Catecholamines increase lung edema clearance in rats with increased left atrial pressure

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Catecholamines increase lung edema clearance in rats with increased left atrial pressure. J Appl Physiol 90: 1088–1094, 2001.—During hydrostatic pulmonary edema, active Na+ transport and alveolar fluid reabsorption are decreased. Dopamine (DA) and isoproterenol (ISO) have been shown to increase active Na+ transport in rat lungs by upregulating Na+-K+-ATPase in the alveolar epithelium. We studied the effects of DA and ISO in isolated rat lungs with increased left atrial pressure (Pla = 15 cmH2O) compared with control rats with normal Pla (Pla = 0). Alveolar fluid reabsorption decreased from control value of 0.51 ± 0.02 to 0.27 ± 0.02 ml/h when Pla was increased to 15 cmH2O (P < 0.001). DA and ISO increased the alveolar fluid reabsorption back to control levels. Treatment with the D1 receptor agonist SCH-23390 inhibited the stimulatory effects of DA (0.30 ± 0.02 ml/h), whereas fenoldopam, a specific D1-receptor antagonist, increased alveolar fluid reabsorption in rats exposed to Pla of 15 cmH2O (0.47 ± 0.04 ml/h). Propranolol, a β-adrenergic-receptor antagonist, blocked the stimulatory effects of ISO; however, it did not affect alveolar fluid reabsorption in control or DA-treated rats. Amiloride (a Na+ channel blocker) and ouabain (a Na+-K+-ATPase inhibitor), either alone or together, inhibited the stimulatory effects of ISO. Colchicine, which disrupts the cellular microtubular transport of ion-transporting proteins to the plasma membrane, inhibited the stimulatory effects of DA, whereas the isomer β-lumicolchicine did not block the stimulatory effects of DA. These data suggest that DA and ISO increase alveolar fluid reabsorption in a model of increased Pla by regulating active Na+ transport in rat alveolar epithelium. The effects of DA and ISO are mediated by the activation of dopaminergic D1 receptors and the β-adrenergic receptors, respectively.

EDMA FORMATION as a result of either changes in the hydrostatic and/or oncotic pressure gradients across the pulmonary circulation or increased alveolo-capillary permeability. As such, increased pulmonary capillary wedge pressures can result in pulmonary edema formation (13, 32). Several therapeutic options are available in clinical practice to reduce edema formation; however, approaches to increase alveolar fluid reabsorption (once edema has been formed) are less understood. Previous reports have suggested that vectorial Na+ transport and thus alveolar fluid reabsorption across the alveolocapillary barrier are important in keeping the air spaces free of edema (16, 23, 29). Alveolar fluid reabsorption is regulated in epithelial cells by the rate of sodium entry, via the apical Na+ channels, coupled to the rate of Na+ extrusion, via the basolateral Na+-K+-ATPase function in the alveolar epithelium (3, 4, 27).

Recently, it has been shown that alveolar fluid reabsorption is impaired in the presence of elevated left atrial pressures (Pla) (Refs. 7 and 22, and Saldias FJ, Azzam ZS, Ridge KM, Yeldandi A, Rutschman DH, Schraufnagel D, Sznaider JI, unpublished observations). The purpose of this study was to determine whether DA and ISO would increase alveolar fluid reabsorption in a model of increased Pla and investigate mechanisms contributing to these effects.

METHODS AND MATERIALS

Isolated-perfused lung. The lungs and heart of rats anesthetized with 50 mg/kg body wt of intraperitoneal pentobarbital were removed en bloc after a 10-min ventilation with 100% O2 and anticoagulation with heparin as previously described (23, 28). The pulmonary artery and left atrium were catheterized and perfused continuously with a solution of 3% bovine serum albumin (BSA) in buffered physiological salt solution (135.5 mM Na+, 119.1 mM Cl−, 25 mM HCO3−, 4.1 mM K+, 2.8 mM Mg2+, 2.5 mM Ca2+, 0.8 mM SO42−, 8.3 mM glucose). Trace amounts of fluorescein-labeled (FITC)
albumin were also added to the perfusate. The recirculating volume of the constant-pressure perfusion system was 90 ml; arterial and venous pressures were set at 15 and 0 cmH2O, respectively, in the group of rats with normal Pla and 20 and 15 cmH2O, respectively, in the increased Pla study groups. The vascular pressures were recorded every 10 s with a multichannel recorder (Cyber Sense, Nicholasville, KY). The lungs were immersed in a “pleural” bath (100 ml) filled with the same BSA solution. The entire system was maintained at 37°C in a water bath. Perfusate pH was maintained at 7.40 by bubbling with a gas mixture of 95% O2-5% CO2. The lungs were then instilled via tracheal cannula in two sequential phases with a total of 5-ml volume of the BSA solution containing 0.1 mg/ml Evans blue dye-labeled (EBD; Sigma Chemical, St. Louis, MO) albumin, 0.02 μCi/ml of 22Na+ (Du Pont-NEN, Boston, MA) and 0.12 μCi/ml of [3H]mannitol (Du Pont-NEN). Samples were taken from the instillate, perfusate, and bath solutions after an equilibration time of 10 min from the instillation and 60 min later. To ensure a homogeneous sampling of the instillate, a volume of 2 ml was aspirated and reintroduced into the air spaces three times before each sample was removed. All samples were centrifuged at 3,000 g for 10 min. Absorbance analysis of the supernatant or EBD albumin was performed at 620 nm in a Hitachi model U2000 spectrometer (Hitachi, San Jose, CA). Analysis of FITC-albumin (excitation 487 nm and emission 520 nm) was performed in a Perkin-Elmer fluorometer (model LS-3B, Perkin-Elmer, Oakbrook, IL). Scintillation counts (for 22Na+ and [3H]mannitol) were measured in a Beckman beta counter (model LS 6500, Beckman Instruments, Fullerton, CA).

Calculations. The mathematical calculation of lung liquid clearance, the movement of sodium, and the flux of mannitol were described elsewhere (23). Briefly, the amount of instilled EBD-albumin remains constant during the experimental protocol; thus any change in its concentration at a given time (t) will reflect the change in the air space volume (V(t))

\[ V_{[EBD]_0} = V_{[EBD]_t} \]

(1)

\[ V_i = V_{[EBD]_0}/[EBD]_t \]

(2)

\[ J = (V_i - V_o)/t \]

(3)

where \( V_o \) is the initial known volume instilled instilled into rat air spaces containing a known concentration of Evans blue dye-albumin [EBD]0; \( V_i \) and [EBD]t are the alveolar fluid volume and EBD concentration in the instillate at time \( t \), respectively; and \( J \) is the volume flux during a time period (t).

The sodium concentration is equal and constant in all the compartments, and because 22Na+ is instilled only in the air space, the disappearance of the radioactive tracer from the air spaces reflects the total or unidirectional Na+ outflux from the air space (\( J_{Na, out} \)). The passive or bidirectional Na+ flux between the air space and the other compartments is the difference between the unidirectional \( J_{Na, out} \) and active Na+ outflux (\( J_{Na, out} = [Na+]J \)). The passive sodium movement can be calculated by

\[ J_{Na, in} = [Na^+]d(lnC_i - lnC_o)/(lnV_i - lnV_o) \]

(4)

where \( C_o \) and \( C_i \) are the concentrations of 22Na+ initially and at time \( t \), respectively, and [Na+] is the constant Na+ concentration in the buffered salt albumin solution.

Similarly, the mannitol flux (typically expressing the surface area permeability \( P_{A} \)) is given by

\[ P_A = J(lnM_i - lnM_o)/(lnV_i - lnV_o) \]

(5)

where \( M_o \) and \( M_i \) are [3H]mannitol concentrations initially and at time \( t \), respectively.

The fraction of FITC-albumin that appears in the alveolar space during the experimental protocol was used to calculate the albumin flux from the pulmonary circulation into the alveolar space.

Study groups. One hundred nineteen specific pathogen-free male Sprague-Dawley rats (275–325 g) were acquired from Harlan Sprague Dawley (Indianapolis, IN). DA, ISO, SCH-23390, colchicine, and β-lumicolchicine were purchased from Sigma Chemical. Ouabain and propranolol were purchased from RBI (Natick, MA), and fenoldopam was generously provided by Neurex (Menlo Park, CA).

Control group of rats studied at Pla 0 cmH2O (n = 7) and Pla 15 cmH2O (n = 7). Rat lungs were instilled with 10−4 M DA into the air space at Pla 0 cmH2O (n = 8) and Pla 15 cmH2O (n = 7). Rat lungs were perfused with 10−6 M ISO through the pulmonary circulation at Pla 0 cmH2O (n = 6) and Pla 15 cmH2O (n = 6).

To evaluate the dopaminergic D1-receptor pathway, we studied alveolar fluid reabsorption by instilling 10−6 M fenoldopam, a specific D1-receptor agonist, into rat air spaces exposed to Pla 15 cmH2O (n = 6). We also studied the effect of dopaminergic receptor-1 antagonist SCH-23390 by instilling rat lungs with 10−4 M SCH-23390 into the air space at Pla 15 cmH2O either alone (n = 3) or with 10−4 M DA (n = 4).

To evaluate the β-adrenergic pathway, we instilled the β-adrenergic blocker 10−4 M propranolol into the rat air spaces at Pla 15 cmH2O either alone (n = 5) or in the presence of 10−4 M DA (n = 5) or ISO 10−6 M (n = 5).

To examine the contributory role of the amiloride-sensitive Na+ pathways and basolateral Na+/-K+/-ATPase on dopaminergic effects, we instilled 10−4 M amiloride (Na+ channel blocker) into the rat air spaces (n = 4) and perfused the lungs with 5 × 10−4 M ouabain (Na+/-K+/-ATPase blocker) either alone (n = 7) or both agents together (n = 6) in rat lungs exposed to Pla 15 cmH2O and in the presence of DA (amiloride + DA, n = 4, ouabain + DA, n = 6, and both antagonists with DA, n = 4) in rat lungs with Pla 15 cmH2O.

To evaluate the role of cell microtubular transport system on alveolar fluid reabsorption modulation by dopamine, we studied rats treated with colchicine (0.25 mg/100 g body wt) injected intraperitoneally 15 h before the experiments at Pla 15 cmH2O either alone (n = 5) or with 10−4 M DA (n = 6) instilled into the rat air spaces. We also studied the effects of 0.25 mg/100 g body wt of β-lumicolchicine injected intraperitoneally 15 h before the experiments at Pla 15 cmH2O either alone (n = 4) or with 10−4 M DA (n = 4) instilled into the rat air spaces. β-Lumicolchicine is an isomer of colchicine that does not bind tubulin and does not depolymerize microtubules; however, it shares other properties of colchicine, such as inhibition of protein synthesis (37).

Statistical analysis. Data are presented as means ± SE; n is the number of animals in each study group. One-way analysis of variance was used when multiple comparisons were made followed by a multiple comparison test (Tukey’s) when the F statistic indicated significance. Results were considered significant when \( P < 0.05 \).

RESULTS

Alveolar fluid reabsorption. As depicted in Fig. 1, alveolar fluid reabsorption in rat lungs exposed to Pla of 15 cmH2O was decreased by ~45% compared with control rats with Pla of 0 cmH2O (from 0.51 ± 0.02 to 0.27 ± 0.02 ml/h, \( P < 0.001 \)). Treatment with DA or ISO restored alveolar fluid reabsorption to control lev-
els in rat lungs exposed to elevated Pla (0.44 ± 0.03 and 0.52 ± 0.02 ml/h, respectively).

To determine whether the effects of DA in rat lungs exposed to increased Pla occurred via D₁ receptors, 10⁻⁶ M fenoldopam (a specific D₁ agonist) were instilled into the air spaces. Fenoldopam increased alveolar fluid reabsorption to control levels (0.47 ± 0.04 ml/h). As shown in Fig. 2A, instillation of the specific D₁ antagonist SCH-23390 in the rat air spaces prevented the DA-mediated increase in alveolar fluid reabsorption. As depicted in Fig. 2B, the instillation of the β-adrenergic-receptor antagonist 10⁻⁴ M propranolol inhibited the stimulatory effects of ISO; however, in DA-treated lungs, propranolol did not affect the rate of alveolar fluid reabsorption.

As shown in Fig. 3, instillation of 10⁻⁴ M amiloride into the air spaces and/or the perfusion of 5 × 10⁻⁴ M ouabain in the pulmonary circulation inhibited alveolar fluid reabsorption in rat lungs with Pla of 15 cmH₂O. These data suggest that DA increased alveolar fluid reabsorption in this model by regulating the amiloride-sensitive Na⁺ pathways and Na⁺-K⁺-ATPase in the alveolar epithelium.

As depicted in Fig. 4, alveolar fluid reabsorption was decreased in rats pretreated with either colchicine or β-lumicolchicine and then exposed to increased Pla.

Fig. 1. Dopamine (DA) and isoproterenol (ISO) increased alveolar fluid reabsorption in rat lungs exposed to left atrial pressure (Pla) of 0 (left) and 15 cmH₂O (right). Bars represent means ± SE. *P < 0.001 vs. control (CT) group with Pla 0 cmH₂O; †P < 0.001 vs. control group with Pla 0 cmH₂O.

Fig. 2. A: fenoldopam (Fen) increased alveolar fluid reabsorption in rat lungs exposed to Pla of 15 cmH₂O compared with CT. SCH-23390 prevented the DA-mediated increase in lung liquid clearance in rats exposed to Pla 15 cmH₂O. *P < 0.01 vs. other study groups. B: propranolol (PRO) inhibited the stimulatory effects of ISO; however, it did not affect lung liquid clearance in the CT group or when instilled together with DA. Bars represent means ± SE. *P < 0.001 vs. the other study groups.
compared with control rats (from 0.51 to 0.18 ± 0.07 to 0.34 ± 0.01 ml/h). Treatment with DA increased alveolar fluid reabsorption in β-lumicolchicine-treated rats to 0.50 ± 0.04 ml/h but had no effects in the colchicine-treated rats.

**Epithelial permeability.** As shown in Table 1, alveolar epithelial permeability to the small solutes, as measured by 22Na and [3H]mannitol flux, was significantly increased in the rat lungs exposed to Pla of 15 cmH₂O compared with control rats. The movement of FITC-albumin from the pulmonary circulation into the air spaces was slightly increased in all rat lungs exposed to Pla 15 cmH₂O compared with control rats (Pla 0 cmH₂O).

The pulmonary circulation flow rate did not change among the different study groups (Table 1). The Na⁺ concentration was ~135 meq/ml in all compartments: instillate, perfusate, and pleural bath.

**DISCUSSION**

During congestive heart failure with increased Pla, patients can develop cardiogenic pulmonary edema. Recently, it has been shown that, in animal models of increased pulmonary vascular pressures, there is not only increased edema formation but also impairment of alveolar fluid reabsorption (7, 22, Saldias et al., unpublished observations). Additionally, in some patients with hydrostatic pulmonary edema, the alveolar fluid reabsorption was preserved, whereas in other patients, the ability to clear edema was impaired (35). We reason that, in patients suffering from chronic heart failure, the neurohumoral axis is activated, which results in increased endogenous catecholamines (8, 10, 30). Thus it is possible that, in patients with increased levels of endogenous catecholamines, alveolar fluid reabsorption was inhibited in rat lungs perfused with 5 × 10⁻⁴ M ouabain (OUAB) and/or instilled with 10⁻⁴ M amiloride (AMI). DA did not stimulate clearance in the presence of these antagonists (AMI vs. AMI + DA, OUAB vs. OUAB + DA, OUAB + AMI vs. OUAB + AMI + DA), P > 0.05. Bars represent means ± SE. *P < 0.05 vs. DA-treated rats and both CT groups; †P < 0.001 vs. CT group and DA groups exposed to Pla 15 cmH₂O.
tion is preserved (20, 21). We report here that, in an isolated rat lung model with acute increase in Pla, there was decreased alveolar fluid reabsorption. Our data are concordant with a previous report showing that the alveolar fluid clearance was normal in sheep exposed to moderate left atrial hypertension. In contrast, in adrenalectomized sheep where the secretion of endogenous catecholamines was abolished, the clearance was significantly reduced (7).

DA has been used clinically to induce natriuresis in patients with pulmonary edema by inhibiting the Na\(^+\)-K\(^+\)-ATPase activity in the renal tubular epithelium (17). In contrast, DA enhanced active Na\(^+\) transport and increased alveolar fluid reabsorption in normal rat lungs and in a model of lung injury induced by exposure of rats to 100% oxygen for 64 h (3, 27). In accord with these data, we are reporting that, in a model of increased Pla, DA, via the D\(_1\) receptors, and ISO, via \(\beta\)-adrenergic receptors, increased alveolar fluid reabsorption. These effects were blocked by the D\(_1\)-receptor antagonist SCH-23390 and increased by the \(\beta\)-agonist fenoldopam (Fig. 2A). The \(\beta\)-adrenergic-receptor antagonist propranolol did not inhibit the stimulatory effects of DA (Fig. 2B). These results suggest that the DA effects in this model are mediated by the dopaminergic (D\(_1\)) and not the \(\beta\)-adrenergic pathway.

The effects of DA and ISO were inhibited by ouabain and amiloride, confirming that \(\beta\)-adrenergic and dopaminergic agonists increase lung edema clearance by stimulating the alveolar epithelial Na\(^+\)-K\(^+\)-ATPase function and amiloride-sensitive Na\(^+\) pathways in rat lungs with increased Pla (Fig. 3), as has been previously reported in control rats (3, 4, 28). Upregulation of Na\(^+\)-K\(^+\)-ATPase function could be due to increased transcription, translation, protein assembly, recruitment, and translocation to the plasma membrane from intracellular pools and metabolic activation (5, 6).

Recent studies have suggested that the cell microtubular transport system and cytoskeleton proteins are involved in Na\(^+\) pump recruitment from intracellular pools to the plasma membrane (6). Therefore, we tested in physiological experiments whether the stimulatory effects of DA and ISO in rat lungs exposed to increased Pla occur by stimulation of preexisting membrane-bound Na\(^+\) pumps or by recruitment of Na\(^+\)-K\(^+\)-ATPase proteins from intracellular pools to the cell plasma membrane. We reasoned that cell microtubular transport disruption by colchicine could provide information about whether the stimulatory effects of DA and ISO on active Na\(^+\) transport and lung edema clearance in rat lungs with increased Pla could be due to Na\(^+\) pump recycling. We indeed observed that colchicine inhibited DA stimulation of edema clearance in rat lungs with increased Pla (Fig. 4). Meanwhile, the isomer \(\beta\)-lumicolchicine, which shares many colchicine properties with the exception of inhibiting cell microtubular transport (27, 28), did not inhibit the DA modulation of lung edema clearance. These results suggest that, in a model of increased Pla, DA and ISO upregulation of lung edema clearance is mediated by recruitment of Na\(^+\) pumps from intracellular pools to the plasma membrane of alveolar epithelial cells.

The data presented in this report support the notion that increased pulmonary capillary hydrostatic pressures represent a model of lung injury that impairs

### Table 1. Alveolar epithelial permeability to small solutes

<table>
<thead>
<tr>
<th>Left Atrial Pressure, cmH(_2)O</th>
<th>Sodium Flux, ml/h</th>
<th>Mannitol Flux, ml/h</th>
<th>Albumin Flux, ml/h</th>
<th>Perfusate Flow, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 0</td>
<td>1.07 ± 0.16(^a)</td>
<td>0.52 ± 0.03(^a)</td>
<td>0.04 ± 0.01(^\dagger)</td>
<td>9.0 ± 1.3</td>
</tr>
<tr>
<td>Dopamine 15</td>
<td>1.89 ± 0.27</td>
<td>0.94 ± 0.21</td>
<td>0.11 ± 0.02</td>
<td>11.7 ± 0.2</td>
</tr>
<tr>
<td>Fenoldopam 15</td>
<td>2.01 ± 0.17</td>
<td>0.84 ± 0.09</td>
<td>0.09 ± 0.01</td>
<td>12 ± 0.0</td>
</tr>
<tr>
<td>SCH-23390+ dopamine 15</td>
<td>1.54 ± 0.06</td>
<td>0.69 ± 0.09</td>
<td>0.17 ± 0.02</td>
<td>11.4 ± 0.5</td>
</tr>
<tr>
<td>Propranolol 15</td>
<td>2.50 ± 0.30</td>
<td>1.05 ± 0.17</td>
<td>0.12 ± 0.01</td>
<td>12 ± 0.0</td>
</tr>
<tr>
<td>Dopamine + propranolol 15</td>
<td>1.91 ± 0.35</td>
<td>0.78 ± 0.09</td>
<td>0.13 ± 0.03</td>
<td>10 ± 0.5</td>
</tr>
<tr>
<td>Amiloride 15</td>
<td>2.19 ± 0.31</td>
<td>1.08 ± 0.17</td>
<td>0.13 ± 0.03</td>
<td>12 ± 0.0</td>
</tr>
<tr>
<td>Dopamine + amiloride 15</td>
<td>1.87 ± 0.21</td>
<td>0.88 ± 0.02</td>
<td>0.15 ± 0.03</td>
<td>11.5 ± 0.5</td>
</tr>
<tr>
<td>Ouabain 15</td>
<td>1.61 ± 0.13</td>
<td>0.70 ± 0.08</td>
<td>0.10 ± 0.02</td>
<td>11.4 ± 0.6</td>
</tr>
<tr>
<td>Dopamine + ouabain 15</td>
<td>2.04 ± 0.31</td>
<td>1.13 ± 0.19</td>
<td>0.18 ± 0.02</td>
<td>11.5 ± 0.5</td>
</tr>
<tr>
<td>Ouabain + amiloride 15</td>
<td>1.76 ± 0.15</td>
<td>0.74 ± 0.06</td>
<td>0.11 ± 0.02</td>
<td>11.6 ± 0.4</td>
</tr>
<tr>
<td>Dopamine + ouabain + amiloride</td>
<td>1.58 ± 0.07</td>
<td>0.58 ± 0.06</td>
<td>0.09 ± 0.01</td>
<td>10.7 ± 0.9</td>
</tr>
<tr>
<td>Colchicine 15</td>
<td>1.83 ± 0.08</td>
<td>0.71 ± 0.12</td>
<td>0.10 ± 0.01</td>
<td>9.5 ± 1.6</td>
</tr>
<tr>
<td>Lumicolchicine 15</td>
<td>2.12 ± 0.24</td>
<td>0.94 ± 0.10</td>
<td>0.21 ± 0.02</td>
<td>11 ± 0.5</td>
</tr>
<tr>
<td>Dopamine + colchicine 15</td>
<td>1.89 ± 0.26</td>
<td>0.95 ± 0.23</td>
<td>0.19 ± 0.03</td>
<td>9.4 ± 0.9</td>
</tr>
<tr>
<td>Dopamine + lumicolchicine 15</td>
<td>1.71 ± 0.38</td>
<td>0.69 ± 0.04</td>
<td>0.19 ± 0.03</td>
<td>10 ± 1.3</td>
</tr>
<tr>
<td>Albumin Flux, ml/h</td>
<td>0.16* 0.52</td>
<td>*0.27 0.94</td>
<td>*0.09 0.17</td>
<td>11.7 ± 0.3</td>
</tr>
<tr>
<td>Mannitol Flux, ml/h</td>
<td>0.10* 0.35</td>
<td>0.06 1.07</td>
<td>0.17 0.84</td>
<td>10.1 ± 0.5</td>
</tr>
<tr>
<td>Sodium Flux, ml/h</td>
<td>0.06 0.30</td>
<td>0.15 1.05</td>
<td>0.12 0.94</td>
<td>11.5 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. Passive movement of small solutes across the epithelial barrier of rat lungs exposed to left atrial pressure (Pla) of 15 cmH\(_2\)O did not change significantly in study groups vs. control rat lungs with increased Pla. However, they were increased significantly in control and dopamine (DA) groups with Pla 15 cmH\(_2\)O vs. rat lungs with normal pulmonary circulation pressures. Albumin movement increased significantly in control and DA groups with Pla 15 cmH\(_2\)O vs. rat lungs with Pla 0 cmH\(_2\)O. In rat lungs with Pla 15 cmH\(_2\)O, there were no significant differences in albumin flux (\(P > 0.05\)) among study groups. Perfusate flow did not change significantly in all study groups (\(P > 0.05\)). *\(P < 0.05\) vs. rat lungs with Pla 15 cmH\(_2\)O.
alveolar fluid reabsorption. Our data agree with reports in sheep (7, 11) and rats (Saldias et al., unpublished observations) in which the rate of alveolar fluid reabsorption was impaired when hydrostatic pulmonary circulation pressures were increased.

The epithelial permeability to small solutes and to albumin was slightly increased compared with rats groups with normal Pla. These observations are similar to studies in which increased permeability of tracers across the alveolocapillary barrier was reported when Pla increased (19, 34, 36). We reason that this is possibly due to capillary stress failure or stretch pore phenomena that may transiently affect the permeability of the alveolocapillary barrier (2, 36).

This report demonstrates the beneficial effects of DA and ISO by improving alveolar fluid reabsorption in a model of increased hydrostatic pulmonary circulation pressures. Left heart failure with resultant decrease in effective arterial volume is characterized mainly by decreased cardiac output and left atrial enlargement (1, 14). Consequently, this may lead to increased levels of atrial natriuretic peptides, angiotensin II, endothelin, and possibly endogenous ouabain-like substances (12, 15, 24, 30). It has been reported that atrial natriuretic peptides instilled in the rat air spaces decreased the active Na\(^+\) transport and alveolar fluid reabsorption (18, 33). Also, endogenous ouabain-like substances may decrease alveolar fluid reabsorption by inhibiting alveolar Na\(^+\)-K\(^+\)-ATPase. We reason that DA and ISO can counteract these decreases in active Na\(^+\) transport and increase alveolar fluid reabsorption.

In summary, we report that DA and ISO increase alveolar fluid reabsorption in a model of increased Pla. The effects of DA are mediated by the activation of dopaminergic D\(_1\) receptors, whereas the effects of ISO are mediated by the activation of \(\beta\)-adrenergic receptors that cause an upregulation of the amiloride-sensitive Na\(^+\) pathways and Na\(^+\)-K\(^+\)-ATPase. This new information is of potential clinical relevance in the treatment of patients with cardiogenic pulmonary edema.

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