Regulation of Lung Edema Clearance by Dopamine

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The outcome of patients with acute hypoxemic respiratory failure improves when lung epithelial function is restored and pulmonary edema resolves [1,2]. Pulmonary edema is cleared from the alveoli by active Na^+ transport, with Na^+ moving vectorially across the alveolar epithelium, entering the cell via apical amiloride-sensitive Na^+ channels and extruding from the cell via the basolaterally located Na,K-ATPase. Water follows the Na^+ gradients isosmotically, resulting in alveolar fluid reabsorption [3]. In the kidney, dopamine inhibits Na,K-ATPase, which decreases Na^+ reabsorption and causes natriuresis [4,5]. It was recently demonstrated that dopamine increases alveolar fluid reabsorption by increasing Na,K-ATPase activity in the lung [6]. In this review we discuss the mechanisms of dopamine regulation of Na,K-ATPase and lung edema clearance.

Regulation of Na,K-ATPase by dopamine

The role of dopamine in regulating renal function was recognized in the early 1970s when it was shown that dopamine increases sodium excretion and glomerular filtration rate [3,4]. Further studies demonstrated that dopamine was produced in the kidney proximal tubule, acting in a paracrine and autocrine fashion to increase urinary sodium excretion [7–9] due to its ability to inhibit the Na,K-ATPase [10].

The Na,K-ATPase is a transmembrane protein composed of two subunits, α and β. The α-subunit contains binding sites for ATP hydrolysis, Na^+, K^+ and cardiac glycosides such as ouabain [10]. There are at least three isoforms of α (α1, α2 and α3), each differing in its affinity to sodium, ouabain and tissue distribution. The β-subunit is thought to be responsible for incorporating the α-subunit into the plasma membrane. There are at least three isoforms of β-subunit [10–12].

The hemodynamic effects of dopamine are mediated via α and β adrenergic receptors and dopaminergic receptors, whereas the natriuretic effects including the inhibition of the Na,K-ATPase are mediated by the dopaminergic receptors, i.e., G protein-coupled receptors [13]. There are at least five receptor subtypes, which are divided into two main dopamine receptor subclasses: D1-like (D1 and D5) and D2-like receptors (D2, D3 and D4) [13,14]. In the distal segments of the kidney tubule, D1 stimulation leads to activation of adenylate cyclase, increased levels of cAMP and protein kinase A, leading to Na,K-ATPase inhibition either directly or by phosphorylation of the α1-Na,K-ATPase and cAMP-regulated phosphoprotein (DARPP-32), a potent inhibitor of protein phosphatase 1A [9,15,16].

Dopamine effect on lung sodium transport

The lung alveolar epithelium actively reabsorbs fluid from the alveolar space [17,18] via sodium transport by generating a gradient of Na^+, which enters the alveolar epithelial cells through apical amiloride-sensitive Na^+ channels and is pumped out of the cell by the Na,K-ATPase located in the cell basolateral membrane. This is an active metabolic process that consumes ATP [19,20]. Dopamine has been shown to increase, in a dose-dependent manner, lung edema clearance in rats by 40–70% above the control clearance levels [Figure 1] via activation of dopaminergic D1 receptors expressed in the basolateral membrane of alveolar type II cells [5,21].

Clearance of edema during lung injury

Several studies in models of lung injury have demonstrated that alveolar fluid clearance is impaired in parallel with decreased Na,K-ATPase function. It is known that adult rats exposed to 100% oxygen for 72 hours die from pulmonary edema. After 64 hours of exposure to 100% O_2 there is an increase in permeability to solutes and a significant decrease in the lung's ability to clear edema [22,23]. The

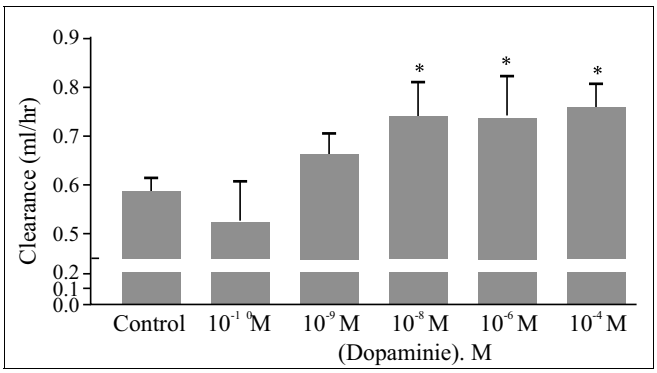

Figure 1. Dose response of increased lung liquid clearance in response to increasing concentrations of dopamine in the isolated perfused lung. Dopamine at the indicated concentrations was added to the instillate. *$P < 0.05$ as compared with controls. With permission from Barnard et al. [6].

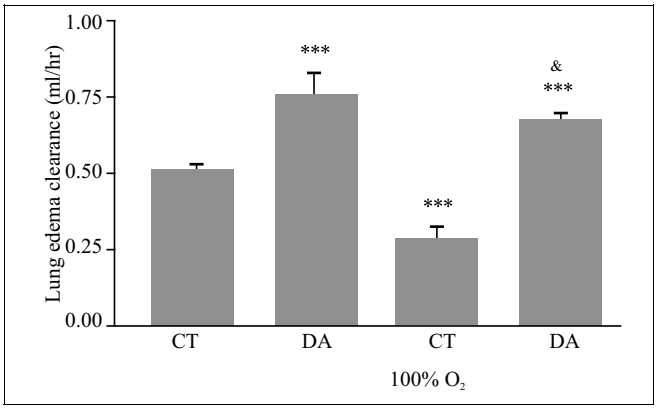

Figure 2. Exposure to hyperoxia decreased lung liquid clearance in adult rats. Dopamine increased lung edema clearance in room air breathing rats and after 64 h of exposure to 100% oxygen. $^{*}P < 0.05$ and $^{***}P < 0.001$ compared with room air breathing control rats. $^{\&}P < 0.001$ compared with hyperoxia-injured control rat lungs. CT: control group; DA: 10^5 M dopamine instilled into airspace. With permission from Saldias et al {28].

decrease in clearance occurs in association with decreased Na,K-ATPase activity in alveolar epithelial cells [22,23].

Mechanical ventilation with high tidal volume and high peak airway pressures induces production of chemokines and metalloproteinases and causes ventilator-induced lung injury [24–26]. Interestingly, it has been reported that during ventilator-induced lung injury there is not only injury but also a decrease in alveolar epithelial fluid reabsorption and decreased alveolar epithelial Na,K-ATPase activity [27]. In both models of lung injury, hyperoxia and ventilator-induced lung injury, dopamine increased alveolar fluid reabsorption by upregulating the Na,K-ATPase function [Figure 2] [28,29].

Regulation of Na,K-ATPase by dopamine in alveolar epithelial cells.

Na,K-ATPase function in the lung can be regulated by short-term or long-term mechanisms. Several studies have suggested that dopamine increases alveolar fluid reabsorption (short-term) in normal lungs and animal models of lung injury by regulating the alveolar epithelial Na,K-ATPase function [5,28–31]. Apparently, the dopamine short-term effects in alveolar epithelial-type II cells cause translocation of preformed Na,K-ATPase pumps from intracellular pools (i.e., late endosomal compartment) to the cell plasma membrane [1,32,33]. This rapid recruitment is regulated by the cell actin cytoskeleton and the microtubuli. Disruption of the cell microtubular transport system by colchicine blocks the stimulatory effects of dopamine on Na,K-ATPase translocation and impairs the lung's ability to clear edema in normal and injured lungs [5,28,29]. The isomer β lumicolchicine, which shares many of the colchicine properties with the exception of disruption of the microtubular transport, does not inhibit the dopaminergic stimulation of lung edema clearance [5,28,29].

Further studies have shown that Na,K-ATPase activity increased twofold in alveolar type II cells following 15 minutes of incubation with dopamine or fenoldopam – a specific dopaminergic D1 agonist – but was not changed with the specific dopaminergic D2 agonist quinipirole. Down-regulation of diacylglycerol-sensitive (conventional and novel) protein kinase C by pretreatment with phorbol 12-myristate 13-acetate or by preincubation with bisindolylmaleimide prevented the DA-mediated increase in Na,K-ATPase activity and translocation of Na,K-pumps to the basolateral membranes [32]. Accordingly, dopamine increased Na,K-ATPase activity in alveolar epithelial type II cells by recruiting sodium pumps into the plasma membrane from an intracellular compartment via a novel protein kinase C-dependent pathway [32] [Figure 3].

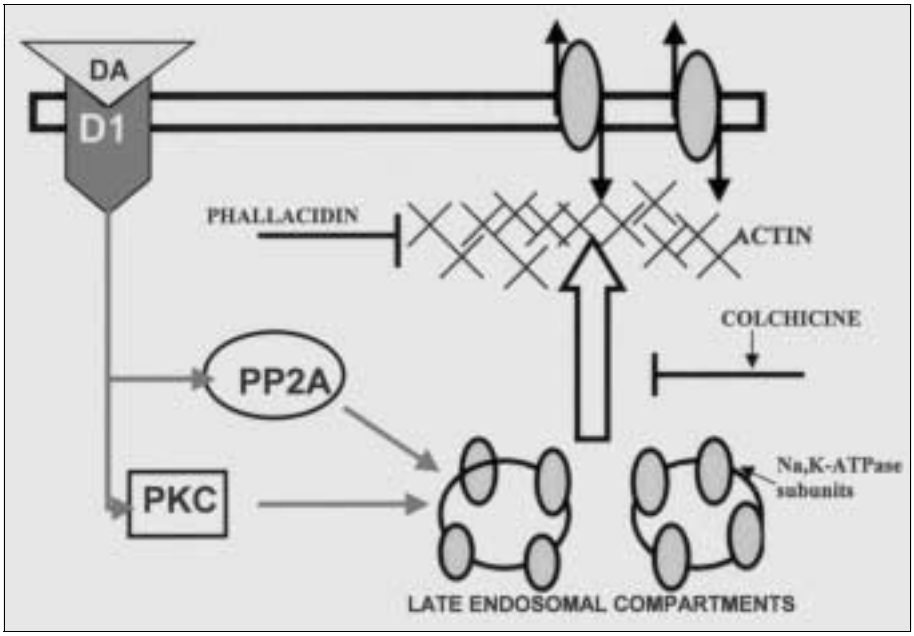

Figure 3. Short-term regulation of Na,K-ATPase by dopamine in alveolar epithelial cells. Activation of the D1 dopamine receptor causes translocation of preformed Na,K-ATPase pumps from intracellular pools to the cell plasma membrane. This process is regulated by type 2 serine/threonine protein phosphatases and protein kinase C-dependent pathway.

Recent studies suggest that different types of protein phosphatases play a role in Na,K-ATPase regulation in the kidney and brain, demonstrating the complexity of the signaling pathways that probably are receptor and cell-type specific [34,35]. In the lungs, short-term incubation (1 minute) of alveolar epithelial cells with a D1 agonist increased Na,K-ATPase activity by translocation of the Na,K-ATPase from intracellular pools to the basolateral membranes without changing the total Na,K-ATPase protein abundance in cell lysates [33]. The D1-mediated Na,K-

ATPase translocation to the basolateral membranes was regulated by type 2 serine/threonine protein phosphatases [33] [Figure 3].

Long-term regulation of Na,K-ATPase by dopamine in alveolar cells

The mitogen-activated protein kinase/extracellular-regulated kinase cascade is a major signaling system whereby cells transduce extracellular signals into intracellular responses. ERK proteins (ERK1/2) have many substrates including the ternary complex factor Elk-1, a member of the Ets family of transcription factors that is recruited by serum response factor to bind serum response elements located in the promoters of many genes and also in the 5′ flanking region of the Na,K-ATPase gene [36]. Dopamine has an inhibitory role on the ERK pathway in most cell types although recent reports suggest that dopamine activates ERK proteins in Chinese hamster ovary cells [37] and neurons [38].

Huff et al. [39] and Guerrero et al. [40] demonstrated that dopamine, through activation of D2 but not D1 receptors, regulates β1-subunit mRNA and protein abundance via an ERK-dependent mechanism, leading to an increase in Na,K-ATPase pumps in the basolateral membrane of alveolar epithelial type II cells, causing an increase in the Na,K-ATPase activity. These data suggest that the MAPK/ERK pathway is an important mechanism in the long-term regulation of Na,K-ATPase by dopamine in alveolar epithelium [Figure 4].

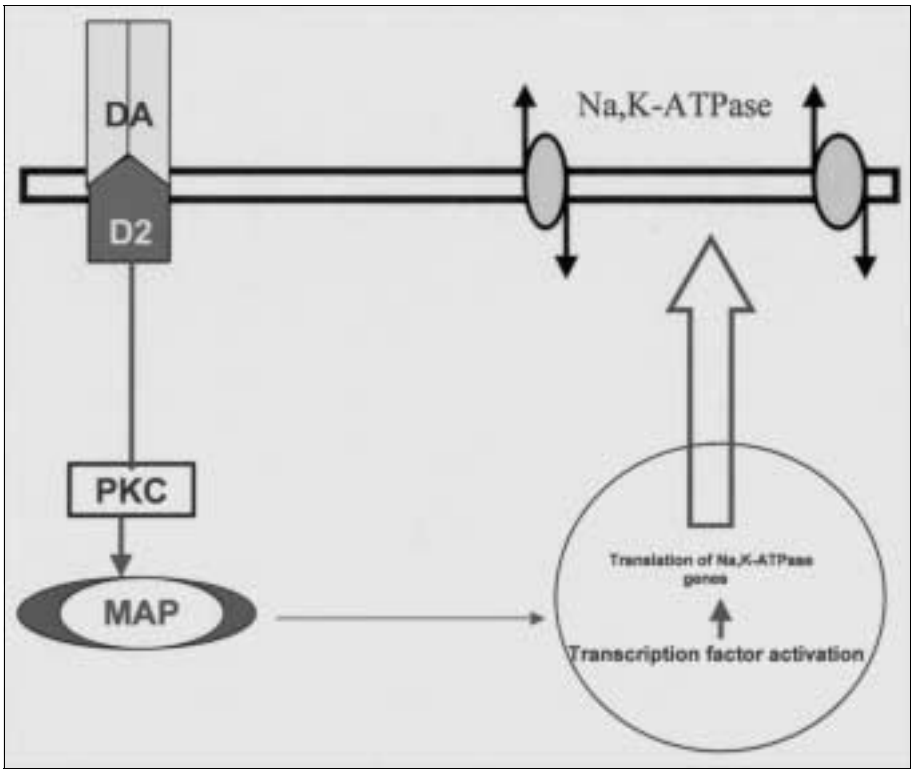

Figure 4. Long-term regulation of Na,K-ATPase by dopamine in alveolar epithelial cells. Activation of the D2 dopamine receptor regulates β1-subunit mRNA and protein abundance via an ERK-dependent mechanism, leading to an increase in Na,K-ATPase pumps in the basolateral membrane of alveolar epithelial type II cells.

Summary

In the kidney, dopamine inhibits Na,K-ATPase, which results in natriuresis because less Na^+ is reabsorbed by the proximal and distal tubules. In contrast, dopamine stimulates Na,K-ATPase activity in the alveolar epithelium, leading to increased alveolar fluid reabsorption. Importantly, dopamine increases alveolar fluid reabsorption not only in normal alveolar epithelium but also in models of lung injury. Dopamine short-term regulation of alveolar epithelial Na,K-ATPase occurs via D1 receptor activation, protein kinase C and protein phosphatase 2A pathways, leading to increased Na,K-ATPase activity by recruiting sodium pumps from the intracellular compartment to the basolateral membranes. Conversely, D2 receptor activation by long-term dopamine regulates (~ 24 hours) alveolar epithelial Na,K-ATPase via the MAPK pathway, which results in *de novo* synthesis of Na,K-ATPase proteins. Conceivably, by increasing Na,K-ATPase activity and promoting alveolar fluid reabsorption, dopamine can be of clinical relevance for the treatment of patients with acute hypoxemic respiratory failure due to pulmonary edema.

ERK = extracellular-regulated kinase
MAPK/ERK = mitogen-activated protein kinase/extracellular-regulated kinase

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