Halothane Decreases Na,K-ATPase, and Na Channel Activity in Alveolar Type II Cells

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Background: Halothane alters surfactant biosynthesis and metabolism of alveolar type II cells. In addition to synthesizing surfactant, alveolar type II cells actively transport sodium (Na) from the alveolar space to the interstitium. Na enters the cells through amiloride-sensitive Na channels or Na cotransporters and is extruded by a Na pump. The purpose of this study was to examine the effects of halothane on Na transport activities.

Methods: Epithelial type II cells from adult rat lungs were exposed to halothane concentrations of 1, 2, and 4% from 0.5–4 h. In some experiments, cells that were exposed to 1% halothane for 1 h were allowed to recover after replacement of the medium for 15 and 30 min. Na transport was then evaluated by direct measurement of radiolabeled ions uptake. In addition, the effects of halothane were assessed in the absence of extracellular calcium (Ca) with or without 1,2-bis(2-amino-phenoxy)ethane-N,N,N′,N′-tetraacetic acid, an intracellular Ca chelating agent.

Results: Exposure of epithelial type II cells to halothane reduced the activity of sodium, potassium-adenosine triphosphatase, and amiloride-sensitive Na channels, whereas Na cotransporters were unchanged. The decrease in sodium, potassium-adenosine triphosphatase activity was maximal for 30 min of exposure and reached 50, 42, and 56% for halothane concentrations of 1, 2, and 4%, respectively, and did not change for longer exposure times. This effect was not pre-

vented by either the absence of extracellular Ca or 1,2-bis(2-amino-phenoxy)ethane-N,N,N′,N′-tetraacetic acid pretreatment. Exposure for 45 min to 1% halothane also decreased Na channel activity by 46%. These effects were completely reversible after 30 min of recovery.

Conclusions: Sodium, potassium-adenosine triphosphatase, and amiloride-sensitive Na channel activities are impaired by halothane in alveolar type II cells in vitro. This inhibition could reduce transepithelial Na transport. (Key words: Halogenated anesthetic; lung; sodium channels.)

HALOTHANE and the volatile anesthetic agents can modulate ion channel function or ion transport in different tissues. 1, 2 Because of the hypnotic effects of these agents, attention has focused mainly on the central nervous system, and several studies have reported that halothane exposure depressed voltage-gated sodium (Na) channels and potassium (K) channels. 1, 2 Recently, however, halothane was shown to inhibit Na/calcium (Ca) exchanger and Ca channels in heart cells 3 and to decrease ion transport in canine tracheal epithelium, an effect that may contribute to decreased mucous clearance in the perioperative period. 4 Taken together, these studies suggest that halothane interferes with ion transport in many different cell types. 5 Lung alveolar epithelium is directly exposed to volatile anesthetic agents; however, little information is available regarding the effects of halothane on pulmonary cell function. Alveolar type II (ATII) cells play a major role in the maintenance of the structural and functional integrity of the alveolar space. In addition to synthesizing surfactant, a substance that prevents end expiratory alveolar collapse, ATII cells also play a major role in maintaining the alveolar space fluid free by actively transporting Na from the alveolar space to the interstitium. 5 Sodium enters alveolar cells through a variety of different pathways, including apical Na channels, Na-H + antipor, and Na cotransporters with substrates such as amino acids, phosphate, or sugars and is extruded at the basolateral membrane by a sodium, potassium-adenosine triphosphatase (Na,K-ATPase) pump. 6 Water follows to maintain isoosmolar condi-

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Anesthesiology, V 88, No 6, Jun 1998
tions, probably by a predominant transcellular route through specific water channels channel-forming integral membrane protein of 28 kDa (CHIP 28). A recent study from our laboratory reported that halothane could alter surfactant biosynthesis in ATII cells and reduce the high energy phosphate metabolism of these cells. The goal of the current study was to evaluate the effects of halothane on Na transport in cultured rat ATII cells. The activities of several Na transporters, i.e., Na channels, Na-coupled alanine and phosphate cotransporters, and Na,K-ATPase activity were evaluated by direct measurements of radiolabeled ions uptake.

Materials and Methods

The handling procedures in this protocol conformed to the Guiding Principle in the Care and Use of Animals approved by the Council of the American Physiologic Society.

Materials

Reagents were obtained from the following sources: RbCl (1-8 mCi/mg Rb) and Na (0.1 mCi/mg Na) from Amersham (Amersham, United Kingdom); K$_{2}$H$_{2}$PO$_{4}$ (900-1000 mCi/mmol) and I$^{-}$H alanine (40-60 mCi/mmol) from Du Pont-New England Nuclear (Boston, MA); elastase from Worthington Biochemical (Freehold, NJ); and halothane (Trofilex, United Kingdom). All chemicals of the highest grade available were purchased from Sigma (St. Louis, MO). Culture media and reagents were from Gibco-BRL (Paisley, United Kingdom). Plasticware was from Costar (Cambridge, MA).

Cell Culture

Alveolar type II cells were isolated from the lungs of adult Sprague-Dawley, specific pathogen-free rats (200-250 g) as previously described. Poole cells from four to six rats were prepared as follows. Rats were anesthetized with 30 mg/kg intraperitoneal sodium pentobarbital and injected intravenously with 1 U/kg heparin sodium. After tracheotomies were performed, the animals were exsanguinated, and the lungs were perfused via the pulmonary artery with solution II containing (in mm) 140 NaCl, 5 KCl, 10 HEPES-Tris pH 7.5 (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid buffered with Tris (hydroxymethylaminomethane), 2 CaCl$_{2}$, 1.3 MgSO$_{4}$, 2.5 sodium phosphate buffer (Na$_{2}$HPO$_{4}$ and NaH$_{2}$PO$_{4}$, pH 7.5), at pH 7.4 at 22°C. The lungs were then removed from the thorax and the airways lavaged to total lung capacity (8-10 ml) five times with solution I containing (in mm) 140 NaCl, 5 KCl, 10 HEPES-Tris, 0.2 EGTA (ethylene glycol-bis-(β-aminoethyl ether), N,N'-tetra-acetic acid), 2.5 sodium phosphate buffer, 6-n-glucose, at pH 7.4 at 22°C to remove macrophages. The thorax and airways were then washed twice with solution II. Then the lungs were filled with 12-15 ml of elastase solution (4 U/ml prepared in solution II) and incubated in a water bath in air at 37°C for 10 min, after which additional elastase solution was instilled for another 10-min incubation. The lungs were minced in a deoxyribonuclease I solution (0.25 mg/ml), and the enzymatic reactions were stopped with 5 ml of newborn calf serum. The tissue suspension was sequentially filtered through 150- and 30-μm nylon mesh. The filtrate was centrifuged at 150g for 8 min. The cell pellet was suspended in Dubbecco's Modified Eagle's Medium (DMEM) containing 25 mm D-glucose and plated at a density of 10$^{6}$ cells/cm$^{2}$ in 25-cm$^{2}$ plastic dishes at 37°C in a 5% CO$_{2}$ incubator for 1 h to remove macrophages by differential adherence. The unattached cells were then removed and centrifuged at 130g for 8 min. The resulting cell pellet (70% purity and 90% viability) was plated at a density of 5 × 10$^{3}$ cell/cm$^{2}$ in either 24- or 6-well culture dishes. Culture medium was DMEM supplemented with 2 mm L-glutamine, 1 mm sodium pyruvate, 10% fetal calf serum, 50 μ/ml penicillin, 50 μg/ml streptomycin, and 10 μg/ml gentamicin; cells were incubated in a 5% CO$_{2}$/95% air atmosphere at 37°C. The cell purity, assessed using fluorescence with phosphine 3R, was 90 ± 2% after 22 h of incubation. Contaminating cells were principally macrophages.

Halothane Exposure

Experiments were performed at 24 h of culture. At this time, cells were washed gently with DMEM to remove nonadherent cells and were incubated with 500 μl/well DMEM in a 124 air-tight Luftoff chamber at 37°C and 5% CO$_{2}$. The chamber atmosphere was kept continuously saturated with H$_{2}$O. Culture plates were separated into two groups according to halothane or no treatment. Halothane vapor was provided as previously described. Halothane flowed through two Fluotec Mark II vaporizers (Abbott, France) placed on the entrance to the chamber, and a halogen monitor (Capnomac Datex, Helsinki, Finland) determined the concentration of the anesthetic agent exiting the chamber. The chamber was sealed when the desired concentration...
was obtained. After incubation, halothane concentrations in the culture medium were checked by gas-phase chromatography. The effects of halothane on Na,K-ATPase activity and Na-alanine and phosphate transport were assessed after 0.5, 1.0, 2.0, and 4 h of exposure at various concentrations of halothane (1, 2, and 4%). For each concentration of halothane, a control point was obtained with cells issued from the same pool of isolated cells and incubated in the same culture conditions except exposure to halothane. Halothane time points were not matched with control, because we have previously reported that measurements of Na,K-ATPase activity and Na-alanine and phosphate transport did not change over the duration of our experiments (4 h).

22Na influx studies were performed after 45 min of exposure at a halothane concentration of 1%. Finally, the reversibility of the effects of halothane on Na transports was assessed on cells exposed for 30 min at a halothane concentration of 4% and allowed to recover after replacement of cell supernatant by fresh culture medium for 15 and 30 min.

**Assays**

All measurements were performed after the cells were removed from the halothane-containing chamber. To minimize evaporation of the volatile anesthetic agent, cells were immediately washed and the uptakes were started in the first minute after the end of exposure at 37°C in a 5% CO₂ incubator without halothane. 22Na Influx Studies. Influx of 22Na was assayed, as previously described, after depleting the cells of Na with 45 min of incubation in a Na-free solution in the halothane-containing chamber, NaCl being substituted by N-methyl-D-glucamine. The solution was then changed to one consisting of (in mM) 140 NaCl, 35 KCl, 96 N-methyl-D-glucamine, and 1 ouabain (to block the efflux of 22Na through Na-K-ATPase), supplemented with 0.5 μCi/ml 22Na. Uptake was performed during 5 min in the absence or presence of 0.01 mM amiloride. Amiloride-sensitive 22Na influx was determined by the difference between the values measured in the absence or presence of amiloride.

Uptake of Phosphate and Alanine. The uptake of alanine and phosphate was performed, as previously described, at 37°C in a buffered solution which contained (in mM) 137 NaCl, 5.4 KCl, 2.8 CaCl₂, 1.2 MgSO₄, and 14 HEPES (pH 7.4). In the Na-free solution, NaCl was replaced with N-methyl-D-glucamine. After removal of culture medium, cells were washed and incubated for 10 min in the presence of K₃H₄PO₄ (0.5 µCi/ml) or L-3H-alanine (1 µCi/ml), with 100 µM of KH₂PO₄, or L-alanine. All steps were performed at 37°C. At the end of the incubation, the uptake was stopped by washing the cells three times with 1 ml/well of ice-cold solution (in mM): 137 NaCl and 5 HEPES-Tris (pH 7.4). The Na-dependent uptake of phosphate and alanine was calculated as the difference between the uptake of phosphate or alanine in the presence and absence of Na.

**86Rb Influx Studies.** Measurements of influx of rubidium (Rb) were performed at 37°C in a solution derived from Eagle's Essential Medium, which contained (in mM) 120 NaCl, 5 RbCl, 1 MgSO₄, 0.15 Na₂HPO₄, 0.2 NaH₂PO₄, 4 NaHCO₃, 1 CaCl₂, 5 glucose, 4 nonessential amino acid, and 20 HEPES. The osmolality was adjusted by addition of mannitol to 350 mOsm/kg and adjusting the pH to 7.4. After the removal of the culture medium, cells were washed and incubated with or without ouabain (1 mM) for 5 min in the presence of 86Rb (0.5 µCi/ml). Uptake was stopped by removing the incubation medium and washing the cells three times with 1 ml/well of ice-cold rinse solution containing (in mM) 140 N-methyl-D-glucamine, 1.2 MgCl₂, 3 BaCl₂, and 10 HEPES. Ouabain-sensitive influx of Rb calculated by the difference between uptake of Rb with or without ouabain was used as an indicator of Na,K-ATPase activity. After incubations, cells were solubilized in 0.5% Triton X-100, and tracer activities were determined by liquid scintillation counting. The remainder of each sample was used for assessing the protein content per well.

**Data Analysis**

Uptake of phosphate, alanine, Na, and Rb was expressed as nanomoles per milligram of protein. For evaluation of the recovery, values were expressed as a percentage of appropriate control values. Results are presented as means ± SD of three to six independent experiments done in triplicate.

Values obtained in cells exposed to halothane were compared with those obtained in control cells for each experiment by analysis of variance followed by Fisher’s correction for multiple comparisons. A two-way analysis of variance was used to assess the effects of halothane and Ca-free culture conditions and 1.2bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA) addition.

**Results**

Effects of Halothane on Ouabain-Sensitive Influx of 86Rb

Na,K-ATPase activity was evaluated by the ouabain-sensitive component of the influx of 86Rb (OsRb), calcu-
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![Graph showing the time- and concentration-dependent effect of exposure to halothane on ouabain-sensitive 82Rb influx in alveolar type II cells.](image)

Fig. 1. Time- and concentration-dependent effect of exposure to halothane on ouabain-sensitive 82Rb influx in alveolar type II cells. Cells were exposed to halothane concentrations of 1, 2, or 4% for up to 4 h, and ouabain-sensitive Rb influx was measured. Data represent the means ± SD of four experiments done in triplicate. All values for each concentration of halothane were significantly different from the value of the respective control group at time zero (P < 0.05).

Effects of Halothane on Sodium-dependent Uptake of Phosphate and Alanine

Uptake of phosphate and alanine was not modified by halothane, regardless of the concentration or the duration of exposure (fig. 3).

Recovery of Sodium Transport after Exposure to Halothane

When ATII cells were allowed to recover from exposure to halothane, 22Na amiloride-sensitive and OsRb influx returned to control values within 30 min (fig. 4).

Effects of Decreased Concentration of Extracellular Calcium on Halothane-induced Inhibition of Na,K-ATPase Activity

In an attempt to evaluate whether halothane-induced inhibition of Na,K-ATPase activity could be attributed to an increase in intracellular Ca, two experiments were performed. First, control cells were incubated with a Ca ionophore ionomycin (10^-6 M). Ionomycin induced a 40% decrease in Na,K-ATPase activity and a 60% decrease in amiloride-sensitive influx of 22Na, but it had no effect on Na-dependent uptake of phosphate and alanine (data not shown). These results suggested that an increase in concentration of intracellular Ca could inhibit Na,K-ATPase and Na channel activities. Second, we tested whether the decrease in Na,K-ATPase activity produced by exposure to halothane was dependent on the presence of external Ca or on the release on intracellular Ca. As shown in table 1, the removal of the extracellular Ca or chelation of intracellular Ca by BAPTA increased influx of OsRb in control cells by 74% and 82%, respectively, but did not prevent the halothane-induced decrease in Na,K-ATPase activity.

Discussion

This study demonstrates that exposure of alveolar epithelial type II cells to halothane inhibits Na ion vectorial transport in vitro. The Na,K-ATPase and Na channels are the major targets of the halothane effect, and their activities were impaired for short-duration exposures at low concentrations of halothane.

Na,K-ATPase and Na channel are the two major proteins involved in Na transport in alveolar epithelial cells. In our study, halothane induced a decrease in Na,K-ATPase activity and amiloride-sensitive influx of Na. The finding that the decrease in amiloride-sensitive influx was related to a decrease in Na channel activity rather
than to Na-H\(^+\) inhibition is supported by a recent preliminary report, which indicates that halothane initiated a significant intracellular alkalization in an alveolar rat cell line.\(^{15}\) Because halothane induced a concomitant decrease in influx of OsRb and amiloride-sensitive Na, it is not possible to determine whether the inhibition of Na,K-ATPase is the cause or the consequence of the reduced rate of Na entry through Na channels.\(^{16}\) In the current study, several lines of evidence indicate that halothane-induced Na,K-ATPase and Na channel activity

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**Fig. 2.** Effect of exposure to halothane on influx of \(^{22}\)Na in alveolar type II cells. Cells were exposed to halothane (concentration of 1% for 45 min). During this time, cells were depleted in a Na-free medium. At the end of exposure, influx of \(^{22}\)Na was measured in the presence of 1 mm ouabain to block the efflux of \(^{22}\)Na through Na,K-ATPase in the presence or absence of 100 \(\mu\)m amiloride. Data represent the means ± SD of six experiments done in triplicate. *Significantly different from the control value (\(P < 0.01\)).

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**Fig. 3.** Time- and concentration-dependent effect of exposure to halothane on Na-dependent uptake of phosphate and alanine in alveolar type II cells. Cells were exposed to halothane concentrations of 1, 2, or 4% for up to 4 h. Then, uptake of phosphate (0.1 mm) and alanine (0.1 mm) was performed. Data represent the means ± SD of three experiments done in triplicate. Values obtained for each concentration of halothane were not significantly different from the value of the respective control group at time zero.
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Ouabain-sensitive $^{86}$Rb influx

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<tr>
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<th>% of control value</th>
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<tr>
<td>Halothane</td>
<td>150</td>
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<tr>
<td>Recovery 15 min</td>
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<td>Recovery 30 min</td>
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Amiloride-sensitive $^{22}$Na influx

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<th>% of control value</th>
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<tr>
<td>Halothane</td>
<td>200</td>
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<tr>
<td>Recovery 15 min</td>
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<td>Recovery 30 min</td>
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Fig. 4. Evaluation of the recovery of alveolar type II cells after exposure to halothane. At the end of exposure to halothane (concentration of 1% for 30 min), cells were allowed to recover in a 5% CO$_2$-21%O$_2$-74%N$_2$ humidified incubator after their supernatant was replaced by fresh culture medium. Control cells were processed in the same way. Ouabain-sensitive influx of $^{86}$Rb and amiloride-sensitive influx of $^{22}$Na were measured at the end of the exposure and after 15 and 30 min of recovery. Results are expressed as percent of homologous nonexposed cells. Data represent the means ± SD of six experiments done in triplicate. Asterisks indicate significant differences from the control value ($^*P < 0.05$, $^{**}P < 0.01$).

Impairment was not the consequence of irreversible and nonspecific damage: (1) Release of lactate dehydrogenase (LDH), reflecting cell viability, did not increase in cells exposed to halothane$^a$; (2) other pathways of Na transport, Na-phosphate and Na-alanine cotransporters, were not affected by halothane; and (3) the inhibitory effect of halothane on Na transport was rapidly and completely reversible after cessation of delivery of anesthesia and washout. The observation that, in ATII cells, halothane induced a decrease in Na,K-ATPase differs from the results obtained in other cell preparations, in which pharmacologically relevant concentrations of volatile anesthetic agents have little or no effect on Na,K-ATPase activity. In human erythrocytes, Halsey et al. have shown that the Na-K pump was not modified by clinical concentrations of volatile anesthetic agents. In accordance with this latter study, a recent study performed on cerebral synaptic plasma membranes indicated that halothane exposure did not modify Na,K-ATPase activity. Formichova and Kosicka, however, compared the effects of halothane on various ATPase activities in synaptosomal or erythrocyte membranes and found that a minimum alveolar concentration of 3 was required to half-maximally inhibit the Na,K-ATPase activity, but a minimum alveolar

Table 1. Effects of External Calcium Concentration and BAPTA on Halothane-induced Inhibition of Na,K-ATPase Activity in Alveolar Type II Cells

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<th>Ouabain-sensitive $^{86}$Rb Influx (nmol/mg protein/5 min)</th>
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<tr>
<td></td>
<td>1 mm External Calcium</td>
</tr>
<tr>
<td>Control cells</td>
<td>95.1 ± 16.3</td>
</tr>
<tr>
<td>Halothane cells</td>
<td>74.8 ± 16.6*</td>
</tr>
</tbody>
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BAPTA = 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid.

Cells were incubated under halothane (4%) for 1 h in medium containing, respectively, 1 mm, 0 mm external calcium, or 0 mm external calcium and 1 mm BAPTA. At the end of the exposure ouabain-sensitive influx was measured. Data represent mean ± SD of five experiments in which triplicate values were obtained.

* Significantly different from homologous control value, $P < 0.01$.
† Significantly different from the value in the presence of calcium, $P < 0.01$.

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concentration of only 0.75 - 1.15 was necessary for the same inhibition of calcium-transporting ATPase. In this study, Na,K-ATPase activity was strongly inhibited by halothane at a minimum alveolar concentration 1. These data may represent evidence of functional and pharmacologic differences between Na pumps among different tissues.

The mechanisms by which halothane alters Na transport protein remain unknown. Inhibition of the Na pump and Na channels may result from indirect modifications of intracellular mediators, such as ATP, or cytosolic free calcium, or from direct qualitative or quantitative alterations of the proteins.

Halothane was reported previously to reduce ATP content in ATII cells. Therefore, the possibility that depletion of intracellular ATP in halothane-exposed cells might be responsible for the inhibition of Na,K-ATPase activity was examined. Several studies have reported that Na,K-ATPase is directly dependent on cellular concentrations of ATP. When ATII cells were exposed to a halothane concentration of 4% for 1 h, ATP was depleted by only 10%. In a previous study, we reported that depletion of ATP in these cells to a greater degree, achieved by metabolic inhibitors, did not alter influx of OsRb. Taken together, these results suggest that depletion of ATP did not play a major role in halothane-induced inhibition of Na,K-ATPase activity.

Volatile anesthetic agents increase cytoplasmic Ca in several cells and tissues, including hepatocytes, mouse brain synaptosomes, peripheral blood mononuclear cells, and O6 muscle cells. In most studies, this effect is attributed to the release of Ca from intracellular stores or an increase in Ca entry. The intracellular concentration of free Ca ions is one of the most important regulatory systems in the cell. Our results suggest that, in ATII cells, Na,K-ATPase activity is modulated by intracellular concentrations of Ca, inasmuch as ionomycin, a Ca ionophore, reduced influx of OsRb, whereas the absence of extracellular Ca increased influx of OsRb. Halothane-induced inhibition of Na,K-ATPase activity was not prevented, however, by removal of external Ca or by chelating internal Ca by BAPTA. These results suggest that the reduction of Na,K-ATPase activity is not likely related to an increase in concentration of intracellular Ca. Finally, it can not be excluded that halothane induced changes of other intracellular mediators, which could in turn inhibit transport indirectly.

The decrease in the activity of Na,K-ATPase and Na channel may also result from a direct action of halothane on Na transport proteins by binding to the channel or the pump protein itself or by modifying the lipid environment of the protein. Volatile anesthetic agents could induce modification in membrane fluidity, an effect that might affect the activity of numerous membrane proteins, among which are transport systems. A certain degree of fluidity has been shown to be essential for Na,K-ATPase activity. In ATII cells and other epithelial cells, Na-phosphate cotransporter was reported to be very sensitive to the modification of the lipid environment. Because Na-phosphate transport was not affected by halothane, in this study, the decrease in Na,K-ATPase and Na channel activity was probably attributable to changes in the protein itself.

This study demonstrates that halothane, at clinically relevant concentrations and for short-exposure duration, impairs Na transport in ATII cells, in vitro, by decreasing Na,K-ATPase and Na channel activity. Na coupled transport is unchanged regardless of the concentration of halothane or the duration of exposure. These cotransporters are a common route of amino acids and phosphate entry into the cells but only account for 13% of total Na influx into the cells in freshly prepared ATII cells in suspension. Although the direct measurement of circuit short current was not done, the decrease in Na,K-ATPase activity along with the decrease in Na channel activity strongly suggests that halothane reduces the transepithelial Na flux. In alveolar epithelium, transepithelial Na transport plays a major role in the regulation of the alveolar fluid balance. Alveolar edema is obviously associated with a serious impairment of gas exchange, because it increases distance for gas diffusion and severely impairs the ventilation-perfusion relationship. Therefore, inhibition of Na transport by halothane in alveolar epithelium might be of clinical relevance, particularly in patients with pulmonary edema. A recent in vivo study in rats confirmed that halothane causes a reversible decrease in net alveolar epithelial Na and fluid transport. Further studies are needed to investigate the effects of anesthetic agents on alveolar fluid clearance on in vivo models of pulmonary edema.

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