J Bioenerg Biomembr (2007) 39:391–395
DOI 10.1007/s10863-007-9102-1

Regulation of Na,K-ATPase during acute lung injury

Emilia Lecuona · Humberto E. Trejo · Jacob I. Sznajder

Published online: 31 October 2007

Abstract A hallmark of acute lung injury is the accumulation of a protein rich edema which impairs gas exchange and leads to hypoxemia. The resolution of lung edema is effected by active sodium transport, mostly contributed by apical Na^+ channels and the basolateral located Na,K-ATPase. It has been reported that the decrease of Na,K-ATPase function seen during lung injury is due to its endocytosis from the cell plasma membrane into intracellular pools. In alveolar epithelial cells exposed to severe hypoxia, we have reported that increased production of mitochondrial reactive oxygen species leads to Na,K-ATPase endocytosis and degradation. We found that this regulated process follows what is referred as the *P*hosphorylation–*U*biquitination–Recognition–*E*ndocytosis–*D*egradation (PURED) pathway. Cells exposed to hypoxia generate reactive oxygen species which activate PKCζ which in turn phosphorylates the Na,K-ATPase at the Ser18 residue in the N-terminus of the α1-subunit leading the ubiquitination of any of the four lysines (K16, K17, K19, K20) adjacent to the Ser18 residue. This process promotes the α1-subunit recognition by the μ2 subunit of the adaptor protein-2 and its endocytosis trough a clathrin dependent mechanism. Finally, the ubiquitinated Na,K-ATPase undergoes degradation via a lysosome/proteasome dependent mechanism.

Keywords Acute lung injury · Na,K-ATPase · Alveolar epithelium

E. Lecuona · H. E. Trejo · J. I. Sznajder (✉)
Division of Pulmonary and Critical Care Medicine,
Feinberg School of Medicine, Northwestern University,
Chicago, IL 60611, USA
e-mail: j-sznajder@northwestern.edu

The Na,K-ATPase in the alveolar epithelium

The alveolar epithelium is covered by a thin layer of fluid for maintenance of surface tension and host defense which allows normal O_2 and CO_2 exchange (Weibel 1973). The lining fluid is thought to reflect the balance between the passive movement of fluid and solutes across the alveolar–capillary barrier and the active transport of electrolytes (Ware and Matthay 2000; Ng et al. 2004; Mutlu and Sznajder 2005). Active vectorial Na^+ transport in alveolar epithelial cells is mediated by apical Na^+ channels and basolateral Na,K-ATPases resulting in alveolar fluid clearance (Mason et al. 1982; Schneeberger and McCarthy 1986; Matalon et al. 1991; Matalon and O'Brodovich 1999; Vadász et al. 2007). The alveolar epithelium is composed of small, cuboidal type II cells and large, elongated type I cells. Type I cells accounts for about 95%, while type II cells for ~ 5%, of the alveolar surface area (Albertine et al. 2005). Although the two cell types have very different functions, both contribute to alveolar fluid reabsorption (Borok et al. 2002; Johnson et al. 2002; Ridge et al. 2003). Two isoforms of the Na,K-ATPase α-subunit (α1 and α2) and one isoform of the β-subunit (β1) are expressed in alveolar epithelial cells, with the α1-subunit being expressed in both cell types, while the α2-subunit appears to be restricted to alveolar epithelial type I cells (Schneeberger and McCarthy 1986; Ridge et al. 1997; Zhang et al. 1997; Ridge et al. 2003).

Effects of acute lung injury on the Na,K-ATPase

Edema accumulation and impaired gas exchange are hallmarks of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (Ware and Matthay 2000).

Edema accumulates due to changes in hydrostatic and oncotic pressures as well as changes in the filtration and reflection coefficient for proteins (Staub 1974). Many models of ALI, hydrostatic pulmonary edema and patients with ALI/ARDS are characterized by a decreased ability of the lungs to clear edema (Ware and Matthay 2001; Mutlu and Sznajder 2005; Vadász et al. 2007). Commonly in models of ALI and increased left atrial pressures there is an impairment of Na,K-ATPase function.

As such, it has been shown that in models of increased left atrial pressures, alveolar fluid reabsorption is decreased in parallel with a downregulation of Na,K-ATPase function (Campbell et al. 1999; Azzam et al. 2001; Saldias et al. 2001). Other models of ALI where there is a decreased function of Na,K-ATPase activity include hyperoxia-, ventilation-, endotoxin-, oleic acid- and alcohol-induced lung injury (Olivera et al. 1995; Carter et al. 1997; Lecuona et al. 1999; Adir et al. 2003; Koksel et al. 2005; Vadasz et al. 2005; Aytacoglu et al. 2006; Koksel et al. 2006; Hirsch et al. 2007; Mutlu et al. 2007).

This down-regulation of the Na,K-ATPase plays a key role in lung injury models, as the decreased alveolar fluid reabsorption can be over-come by increasing Na,K-ATPase activity. This increase can be accomplished by pharmacological means (i.e. cathecolamines such as adrenergic or dopaminergic agonists) (Saldias et al. 1999; Saldias et al. 2000; Azzam et al. 2001; Saldias et al. 2002; Sartori et al. 2002) or Na,K-ATPase over-expression by adenoviral or electroporation over-expression (Azzam et al. 2002; Adir et al. 2003; Mutlu et al. 2007).

Although, as stated above, impairment of Na,K-ATPase activity has been found in a variety of acute lung injury models, the mechanism by which this downregulation occurs has not been fully elucidated. It is well established that the Na,K-ATPase is subjected to both short- and long-term regulation (Therien and Blostein 2000; Dunbar and Caplan 2001; Clausen 2003; Dada et al. 2003). Short-term regulation involves either 1) direct effects on the kinetics of the enzyme, or 2) translocation of Na,K-ATPases between the plasma membrane and intracellular stores (Ewart and Klip 1995; Therien and Blostein 2000; Teixeira et al. 2003; Bertorello and Sznajder 2005), while long term regulation involves the transcription/translation pathways (Ewart and Klip 1995; Clausen 2003).

The Na,K-ATPase is regulated by the *phosphorylation–ubiquitination–recognition–endocytosis–degradation* (PURED) mechanism in alveolar epithelial cells

Alveolar hypoxia occurs during ascent to high altitudes and in patients with ALI/ARDS (Sartori et al. 2002; Jain and Sznajder 2005) and it is associated with decreased alveolar fluid reabsorption and impaired Na,K-ATPase function (Mairbaurl et al. 1997; Vivona et al. 2001; Litvan et al. 2006).

Studies exploring the mechanism of short-term Na,K-ATPase regulation after hypoxia has been reported in alveolar epithelial cells. Dada et al. described that alveolar epithelial cells exposed to hypoxia (1.5% O_2 for 1 h) have decreased Na,K-ATPase activity due to a concomitant reduction of the Na, K-ATPase protein present at the plasma membrane, without changes in the total amount of Na,K-ATPase protein, suggesting that endocytosis has occured (Dada et al. 2003). Further studies lead to propose that regulation of the Na,K-ATPase under hypoxia followed what is called as the *P*hosphorylation–*U*biquitination–Recognition–*E*ndocytosis–*D*egradation or PURED pathways. As depicted in Fig. 1, PURED reflects a general pathway for the internalization and degradation of cell surface proteins that emerged from studies in yeast, involving a series of events where phosphorylation acts as a signal for ubiquitination, which leads to the endocytosis

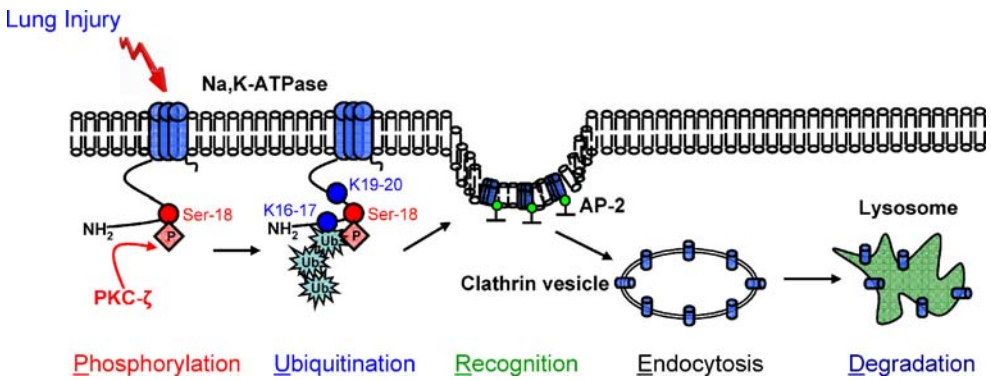

Fig. 1 PURED pathway. The Na,K-ATPase follows the PURED pathway under hypoxia conditions. PKCζ *P*hosphorylates the Na,K-ATPase α1-subunit at the Ser18 with consequent *U*biquitination on any of the four lysines surrounding this serine. This process makes the protein available for *R*ecognition by the adaptor protein-2 and its *E*ndocytosis via a clathrin-dependent mechanism that will lead to the traffic of the protein to the lysosome for *D*egradation

and degradation of the membrane protein (Hicke 1997; Roth et al. 1998; Terrell et al. 1998; Kelm et al. 2004). The same chain of events has been shown to be true in mammalian membrane protein as well (Dada et al. 2003; Haglund et al. 2003; Hicke and Dunn 2003; Comellas et al. 2006; Leithe and Rivedal 2007).

Phosphorylation The Na,K-ATPase α1-subunit has several consensus phosphorylation sites (Beguin et al. 1994) and phosphorylation/dephosphorylation has been proposed in the regulation of the Na,K-ATPase trafficking between intracellular compartments (Pedemonte et al. 2005). In particular, phosphorylation at the Ser18 in the N-terminus domain of the Na,K-ATPase α1-subunit has been shown to modulate its endocytosis (Chibalin et al. 1998; Chibalin et al. 1999). In alveolar epithelial cells exposed to hypoxia (1.5% O_2 for 1 h), endocytosis of the Na,K-ATPase was associated with phosphorylation in the Ser18 residue by the atypical PKCζ, which was shown to be activated by hypoxia generated reactive oxygen species (ROS) (Dada et al. 2003).

Ubiquitination Ubiquitination is a dynamic and reversible process, where proteins are tagged by the 76-amino acid globular protein ubiquitin. Tagging results in covalent conjugation of ubiquitin to the target protein and it is essential for the proteolysis of most proteins, during both constitutive degradation and degradation as a result of changes in the cellular environment (Glickman and Ciechanover 2002). Conjugation of ubiquitin to a protein can also regulate its activity or location (Hicke 1997; Glickman and Ciechanover 2002; Haglund et al. 2003). A role for ubiquitination of the Na,K-ATPase α1-subunit in its endocytosis and degradation was proposed by Coppi and Guidotti (1997), although first direct evidence was provided in the hypoxia-induced Na,K-ATPase system (Comellas et al. 2006; Dada et al. 2007). In these reports it was shown that alveolar epithelial cells exposed to 1.5% O_2 have increased Na,K-ATPase-ubiquitin conjugates at the plasma membrane and by mutating four lysines at the N-terminus of the Na,K-ATPase α1-subunit (K16-17-19-20), they demonstrated the requirement of ubiquitination in the hypoxia-induced endocytosis and degradation. More importantly, phosphorylation of Ser18 was demonstrated to be necessary for ubiquitination to occur, demonstrating that this is a sequencial process part of the PURED system.

Recognition and endocytosis The traffic from different intracellular compartments of eukaryotic cells involves the self-assembly of multilayered cytosolic coat scaffolds (Stagg et al. 2007). These scaffolds include clathrin, coat protein complex I (COPI) and coat protein complex II (COPII). Adaptor protein (AP) complexes link different types of cargo with these proteins that can self-assemble as a lattice to form a scaffold that collects and concentrates AP-cargo complexes into membrane patches (Stagg et al. 2007). The endocytosis of the Na,K-ATPase is a clathrin-coated mediated mechanism, dependent on the phosphorylation of the Ser18 residue and binding of the μ2-subunit of adaptor protein 2 (AP-2) to the Y^{537}LEL motif of the Na,K-ATPase α1-subunit (Done et al. 2002). This mechanism of recognition is shared by the hypoxia-induced Na,K-ATPase endocytosis, as alveolar epithelial cells expressing a Na,K-ATPase α1-subunit mutation in the AP-2 recognition binding site (Y537A) failed to undergo endocytosis (Chen et al. 2006).

Degradation Lysosome and proteasome are the organelles where the degradation of proteins occurs (Reinstein and Ciechanover 2006). Plasma membrane proteins, such as the Na,K-ATPase are thought to be degraded by the lysosome with ubiquitination playing a role in the endocytotic pathway (Piper and Luzio 2007). Inhibitors of both, lysosome and proteasome, prevented the degradation of the plasma membrane associated Na,K-ATPase in alveolar epithelial cells during hypoxia (Comellas et al. 2006), which suggests that ubiquitination of the Na,K-ATPase is necessary for its endocytosis and traffic to the lysosome where it is degraded.

Conclusions

In summary, during acute lung injury, alveolar fluid reabsorption is impaired in part due to inhibition of Na,K-ATPase activity via its regulated endocytosis. In hypoxia induced alveolar epithelial cell dysfunction we propose a model (Fig. 1) where activation of atypical PKCζ induces the phosphorylation of the Na,K-ATPase α1-subunit at the Ser18 with consequent ubiquitination on any of the four lysines surrounding this residue (Ser18). This process makes the protein available for recognition by the adaptor protein-2 and its endocytosis via a clathrin-dependent mechanism that will lead to the traffic of the protein to the lysosome for degradation.

Acknowledgment Supported in part by: HL48129 and PO1-HL71643.

References

Adir Y, Factor P, Dumasius V, Ridge KM, Sznajder JI (2003) Na,K-ATPase gene transfer increases liquid clearance during ventilation-induced lung injury. Am J Respir Crit Care Med 168:1445–1448

Albertine K, Williams M, Hyde D (2005) Anatomy of the lungs. Murray and Nadel's textbook of respiratory medicine Edited by Mason and Broaddus

Aytacoglu B, Calkoglu M, Tamer L, Coskun B, Sucu N, Köse N, Aktas S, Dikmengil M (2006) Alcohol-induced lung damage and increased oxidative stress. Respiration 73:100–104

Azzam ZS, Saldias FJ, Comellas A, Ridge KM, Rutschman DH, Sznajder JI (2001) Catecholamines increase lung edema clearance in rats with increased left atrial pressure. J Appl. Physiol 90:1088–1094

Azzam ZS, Dumasius V, Saldias FJ, Adir Y, Sznajder JI, Factor P (2002) Na,K-ATPase overexpression improves alveolar fluid clearance in a rat model of elevated left atrial pressure. Circulation 105:497–501

Beguin P, Beggah A, Chibalin A, Burgener-Kairuz P, Jaisser F, Mathews P, Rossier B, Cotecchia S, Geering K (1994) Phosphorylation of the Na,K-ATPase alpha-subunit by protein kinase A and C in vitro and in intact cells. Identification of a novel motif for PKC-mediated phosphorylation. J Biol Chem 269:24437–24445

Bertorello A, Sznajder JI (2005) The dopamine paradox in lung and kidney epithelia. Sharing the same target but operating different signaling networks. Am J Respir Cell Mol Biol 33:432–437

Borok Z, Liebler JM, Lubman RL, Foster MJ, Zhou B, Li X, Zabski SM, Kim KJ, Crandall ED (2002) Na transport proteins are expressed by rat alveolar epithelial type I cells. Am J Physiol Lung Cell Mol Physiol 282:L599–L608

Campbell AR, Folkesson HG, Berthiaume Y, Gutkowska J, Suzuki S, Matthay MA (1999) Alveolar epithelial fluid clearance persists in the presence of moderate left atrial hypertension in sheep. J Appl Physiol 86:139–151

Carter EP, Wangensteen OD, O'Grady SM, Ingbar DH (1997) Effects of hyperoxia on type II cell Na-K-ATPase function and expression. Am J Physiol 272:L542–L551

Chen Z, Krmar RT, Dada L, Efendiev R, Leibiger IB, Pedemonte CH, Katz AI, Sznajder JI, Bertorello AM (2006) Phosphorylation of adaptor protein-2 {micro}2 is essential for Na+,K+-ATPase endocytosis in response to either G protein-coupled receptor or reactive oxygen species. Am J Respir Cell Mol Biol 35:127–132

Chibalin AV, Pedemonte CH, Katz AI, Feraille E, Berggren PO, Bertorello AM (1998) Phosphorylation of the catalytic a-subunit constitutes a triggering signal for Na+,K+-ATPase endocytosis. J Biol Chem 273:8814–8819

Chibalin AV, Ogimoto G, Pedemonte CH, Pressley TA, Katz AI, Feraille E, Berggren PO, Bertorello AM (1999) Dopamine-induced endocytosis of Na+,K+-ATPase is initiated by phosphorylation of Ser-18 in the rat a subunit and is responsible for the decreased activity in epithelial cells. J Biol Chem 274:1920–1927

Clausen T (2003) Na+-K+ pump regulation and skeletal muscle contractility. Physiol Rev 83:1269–1324

Comellas AP, Dada LA, Lecuona E, Pesce LM, Chandel NS, Quesada N, Budinger GRS, Strous GJ, Ciechanover A, Sznajder JI (2006) Hypoxia-mediated degradation of Na,K-ATPase via mitochondrial reactive oxygen species and the ubiquitin-conjugating system. Circ Res 98:1314–1322

Coppi MV, Guidotti G (1997) Ubiquitination of Na,K-ATPase [alpha] 1 and [alpha]2 subunits. FEBS Letters 405:281–284

Dada LA, Chandel NS, Ridge KM, Pedemonte C, Bertorello AM, Sznajder JI (2003) Hypoxia-induced endocytosis of Na,K-ATPase in alveolar epithelial cells is mediated by mitochondrial reactive oxygen species and PKC-{zeta}. J Clin Invest 111:1057–1064

Dada LA, Welch LC, Zhou G, Ben-Saadon R, Ciechanover A, Sznajder JI (2007) Phosphorylation and ubiquitination are necessary for Na,K-ATPase endocytosis during hypoxia. Cell Signal 19:1893–1898

Done SC, Leibiger IB, Efendiev R, Katz AI, Leibiger B, Berggren P-O, Pedemonte CH, Bertorello AM (2002) Tyrosine 537 within the Na+,K+-ATPase alpha-subunit is essential for AP-2 binding and clathrin-dependent endocytosis. J Biol Chem 277:17108–17111

Dunbar LA, Caplan MJ (2001) Ion pumps in polarized cells: sorting and regulation of the Na+,K+-and H+,K+-ATPases. J Biol Chem 276:29617–29620

Ewart HS, Klip A (1995) Hormonal regulation of the Na+-K+-ATPase: mechanisms underlying rapid and sustained changes in pump activity. Am J Physiol 269:C295–C311

Glickman MH, Ciechanover A (2002) The ubiquitin–proteasome proteolytic pathway: destruction for the sake of construction. Physiol Rev 82:373–428

Haglund K, Di Fiore PP, Dikic I (2003) Distinct monoubiquitin signals in receptor endocytosis. Trends Biochem Sci 28:598–604

Hicke L (1997) Ubiquitin-dependent internalization and down-regulation of plasma membrane proteins. Faseb J 11:1215–1226

Hicke L, Dunn R (2003) Regulation of membrane protein transport by ubiquitin and ubiquitin-binding proteins. Annu Rev Cell Dev Biol 19:141–172

Hirsch J, Hansen KC, Sapru A, Frank JA, Chalkley RJ, Fang X, Trinidad JC, Baker P, Burlingame AL, Matthay MA (2007) Impact of low and high tidal volumes on the rat alveolar epithelial type II cell proteome. Am J Respir Crit Care Med 175:1006–1013

Jain M, Sznajder JI (2005) Effects of hypoxia on the alveolar epithelium. Proc Am Thorac Soc 2:202–205

Johnson MD, Widdicombe JH, Allen L, Barbry P, Dobbs LG (2002) Alveolar epithelial type I cells contain transport proteins and transport sodium, supporting an active role for type I cells in regulation of lung liquid homeostasis. Proc Natl Acad Sci U S A 99:1966–1971

Kelm KB, Huyer G, Huang JC, Michaelis S (2004) The internalization of yeast step6 follows an ordered series of events involving phosphorylation, ubiquitination, recognition and endocytosis. Traffic 5:165–180

Koksel O, Kaplan MB, Ozdulger A, Tamer L, Degirmenci U, Cinel L, Basturk M, Kanik A (2005) Oleic acid-induced lung injury in rats and effects of caffeic acid phenet hyl ester. Exp Lung Res 31:483–496

Koksel O, Ozdulger A, Tamer L, Cinel L, Ercil M, Degirmenci U, Unlu S, Kanik A (2006) Effects of caffeic acid phenethyl ester on lipopolysaccharide-induced lung injury in rats. Pulm Pharmacol Ther 19:90–95

Lecuona E, Saldias F, Comellas A, Ridge K, Guerrero C, Sznajder JI (1999) Ventilator-associated lung injury decreases lung ability to clear edema in rats. Am J Respir Crit Care Med 159:603–609

Leithe E, Rivedal E (2007) Ubiquitination of gap junction proteins. J Membr Biol DOI 10.1007/s00232-007-9050-z

Litvan J, Briva A, Wilson MS, Budinger GRS, Sznajder JI, Ridge KM (2006) Beta-adrenergic receptor stimulation and adenoviral overexpression of superoxide dismutase prevent the hypoxia-mediated decrease in Na,K-ATPase and alveolar fluid reabsorption. J Biol Chem 281:19892–19898

Mairbaurl H, Wodopia R, Eckes S, Schulz S, Bartsch P (1997) Impairment of cation transport in A549 cells and rat alveolar epithelial cells by hypoxia. Am J Physiol 273:L797–806

Mason R, Williams M, Widdicombe J, Sanders M, Misfeldt D, Berry LJ (1982) Transepithelial transport by pulmonary alveolar type II cells in primary culture. Proc Natl Acad Sci U S A 79:6033–6037

Matalon S, O'Brodovich H (1999) Sodium channels in alveolar epithelial cells: molecular characterization, biophysical properties, and physiological significance. Annu Rev Physiol 61:627–661

Matalon S, Bridges RJ, Benos DJ (1991) Amiloride-inhibitable Na+ conductive pathways in alveolar type II pneumocytes. Am J Physiol 260:L90–96

Mutlu GM, Sznajder JI (2005) Mechanisms of pulmonary edema clearance. Am J Physiol Lung Cell Mol Physiol 289:L685–L695

Mutlu GM, Machado-Aranda D, Norton JE, Bellmeyer A, Urich D, Zhou R, Dean DA (2007) Electroporation-mediated gene transfer of the Na+,K+-ATPase rescues endotoxin-induced lung injury. Am J Respir Crit Care Med 176:582–590

Ng AW, Bidani A, Heming TA (2004) Innate host defense of the lung: effects of lung-lining fluid pH. Lung 182:297–317

Olivera WG, Ridge KM, Sznajder JI (1995) Lung liquid clearance and Na,K-ATPase during acute hyperoxia and recovery in rats. Am J Respir Crit Care Med 152:1229–1234

Pedemonte CH, Efendiev R, Bertorello A (2005) Inhibition of Na,K-ATPase by dopamine in proximal tubule epithelial cells. Semin Nephrol 25:322–327

Piper RC, Luzio JP (2007) Ubiquitin-dependent sorting of integral membrane proteins for degradation in lysosomes. Curr Opin Cell Biol 19:459–465

Reinstein E, Ciechanover A (2006) Narrative review: protein degradation and human diseases: the ubiquitin connection. Ann Intern Med 145:676–684

Ridge K, Rutschman D, Factor P, Katz A, Bertorello A, Sznajder J (1997) Differential expression of Na-K-ATPase isoforms in rat alveolar epithelial cells. Am J Physiol 273:L246–L255

Ridge KM, Olivera WG, Saldias F, Azzam Z, Horowitz S, Rutschman DH, Dumasius V, Factor P, Sznajder JI (2003) Alveolar type 1 cells express the a2 Na,K-ATPase which contributes to lung liquid clearance. Circulation Res 92:453–460

Roth AF, Sullivan DM, Davis NG (1998) A large PEST-like sequence directs the ubiquitination, endocytosis, and vacuolar degradation of the yeast a-factor receptor. J Cell Biol 142:949–961

Saldias FJ, Comellas A, Ridge KM, Lecuona E, Sznajder JI (1999) Isoproterenol improves ability of lung to clear edema in rats exposed to hyperoxia. J Appl Physiol 86:30–35

Saldias FJ, Lecuona E, Comellas AP, Ridge KM, Rutschman DH, Sznajder JI (2000) b-Adrenergic stimulation restores rat lung ability to clear edema in ventilator-associated lung injury. Am J Respir Crit Care Med 162:282–287

Saldias FJ, Azzam ZS, Ridge KM, Yeldandi A, Rutschman DH, Schraufnagel D, Sznajder JI (2001) Alveolar fluid reabsorption is impaired by increased left atrial pressures in rats. Am J Physiol Lung Cell Mol Physiol 281:L591–597

Saldias FJ, Comellas AP, Pesce L, Lecuona E, Sznajder JI (2002) Dopamine increases lung liquid clearance during mechanical ventilation. Am J Physiol Lung Cell Mol Physiol 283:L136–143

Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, Hutter D, Turini P, Hugli O, Cook S, Nicod P, Scherrer U (2002) Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med 346:1631–1636

Schneeberger EE, McCarthy KM (1986) Cytochemical localization of Na+-K+-ATPase in rat type II pneumocytes. J Appl Physiol 60:1584–1589

Stagg SM, LaPointe P, Balch WE (2007) Structural design of cage and coat scaffolds that direct membrane traffic. Curr Opin Struck Biol 17:221–228

Staub NC (1974) Pulmonary edema. Physiol Rev 54:678–811

Teixeira VL, Katz AI, Pedemonte CH, Bertorello AM (2003) Isoform-specific regulation of Na+,K+-ATPase endocytosis and recruitment to the plasma membrane. Ann N.Y. Acad Sci 986:587–594

Terrell J, Shih S, Dunn R, Hicke L (1998) A function for monoubiquitination in the internalization of a G protein-coupled receptor. Mol Cell 1:193–202

Therien AG, Blostein R (2000) Mechanisms of sodium pump regulation. Am J Physiol Cell Physiol 279:C541–566

Vadasz I, Morty RE, Kohstall MG, Olschewski A, Grimminger F, Seeger W, Ghofrani HA (2005) Oleic acid inhibits alveolar fluid reabsorption: a role in acute respiratory distress syndrome? Am J Respir Crit Care Med 171:469–479

Vadász I, Raviv S, Sznajder J (2007) Alveolar epithelium and Na, K-ATPase in acute lung injury. Intensive Care Med 33:1243–1251

Vivona ML, Matthay M, Chabaud MB, Friedlander G, Clerici C (2001) Hypoxia reduces alveolar epithelial sodium and fluid transport in rats. reversal by beta-adrenergic agonist treatment. Am J Respir Cell Mol Biol 25:554–561

Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med 342:1334–1349

Ware LB, Matthay MA (2001) Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 163:1376–1383

Weibel ER (1973) Morphological basis of alveolar-capillary gas exchange. Physiol Rev 53:419–495

Zhang XL, Danto SI, Borok Z, Eber JT, Martin-Vasallo P, Lubman RL (1997) Identification of Na(+)-K(+)-ATPase beta-subunit in alveolar epithelial cells. Am J Physiol 272:L85–94