Isoproterenol improves ability of lung to clear edema in rats exposed to hyperoxia

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1Division of Pulmonary and Critical Care Medicine, Michael Reese Hospital, University of Illinois at Chicago, Chicago, Illinois 60616; and 2Departamento de Enfermedades Respiratorias, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Saldíás, F. J., A. Comellas, K. M. Ridge, E. Lecuona, and J. I. Sznaider. Isoproterenol improves ability of lung to clear edema in rats exposed to hyperoxia. J. Appl. Physiol. 86(6): 30–35, 1999.—Exposure of adult rats to 100% O2 results in lung injury and decreases active sodium transport and lung edema clearance. It has been reported that β-adrenergic agonists increase lung edema clearance in normal rat lungs by upregulating alveolar epithelial Na+-K+-ATPase function. This study was designed to examine whether isoproterenol (Iso) increases lung edema clearance in rats exposed to 100% O2 for 64 h. Active Na+ transport and lung edema clearance decreased by ~44% in rats exposed to acute hyperoxia. Iso (10^-5 M) increased the ability of the lung to clear edema in room-air-breathing rats (from 0.50 ± 0.02 to 0.99 ± 0.05 ml/h) and in rats exposed to 100% O2 (from 0.28 ± 0.03 to 0.86 ± 0.09 ml/h; P < 0.001). Disruption of intracellular microtubular transport of ion-transporting proteins by colchicine (0.25 mg/100 g body wt) inhibited the stimulatory effects of Iso in hyperoxia-injured rat lungs, whereas the isomer β-lumicolchicine, which does not affect microtubular transport, did not inhibit active Na+ transport stimulated by Iso. Accordingly, Iso restored the lung’s ability to clear edema after hyperoxic lung injury, probably by stimulation of the recruitment of ion-transporting proteins (Na+-K+-ATPase) from intracellular pools to the plasma membrane in rat alveolar epithelium.

active sodium transport; sodium-potassium-adenosinetriphosphatase; oxidant lung injury; β-adrenergic

IN MAMMALS, it has been shown that prolonged exposure to high concentrations of O2 produces lung injury and pulmonary edema and also increases lung permeability to solutes (6, 15, 18). O2 toxicity primarily affects lung capillaries; meanwhile, the alveolar epithelium appears to be more resistant to oxidant injury (9). The precise concentration of O2 that is toxic to the lung is related to age, nutrition, and animal species’ sensitivity to hyperoxia (15, 18, 19). It has been shown that adult rats exposed to 100% O2 develop lung injury after ~60 h, and almost all die after ~72 h of exposure (9, 24, 25).

Pulmonary edema resolution is effected mostly by active Na+ transport across the alveolar epithelium (22, 26, 29). Na+ is actively transported across alveolar epithelial cells predominantly by the apical Na+ channels and basolaterally located Na+-K+-ATPase (21, 22, 29, 31). We have previously shown that active Na+ transport and lung edema clearance decrease in rats exposed to 100% O2 for 64 h, which was associated with decreased Na+-K+-ATPase activity in alveolar epithelial type II (ATII) cells (23). Previous studies that used either isolated lung or ATII cell preparations have also confirmed that alveolar epithelial Na+ transport (14, 17) and Na+-K+-ATPase activity in ATII cells are inhibited by exposure to O2-derived free radicals (7, 10).

It has been reported that the β-adrenergic agonists terbutaline and isoproterenol (Iso) increase active Na+ transport and lung edema clearance by stimulating the Na+-K+-ATPase function in the alveolar epithelium of healthy rats (8, 16, 28, 30). Recent studies have also suggested that β-adrenergic agonists stimulate lung edema clearance in hyperoxic-injured rat lungs (13, 20). However, the mechanisms involved in β-adrenergic stimulation of lung edema clearance after hyperoxic lung injury have not been completely elucidated.

This study was designed to examine mechanisms by which the β-adrenergic agonist Iso affects lung edema clearance in rats exposed to 100% O2 for 64 h. In the isolated-perfused rat lung model, we demonstrate that, in hyperoxic-injured rat lungs, Iso restores the ability of the lung to clear edema. Experiments in rats treated with colchicine and β-lumicolchicine suggest that the stimulatory effects of Iso are mediated by recruitment and translocation of ion-transporting proteins from intracellular pools to the plasma membrane of alveolar epithelial cells.

MATERIALS AND METHODS

Pathogen-free, male Sprague-Dawley rats weighing 280–320 g were purchased from Harlan Sprague-Dawley (Indianapolis, IN). A total of 80 rat lungs was studied. The animals were provided food and water ad libitum and were maintained on 12:12-h light-dark cycle. Iso, ouabain, colchicine, and β-lumicolchicine were purchased from Sigma Chemical (St. Louis, MO).

Specific protocols. Twenty-eight room-air-exposed rats were studied in the isolated-perfused rat lung model in three groups. Group A was room-air-breathing control rat lungs (n = 10); group B was rat lungs perfused with 10^-6 M Iso through the pulmonary circulation (n = 6). In group C, to evaluate the alveolar epithelial Na+ transport pathway, we studied the effect of the Na+-K+-ATPase antagonist ouabain (5 x 10^-4 M) perfused through the pulmonary circulation alone or associated with 10^-6 Iso (n = 6 in each group).

Fifty-two rats were exposed to 100% O2 for 64 h and were maintained in a 68 x 99 x 83-cm forced-air environmental chamber. O2 concentration in the chamber was continuously monitored with an Oxycheck Critikon (McNeil Laboratories, Irvine, CA). After 64 h of O2 exposure, the rats were studied in four groups. In group D, rat lungs were exposed to 100% O2 for 64 h (n = 10); in group E, hyperoxic rat lungs were...
perfused with 10^{-6} \text{ M Iso} through the pulmonary circulation (n = 6); and in group F, hyperoxic rat lungs were perfused with ouabain (5 \times 10^{-4} \text{ M}) through the pulmonary circulation alone or associated with 10^{-6} \text{ M Iso} (n = 6 in each group). In group G, to examine the possible role of the intracellular microtubular transport system on the stimulatory effects of Iso in hyperoxic rat lungs, we studied lung-liquid clearance in rats previously treated with the inhibitor of microtubule polymerization (colchicine; 0.25 mg/100 g body wt ip \sim 15 h before experiments) alone (n = 6) or associated with 10^{-6} \text{ M Iso} added into the perfusate (n = 6). We also studied the effects of \beta-lumicolchicine (0.25 mg/100 g body wt \sim 15 h before experiments) in the \beta-adrenergic stimulation of lung clearance (n = 6 in each group). The isomer \beta-lumicolchicine does not bind tubulin and does not affect intracellular microtubular transport, but it shares other properties of colchicine, such as inhibition of protein synthesis (34). It is therefore considered an appropriate control to demonstrate that colchicine effects are due to microtubular disruption. The inhibitory effect of colchicine, but not lumicolchicine, on the cell microtubular transport system has been previously reported on bile secretion and hepatic ultrastructure studies (11) and lung edema clearance modulation by \beta-adrenergic agonists in healthy rats (28).

Isolated lungs. The isolated lung preparation was performed as previously described (23, 26, 28). Briefly, rats were anesthetized with pentobarbital sodium (50 mg/kg body wt), tracheotomized, and mechanically ventilated with a tidal volume of 2.5 ml, peak airway pressure of 8 cmH\textsubscript{2}O, and 100% O\textsubscript{2} for 5 min. To degas the lungs, ventilation was stopped, and the tracheal catheter was closed. The chest was opened via a median sternotomy, and 400 U heparin sodium was injected before experiments) alone (\text{BSA}) solution that contained (in mM) 135.5 Na\textsuperscript{+}, 119.1 Cl\textsuperscript{-}, 25 HCO\textsubscript{3}\textsuperscript{-}, 4.1 K\textsuperscript{+}, 2.8 Mg\textsuperscript{2+}, 2.5 Ca\textsuperscript{2+}, 0.8 SO\textsubscript{4}\textsuperscript{2-}, 8.3 glucose, and 3% bovine albumin, with an osmolality of 300 mosmol/kgH\textsubscript{2}O. The pH of the perfusate was monitored continuously throughout the experiment. If the pH deviated from 7.40, then a mixture of 5% CO\textsubscript{2}-95% O\textsubscript{2} was bubbled into the perfusate until the desired pH was obtained. Two sequential bronchoalveolar lavages (BAL) were performed with 3 ml of BSA solution that contained 0.1 mg/ml Evans blue dye (EBD; Sigma Chemical), 0.02 \mu Ci/ml \text{^{22}Na}\textsuperscript{+} (Du Pont-New England Nuclear, Boston, MA), and 0.12 \mu Ci/ml \text{^{3}H} mannitol (Du Pont-New England Nuclear). The epithelial lining fluid (ELF) volume was estimated by the dilution of EBD in the first BAL. The lungs were then instilled with the volume necessary to leave 5 ml in the alveolar space. Finally, the lungs were immersed in a "pleural bath" reservoir containing 100 ml BSA solution maintained at 37°C. This allowed us to follow markers that had moved across the pleural membrane or were drained by the lung lymphatics. Perfusion of the lungs was performed with 90 ml of the same BSA solution containing 0.16 \mu Ci/ml fluorescein-tagged albumin (FITC-albumin, Sigma Chemical). The perfusate was pumped from a lower reservoir to an upper reservoir by a peristaltic pump, and from there it flowed through the pulmonary artery and exited via the left atrium. Pulmonary artery and left atrial pressures were maintained at 12 and 0 cmH\textsubscript{2}O and recorded via a pressure transducer with a zero reference point at the level of the left atrium. Pulmonary artery and left atrial pressures were recorded continuously in a multichannel recorder (Gould 3000 oscillograph recorder, Gould, Cleveland, OH). Pulmonary circulation pressures and flow rates were measured periodically during the experiments.

Samples were drawn from the three reservoirs: air-space instillate, pleural bath, and perfusate at 10 and 70 min after the experimental protocol was started. To ensure homogeneous sampling from the air spaces, 2 ml of instillate were aspirated and reintroduced into the air spaces three times before removing each sample. All samples were centrifuged at 1,000 g for 15 min. Colorimetric analysis of the supernatant for EBD (absorbance at 620 nm) was performed in a model U2000 spectrophotometer (Hitachi Instruments, San Jose, CA). Analysis of FITC-albumin (excitation 487 nm and emission 520 nm) was performed in a fluorescence spectrometer (model LS-3B, Perkin-Elmer, Oakbrook, IL). \text{^{22}Na}\textsuperscript{+} and \text{^{3}H}mannitol were measured in a beta-scintillation counter (Packard Tricarb, Downers Grove, IL). Because the energy spectra overlapped, a series of calibration and quenching curves was specifically developed for accurate measurement of \text{^{22}Na}\textsuperscript{+} and \text{^{3}H} within the same sample by using a scintillation counter.

Calculations. The alveolar lining fluid volume (VELF) was calculated by instilling 3 ml of fluid (V\textsubscript{0}) containing a known concentration of albumin (\text{[EBD]}\textsubscript{0}), tagged by EBD into the air space. After brief mixing occurred, a sample was removed, and the \text{[EBD]} at time t (\text{[EBD]}\textsubscript{t}) was estimated. The amount of EBD is the same in the instillate (V\textsubscript{0} \text{[EBD]}\textsubscript{0}) and in the lung after initial mixing (V\textsubscript{0} + VELF \text{[EBD]}\textsubscript{0}). Equating the two yields

\[ V\text{[EBD]}\textsubscript{0} = V\text{[EBD]}\textsubscript{0} + VELF \]  

or

\[ VELF = V\text{[EBD]}\textsubscript{0} / \text{[EBD]}\textsubscript{t} - V\textsubscript{0} \]  

Similarly, the alveolar fluid volume at time t is estimated by

\[ V\textsubscript{t} = V\text{[EBD]}\textsubscript{0} / \text{[EBD]}\textsubscript{t} \]  

The movement of Na\textsuperscript{+} from the alveolar space during a defined period of time is assumed to be accompanied by isotonic water flux and is given by

\[ J\textsubscript{Na,net} = J\textsubscript{Na,net} - J\textsubscript{Na,net} \]  

where \text{JNa,net} is the net or active Na\textsuperscript{+} transport, \text{JNa,net} is the total or unidirectional Na\textsuperscript{+} outflux from the rat air spaces, and \text{JNa,net} is the passive, bidirectional flux of Na\textsuperscript{+} between the air space and the other compartments. The volume flux \text{J} = J\textsubscript{Na,net}/[Na\textsuperscript{+}] is the average rate of change in the volume and is given by

\[ J = (V\textsubscript{t} - V\textsubscript{0}) / t \]  

As described by Rutschman et al. (26), the passive movement of \text{^{22}Na}\textsuperscript{+} (\text{JNa,net}) is given by

\[ J\textsubscript{Na,net} = [Na\textsuperscript{+}] \times (\text{ln C\textsubscript{t}} - \text{ln C\textsubscript{0}}) / (\text{ln V\textsubscript{t}} - \text{ln V\textsubscript{0}}) \]  

where C\textsubscript{t} is the \text{^{22}Na}\textsuperscript{+} concentration at time t and [Na\textsuperscript{+}] is the constant Na\textsuperscript{+} concentration in the BSA solution.

Similarly, the volume flux of mannitol (typically expressed as PA, permeability-surface area product) is given by

\[ PA = J (\text{ln M\textsubscript{1}} - \text{ln M\textsubscript{2}}) / (\text{ln V\textsubscript{1}} - \text{ln V\textsubscript{2}}) \]  

where M\textsubscript{1} is the \text{^{3}H} mannitol mass at time t.

Albumin flux from the pulmonary circulation into the alveolar space was determined from the fraction of FITC-albumin that appears in the alveolar space during the experimental protocol. These calculations were carried out for each sampling period.
increased after hyperoxic lung injury in rats (Table 1). Due to significant increases in the alveolar epithelial permeability to small solutes in room-air-exposed rats (28, 30), EBD-bound albumin instilled in the air space was not detected in the perfusate or bath compartments in any of the experimental groups. However, the movement of albumin from the pulmonary circulation into the alveolar space significantly increased in animals exposed to hyperoxia, and it was not modified by Iso or ouabain added to the perfusate (Fig. 3).

The movement of protein tracers across the alveolar epithelial barrier was similar to the previously reported rates in normal and injured rat lungs (16, 23, 26, 28, 30). EBD-bound albumin instilled in the air space was not detected in the perfusate or bath compartments in any of the experimental groups. However, the movement of albumin from the pulmonary circulation into the alveolar space significantly increased in animals exposed to hyperoxia, and it was not modified by Iso or ouabain added to the perfusate (Fig. 3).

Results were considered significant when the F statistic indicated significance. When comparisons were made between two experimental groups, an unpaired Student’s t-test was used. When multiple comparisons were made, a one-way analysis of variance was used, followed by a multiple-comparison test (Tukey test) when the F statistic indicated significance. Results were considered significant when P < 0.05.

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Unidirectional Na⁺ Flux, ml/h</th>
<th>Perfusate Flow, ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>1.58 ± 0.05</td>
<td>10.3 ± 0.9</td>
</tr>
<tr>
<td>Iso, 10⁻⁶ M</td>
<td>6</td>
<td>2.64 ± 0.13</td>
<td>9.8 ± 0.8</td>
</tr>
<tr>
<td>Ouab, 5 × 10⁻⁴ M</td>
<td>6</td>
<td>1.22 ± 0.10</td>
<td>11.8 ± 0.9</td>
</tr>
<tr>
<td>Ouab + Iso</td>
<td>6</td>
<td>1.45 ± 0.20</td>
<td>11.2 ± 0.6</td>
</tr>
<tr>
<td>Hyperoxia, 100% O₂</td>
<td>10</td>
<td>2.89 ± 0.35*</td>
<td>10.3 ± 0.8</td>
</tr>
<tr>
<td>100% O₂ + Ouab</td>
<td>6</td>
<td>1.77 ± 0.33</td>
<td>11.8 ± 0.2</td>
</tr>
<tr>
<td>100% O₂ + Ouab + Iso</td>
<td>6</td>
<td>2.52 ± 0.37</td>
<td>11.5 ± 0.4</td>
</tr>
<tr>
<td>100% O₂ + Col</td>
<td>6</td>
<td>3.95 ± 0.88†</td>
<td>11.0 ± 0.8</td>
</tr>
<tr>
<td>100% O₂ + Lumic</td>
<td>6</td>
<td>3.29 ± 0.28**</td>
<td>11.0 ± 1.0</td>
</tr>
<tr>
<td>100% O₂ + Lumic + Iso</td>
<td>6</td>
<td>3.31 ± 0.65*</td>
<td>10.8 ± 0.8</td>
</tr>
<tr>
<td>100% O₂ + Lumic + Ouab</td>
<td>6</td>
<td>3.17 ± 0.31*</td>
<td>11.2 ± 0.8</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of animals. Iso, isoproterenol; Ouab, ouabain; Col, colchicine; Lumic, β-lumicolchicine. Significant difference compared with room-air-breathing control rats, *P < 0.05 and †P < 0.01.

The movement of protein tracers across the alveolar epithelial barrier was similar to the previously reported rates in normal and injured rat lungs (16, 23, 26, 28, 30). EBD-bound albumin instilled in the air space was not detected in the perfusate or bath compartments in any of the experimental groups. However, the movement of albumin from the pulmonary circulation into the alveolar space significantly increased in animals exposed to hyperoxia, and it was not modified by Iso or ouabain added to the perfusate (Fig. 3).

The active Na⁺ transport and lung edema clearance decreased by ~44% in rats exposed to acute hyperoxia compared with room-air-breathing rats (P < 0.01). Iso perfused through the pulmonary circulation increased lung edema clearance, both in room-air-breathing rats (from 0.50 ± 0.02 to 0.99 ± 0.05 ml/h) and rats exposed to 100% O₂ for 64 h (from 0.28 ± 0.03 to 0.86 ± 0.09 ml/h; Fig. 4). The Na⁺-K⁺-ATPase antagonist ouabain inhibited the alveolar epithelial Na⁺ transport stimulated by Iso in control and hyperoxic-injured rat lungs (Fig. 5). Pulmonary artery pressures and flow rates did not change significantly after hyperoxic lung injury in rats (Table 1).
not change with the administration of Iso or ouabain in any experimental group (Table 1).

Active Na\textsuperscript{+} transport and lung edema clearance stimulated by Iso were completely inhibited by colchicine disruption of the cell microtubular transport pathway in hyperoxia-injured rat lungs; meanwhile, the isomer \(\beta\)-lumicolchicine did not affect lung edema clearance modulation by Iso (Fig. 6).

DISCUSSION

Prolonged exposure to high concentrations of \(O_2\) causes lung injury and pulmonary edema and impairs the ability of the lung to exchange \(O_2\) and \(CO_2\) (6, 15, 18). Pulmonary edema is cleared out of the alveolar space by active Na\textsuperscript{+} transport across alveolar epithelial cells, whereas water moves passively, following the ionic gradient through water channels localized in the alveolar epithelium (21, 22, 29, 31). The alveolar epithelium regulates fluid and solute flux across the alveolar-capillary barrier in normal and pathological conditions (13, 16, 20, 23, 26, 28, 30, 33).

It has been reported that acute exposure to hyperoxia decreases alveolar epithelial Na\textsuperscript{+} transport and lung edema clearance in rats, probably due to inhibition of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity in the alveolar epithelium (23). Previous studies have also reported that \(O_2\)-derived free radicals decrease the Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity in isolated-perfused rat lungs (10) and in cultured rat ATII cells (7). It has also been shown that peroxynitrite exposure inhibits \(O_2\) consumption and active Na\textsuperscript{+} transport in ATII cells (14). On the other hand, several studies have demonstrated the ability of \(\beta\)-adrenergic agonists to stimulate active Na\textsuperscript{+} transport and lung edema clearance in normal and injured rat lungs (8, 13, 16, 20, 28, 30). In the present study, we evaluated whether the \(\beta\)-adrenergic agonist Iso could stimulate alveolar epithelial Na\textsuperscript{+} transport in hyperoxic rat lungs, and we examined mechanisms involved in Iso stimulation of lung edema clearance.

We have confirmed that hyperoxia causes pulmonary edema in adult rats, as corroborated by the presence of pleural fluid in the thoracic cavity (volume: 9.1 ± 0.6 ml) and a three- to fourfold increase in the alveolar ELF volume after 64 h of exposure to 100% \(O_2\). The lung permeability to small solutes (Na\textsuperscript{+}, mannitol) and large solutes (albumin) significantly increased after hyperoxia-induced lung injury, probably because of damage of lung capillaries (9, 23, 25, 33, 35). The different results that were obtained with the EBD-albumin and FITC-albumin assay probably represent a higher sensi-
It has been reported that β-adrenergic agonists increase active Na\(^+\) transport and Na\(^+\) pump activity by upregulating the Na\(^+\)-K\(^+\)-ATPase function in ATII cells and lungs of healthy rats (8, 16, 28, 30, 32). Recently, it has been shown that the β-adrenergic agonist terbutaline increases edema clearance in a milder lung-injury model, in which rats were exposed to 100% O\(_2\) for 40 and 60 h (13, 20). In the present study, we also report that the β-adrenergic agonist Iso increases lung edema clearance in a more severe model of hyperoxic lung injury. The stimulatory effect of Iso was proportional larger in rats exposed to 100% O\(_2\) compared with the effect in normoxic rats (−203 and 100% over basal lung clearance, respectively) and restored the ability of the lungs to clear edema to levels similar to those in normal lungs. The effects of Iso were completely inhibited by ouabain, confirming that β-adrenergic agonists increase lung edema clearance by stimulating the alveolar epithelial Na\(^+\)-K\(^+\)-ATPase function in hyperoxic-injured rat lungs, as previously reported in room-air-breathing rats (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 (1, 2, 4, 5). 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 (1, 2, 4). Therefore, we tested, in physiological experiments, whether the stimulatory effects of Iso in hyperoxic-injured rats 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 Iso on active Na\(^+\) transport and lung edema clearance in hyperoxic-injured rat lungs could be caused by recycling of Na\(^+\) pumps. Indeed, we observed that colchicine inhibited Iso stimulation of edema clearance in hyperoxic-injured rat lungs (Fig. 6). Meanwhile, the isomer β-lumicolchicine, which shares many colchicine properties with the exception of inhibition of cell microtubular transport (34), did not inhibit the β-adrenergic modulation of lung edema clearance. These results suggest that, in hyperoxia-injured rat lungs, Iso upregulation of lung edema clearance is mediated by recruitment of Na\(^+\) pumps from intracellular pools to the plasma membrane of alveolar epithelial cells.

We have previously reported that Iso increases lung edema clearance in healthy rats by stimulating the recruitment of Na\(^+\)-K\(^+\)-ATPase proteins to the basolateral membrane of ATII cells (28). The stimulatory effect of Iso on lung edema clearance and Na\(^+\)-K\(^+\)-ATPase function was completely blocked by colchicine disruption of cell microtubular transport system (28). It is known that colchicine interferes with intracellular microtubules’ polymerization by induction of structural changes in the microtubule subunit protein, tubulin. Recent studies have also shown that microtubules are involved in intracellular trafficking of vesicles to the apical and basolateral pole of the cell, and depolymerization of microtubules by colchicine may induce redistribution of ion-transporting proteins in polarized cells (3).

Recently, Bertorello et al. (2) have also shown that Iso increases alveolar epithelial Na\(^+\)-K\(^+\)-ATPase activity by promoting the α-subunit protein insertion in the plasma membrane of rat ATII cells. The recruitment of Na\(^+\) pumps from intracellular pools to the basolateral membrane of ATII cells was prevented by stabilizing the cortical actin cytoskeleton with phallacidin or by blocking anterograde transport with brefeldin A.

O\(_2\) toxicity produces extensive damage to capillary endothelial cells and thus increases lung capillary permeability to solutes, whereas alveolar epithelial cells are more resistant to oxidant injury (9). This might explain the fact that alveolar epithelial cell Na\(^+\)-K\(^+\)-ATPase is not significantly damaged after hyperoxic lung injury, and the Na\(^+\) pump proteins are rather internalized to intracellular compartments ready to be recruited back by the appropriate stimulus, such as β-adrenergic agonists or dopamine (2, 27, 28). It has been previously reported that the Na\(^+\)-K\(^+\)-ATPase α\(_1\)-subunit protein abundance decreases by −35% in ATII cells after 100% O\(_2\) exposure for 60 h (5). Our study shows that hyperoxia decreases Na\(^+\) transport in the alveolar epithelium and that Iso stimulates lung edema clearance, probably by recruitment of Na\(^+\)-K\(^+\)-ATPase proteins from intracellular reservoirs to the plasma membrane of alveolar epithelium.

In summary, this study demonstrates that the β-adrenergic agonist Iso restores the ability of the lung to clear edema after hyperoxic lung injury in rats. Conceivably, Iso stimulation of lung edema clearance is mediated by recruitment of Na\(^+\)-K\(^+\)-ATPase from intracellular pools to the plasma membrane in the alveolar epithelium. Accordingly, Iso could be useful to accelerate the resolution of pulmonary edema and thus may be beneficial in the management of patients with acute, hypoxemic respiratory failure.

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REFERENCES


