteins across the lung epithelial barrier is not altered (Matthay, M. A. et al. 1996; Berthiaume, Y. et al. 2002). This might explain why, in mild-to-moderate lung injury, the capacity of the alveolar epithelium to transport salt and water is not only preserved, but may even be upregulated by stress hormones (Figure 3). When septic shock was induced in rats (Berthiaume, Y. et al. 2002), even though endothelial injury and interstitial pulmonary edema occurred, alveolar epithelial fluid transport was increased by 32%. This enhanced fluid clearance was inhibited by amiloride or propranolol, demonstrating that the augmented fluid clearance depended on endogenous β -adrenergic agonist stimulation of alveolar epithelial sodium transport (Berthiaume, Y. et al. 2002). After short-term hemorrhagic shock, alveolar fluid clearance can also be enhanced by catecholamine-dependent mechanisms (Modelska, K. et al. 1997).

Lung fluid clearance can also be stimulated in lung injury by catecholamine-independent mechanisms (Figure 3). Alveolar fluid clearance is increased in bleomycin induced subacute lung injury, and this increased sodium transport occurs in the presence of decreased expression and function of amiloride-sensitive sodium channels (probably primary ENaC) in alveolar type II cells (Folkesson, H. G. et al. 1998). An increased number of alveolar type II cells were primarily responsible for the two-fold increase in alveolar fluid clearance. In bacterial pneumonia induced by the instillation of *Pseudomonas* into the distal airways, there was a 48% increase in alveolar fluid clearance that could be inhibited by amiloride but not by propranolol (Berthiaume, Y. et al. 2002). Interestingly, this effect was inhibited by an anti-tumour necrosis factor- α (TNF- α) antibody (Berthiaume, Y. et al. 2002). TNF- α is also important in stimulating alveolar fluid clearance after intestinal ischemia-reperfusion (Berthiaume, Y. et al. 2002). Although these results suggest that TNF- α can stimulate alveolar liquid clearance the mechanism involved is still unknown and it is possible that it is not due to a direct effect of

TNF- α on Na⁺ transport since TNF- α is also known to decrease Na⁺ transport in alveolar epithelial cells (Berthiaume, Y. 2003).

Alveolar fluid clearance can also be increased in subacute models of hyperoxic lung injury (Berthiaume, Y. et al. 2002) by upregulating sodium transport by modulating Na⁺, K⁺-ATPase activity (Berthiaume, Y. et al. 2002). However, other experimental data indicate that Na⁺ transport may be downregulated in severe forms of lung injury, perhaps by the effect of inflammatory mediators on either the integrity or function of the alveolar epithelium (Figure 4). In a model of *Pseudomonas* induced septic shock model Pittet et al (Pittet, J. F. et al. 1995), the presence of increased permeability of the alveolar epithelium can lead to a decrease in alveolar liquid clearance and further increase in extravascular lung water compared to sheep that had only an increase in lung endothelial permeability but no significant changes in alveolar epithelial permeability. Recently, Sugita et al (Sugita, M. et al. 2003) demonstrated in a model of ischemia-reperfusion associated with lung transplantation that there is a decrease in alveolar liquid clearance in the presence of severe lung injury. These experimental results suggest that when the integrity and function of the alveolar epithelium are preserved, alveolar liquid clearance can be stimulated, even in the presence of lung interstitial or mild alveolar edema. However, in more severely injured lungs, a marked increase in paracellular permeability to protein leads to significant alveolar epithelium damage and, subsequently to a loss of vectorial salt and water transport capacity of the alveolar epithelial cells (Berthiaume, Y. et al. 1999; Berthiaume, Y. et al. 2002; Sugita, M. et al. 2003) (Figure 5).

Beside changes in alveolar epithelial permeability to protein, could there be changes in the Na⁺ transport mechanism in presence of lung injury that could explain a potential decrease in alveolar liquid clearance in injured lungs? In fact, several inflammatory mediators have been shown to influence Na⁺ transport in alveolar epithelial cells. Reactive oxygen and nitrogen species, can modulate Na⁺ transport and Na⁺ channel activity (Matalon, S. et al. 2003). Although the presence of nitric oxide in the alveolus seems to be essential for amiloride sensitive-sodium transport (Hardiman, K. M. et al. 2001a), reactive oxygen species and NO (Matalon, S. et al. 2003) have also been shown to decrease Na⁺ transport and alveolar liquid clearance especially after mycoplasma lung infection (Hickman-Davis, J. M. et al. 2006) and ventilator induced lung injury (Frank, J. A. et al. 2003). Reactive oxygen species have also to be involved in the lack of response of alveolar liquid clearance to beta-adrenergic agonists stimulation during the resuscitation phase of hemorrhagic shock treatment (Modelska, K. et al. 1999). Reactive oxygen species are involved in the modulation of Na⁺-K⁺-ATPase expression and activity during hypoxia (Guidot, D. M. et al. 2006). Hypoxia (Clerici, C. et al. 2000; Hardiman, K. M. et al. 2001b) and respiratory alkalosis (Myrianthefs, P. M. et al. 2005) also decrease sodium transport and alveolar liquid clearance. Recently, cytokine released during lung injury with TGF β , TNF- α , and IL-1 β have been shown to decrease the activity and expression of Na⁺ channels (Dagenais, A. et al. 2003; Frank, J. et al. 2003; Roux, J. et al. 2005) as well as alveolar liquid clearance (Frank, J. et al. 2003; Roux, J. et al. 2005). The microbial agents themselves can also modulate Na⁺ transport and liquid movement. *Pseudomonas* can inhibit Na⁺ transport and fluid movement across airway epithelial cells (Evans, D. J. et al. 1998), whereas influenza virus can modulate ENaC activity in alveolar type II cells and decrease alveolar liquid clearance (Kunzelmann, K. et al. 2000; Chen, X. J. et al. 2004). Respiratory syncytial virus through the induction of nucleotide release can also inhibits Na⁺ transport and alveolar liquid clearance (Davis, I. C. et al. 2006).

Although there are reasons to believe that beta-adrenergic agonist therapy may be beneficial in patients with acute lung injury, its potential use as a therapy to enhance the resolution of pulmonary edema might be limited by several factors (Berthiaume, Y. et al. 2002). The alveolar epithelium might be too injured in some patients to respond to beta-adrenergic agonist therapy, and circulating factors could also limit the action of β -adrenergic agonists. For example, in the

presence of left atrial hypertension, atrial natriuretic peptide can inhibit the stimulatory effect of β -adrenergic agonists on alveolar fluid clearance (Berthiaume, Y. et al. 2002). In prolonged hemorrhagic shock and resuscitation, cAMP agonists may not stimulate alveolar fluid clearance because oxidant-mediated injury downregulates the response of the alveolar epithelium to β -2 agonists (Berthiaume, Y. et al. 2002). In addition, changes in the activity or expression of ion transport mechanism could also modify the therapeutic effect of the beta-adrenergic agonists. In recent experiments in which the expression of ENaC was decreased with small interfering RNA against alpha ENaC, there was not only a decrease in the amiloride-sensitive alveolar liquid clearance but also an inhibition of terbutaline stimulation of alveolar liquid clearance (Folkesson, H. G. et al. 2006). These results might explain the lack of stimulation of alveolar liquid clearance by beta-adrenergic agonist in ischemia-reperfusion injury (Sugita, M. et al. 2003) since there was a significant decrease in ENaC expression in those lungs. A modulation of the cystic fibrosis transmembrane regulator (CFTR) chloride channel expression might also be important to maintain the response to beta-adrenergic agonist since there is an interdependency between the CFTR and beta adrenergic receptors (Mutlu, G. M. et al. 2005) mice that do not express this channel have a decreased response to beta-adrenergic stimulation (Fang, X. et al. 2002). Thus, a decrease in the expression of ENaC or CFTR in injured lung tissue could lead to decrease response to beta-adrenergic therapy. However, it is possible that by manipulating the expression of those channels, we can restore the response to beta-adrenergic stimulation. For example, treatment with glucorticoids inhibits the effect of TNF- α on the expression of ENaC and restores normal fluid absorption across the alveolar epithelium (Dagenais, A. et al. 2006). Also, lung protective ventilatory strategies may help to preserve normal alveolar epithelial fluid transport properties in the presence of acute lung injury (Frank, J. A. et al. 2002).

5. CONCLUSIONS

Collectively, these observations suggest that in human acute lung injury there could be either significant activation or inhibition of the Na^+ and Cl^- transport mechanisms in lung injury. Since the alterations of alveolar liquid clearance are not the same in different models of lung injury, multiple mechanisms appear to lead to alveolar epithelial cell dysfunction (Figure 5). Furthermore, based on the heterogeneous responses observed in the experimental studies, the variability of the systemic response to injury could also be a determinant of intact versus impaired alveolar fluid clearance. Furthermore, the degree of apoptosis and necrosis of the alveolar type I and II cells are likely to be important (Albertine, K. H. et al. 2002). Although there are a significant number of treatments that could be effective in enhancing alveolar edema clearance *in vivo*, β -adrenergic agonists are the most promising current therapy (Mutlu, G. M. et al. 2004b; Matthay, M. A. et al. 2006), particularly since clinical data from a small study indicates that beta agonist therapy may decrease extravascular lung water in acute lung injury patients (Perkins, G. D. et al. 2006). For these reasons, the NHLBI ARDS network will carry out a randomized placebo controlled phase III trial of aerosolized albuterol for the treatment of acute lung injury. However, pharmacologic approaches to improving alveolar fluid clearance in lung injury are not the only therapeutic option. Based on experimental work (Frank, J. A. et al. 2002), improved alveolar fluid clearance is probably one reason why a lung protective ventilation strategy was successful in reducing mortality in patients with acute lung injury (Brower, R. G. et al. 2004). Thus it is possible that more than one treatment strategy will be necessary to optimize the function of the alveolar epithelium since the degree of lung epithelial and endothelial injury varies among patients with acute lung injury. In the future, biochemical and functional markers of alveolar epithelial injury could be helpful for stratifying lung injury patients in clinical trials (Uchida, T. et al. 2006).

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Figure 1.

The alveolar epithelium is not only a tight epithelium but is also actively involved in the transport of ions and solutes. The predominant ion transport present in the alveolar epithelium is sodium transport. Transepithelial Na⁺ transport involves a Na⁺ channel (ENaC) located at the apical surface of type II and type I cells as well as the Na⁺/K⁺/ATPase located at the basolateral side of the cells. Sodium is absorbed at the apical surface through the Na⁺ channel and is extruded at the basolateral side by the sodium pump (Na⁺/K⁺/ATPase). The role of Cl⁻ transport in this response is still unclear, although CFTR plays a role in cAMP mediated transport. Water is shown to move by the paracellular route although it might also move through water channels.

Figure 2.

Ion and vectorial fluid transport in the lung is mediated by active transport of sodium (and chloride under cAMP stimulated conditions). Sodium transport can be regulated by modulating either the activity (direct modulation of channel activity, channel trafficking or degradation) or the expression of molecules involved in this transcellular transport system (ENaC, Na⁺/K⁺/ATPase). Different pharmacologic agents have been shown to modulate either the activity or the expression of these molecules.

Figure 3.

Mild to moderate lung injury can lead to enhanced edema clearance. This response is due to an activation of epithelial Na⁺ transport due to the endogenous catecholamine response associated with the lung injury. However, in certain types of injury other pathways may be involved. Some inflammatory mediators such as TNF- α might participate to this response.

Figure 4.

Severe lung injury can be associated with decreased edema clearance. This process is mainly due to the enhanced permeability of the alveolar epithelium to protein and electrolytes as well as decreased epithelial Na⁺ transport. Multiple inflammatory molecules are involved in this response such as proteases, TGF β , TNF α , NO, and oxidant. Furthermore, oxidants might inhibit the catecholamine response which is known to enhance Na⁺ transport. It is therefore possible that the intensity of the inflammatory response may transform a mild form of lung injury to a severe form by inducing changes in the function of the alveolar epithelium.

Figure 5.

Lung injury is not a homogeneous process. Different types of injury can be present at the same time in the lung. Some areas may show no structural damage to the epithelium, but there is a decrease in the capacity of the epithelium to transport ions. These dysfunctions are probably influenced in part by inflammatory mediators released by macrophages or neutrophils. In other areas of the lung, the injury is associated with structural damage secondary to the sloughing of the alveolar epithelial cells and increased permeability of the alveolar epithelium. This leads to the formation of a protein-rich hyaline membrane. Interestingly, the same area may contain endothelial cell injury which is more subtle (more vesicles, cells swelling). The degree of injury seems insufficient to explain the severity of the edema. This process involves macrophages and neutrophils. The macrophages, by releasing chemotactic factors, stimulate the migration of activated neutrophils from the microcirculation to the air spaces. By releasing different pro-inflammatory molecules (oxidants, proteases), these neutrophils mediate epithelial damage.