SODIUM TRANSPORT IN AIRWAY EPITHELIUM CORRELATES WITH LUNG COMPLIANCE IN HEALTHY NEWBORN INFANTS

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To study the relation between sodium transport in airway epithelium and postnatal pulmonary adaptation, we measured nasal potential difference at 1 to 4 hours and lung compliance at 21 to 48 hours after birth in 20 healthy infants. Sodium transport correlated with lung compliance (r^2 = 0.40, P < .003). Airway sodium transport plays a role in postnatal pulmonary adaptation. ***(J Pediatr 2005;146:273-6)***

During fetal life, vectorial secretion of Cl^- from the airway epithelium to the luminal space by the airway epithelium is vital for lung growth.[1] At birth, a rapid change to net Na^+ absorption is crucial for facilitating a rapid clearance of lung fluid.[1] The amiloride-sensitive epithelial sodium channel (ENaC) may be a pivotal pathway for transepithelial movement of Na^+ from the apical to the basolateral direction, resulting in osmotic lung fluid absorption. This concept was demonstrated in experiments in which laboratory animals had respiratory distress after injection of amiloride into the airways at birth.[2] In addition, mice that are homozygous for mutations in the ENaC gene, causing loss of function of the α-subunit, died soon after birth as the result of respiratory distress associated with increased wet-to-dry lung weight ratio.[2,3] In human respiratory distress syndrome (RDS), lower transepithelial sodium transport and lower expression of ENaC subunits were measured in preterm infants than in healthy term infants.[4,5] Therefore, in this pilot study we hypothesized that because perinatal liquid clearance is important for normal human perinatal lung adaptation, there is a temporal relation between static lung compliance and airway epithelial sodium transport.

METHODS

The study protocol was approved by the local ethics committee. We studied 20 healthy newborn infants (Table). Informed consent was obtained from the parents. The initial measurements were performed as soon after birth as possible, at 1 to 4 hours of age. The second set of measurements took place at 21 to 48 hours of age. Sodium transport in airway respiratory epithelium was quantified as potential difference over the nasal epithelium. The measurement was based on methods described earlier.[6,7] A silver wire electrode was inserted into a 3-lumen central catheter (23 G, COOK, Bjaeverskov, Denmark) to allow accurate administration of the perfusion fluids. The system for nasal potential difference (N-PD) measurements included a voltmeter and recording device for recording and saving data (Logan Research Ltd, Maidstone, UK). Before the measurement, the circuit was checked by confirming that the negative potential difference of the exocrine glands on the infant's skin was −35 mV or less. The circuit was re-checked, or the electrode replaced, if the readings did not reach −30 mV or were below −60 mV. Measurements were performed on the floor of the nose. Initially, N-PD of both nostrils was recorded and the maximal stabile N-PD was measured for 10 seconds before perfusion of physiologic saline was commenced. The function of the amiloride-sensitive sodium channel was determined by perfusion with amiloride (10^{-4} mol/L). To measure chloride transport, the perfusion was continued with a chloride-free perfusion solution that included 10^{-4} mol/L amiloride. Perfusion was continued for 2 minutes for each solution, during which a stable N-PD for 10 to 20 seconds was achieved. Achievement of amiloride sensitivity was used as the criterion for a successful measurement. The measurement was discontinued if the infant was restless and there was an obvious change of position of the electrode.

In separate experiments, the stability and compatibility from readings of the silver wire exploring electrode was validated in 5 adult volunteers against a conventional method with

ENaC	Epithelial sodium channel	N-PD	Nasal potential difference

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Table. Clinical characteristics, transepithelial nasal potential difference, and static lung compliance of 20 healthy newborn infants at <4 and 21 to 48 hours after birth

Subjects	All (n = 20)	Vaginal delivery (n = 13)	Cesarian section (n = 7)
Male/female	10/10	5/8	5/2
Gestational age, wk	39.1 ± 1.5	39.6 ± 1.4	38.9 ± 1.8
Birth weight, kg	3.7 ± 0.6	3.6 ± 0.4	3.8 ± 0.8
N-PD <4 h, mV			
Basal	−14.3 ± 1.9* (n = 20)	−14.8 ± 2.8* (n = 13)	−13.3 ± 2.2* (n = 7)
Amiloride	−8.8 ± 1.7*† (n = 20)	−8.8 ± 2.3* (n = 13)	−8.7 ± 2.4* (n = 7)
Chloride-free	−15.6 ± 3.0† (n = 11)	−14.9 ± 3.7 (n = 8)	−17.3 ± 5.8 (n = 3)
N-PD 21–48 h, mV			
Basal	−14.6 ± 2.3* (n = 16)	−13.9 ± 3.0* (n = 10)	−15.7 ± 3.8† (n = 6)
Amiloride	−9.0 ± 1.9*† (n = 16)	−8.5 ± 2.5*‡ (n = 10)	−10.0 ± 3.0†‡ (n = 6)
Chloride-free	−15.1 ± 2.7† (n = 9)	−12.0 ± 2.4‡ (n = 6)	−15.6 ± 5.2‡ (n = 3)
Lung compliance <4 h, mL/kPa per kg	17.3 ± 1.4† (n = 19)	15.9 ± 1.3 (n = 12)	18.0 ± 2.8 (n = 7)
Lung compliance 21–48 h, mL/kPa per kg	22.8 ± 2.2† (n = 20)	23.1 ± 2.4 (n = 13)	22.1 ± 4.6 (n = 7)

N-PD, transepithelial nasal potential difference; *LC,* static lung compliance. Statistical comparisons were performed within the subject category (*P < .0001, †P < .005, ‡P < .05).

an agar-bridge electrode.[8] The baseline current was −16.0 (±3.6) and −16.2 (±3.5) mV (not significant, NS) and the amiloride-sensitive current was −6.4 (±1.1) and −6.8 (±3.3) mV (NS), determined with the present method and conventional method, respectively.

Static lung compliance was measured with the double occlusion technique during quiet non-REM sleep with regular respiration, using a computerized pulmonary function testing device (Labmanager 4.52i, Erich Jaeger GmbH, Hoechberg, Germany).[9] Sleep stage of 9 subjects was determined by polysomnogram, which included 2 electroencephalograms (C3A2, O2A1), 2 electro-oculograms, chin electromyogram, airflow, and pulse oximetry registrations. In the remaining 11 subjects, sleep stage was determined by direct observation of eye movements, muscle tension, and regularity of breathing assessed by using airflow signal. Airflow for polysomnogram and lung compliance measurements was measured by using a pressure transducer and a full face mask.

Clinical data are presented as mean ± SD. Study data are expressed as mean ± SEM. Comparisons were performed with the paired t test or the Mann-Whitney U test. The Pearson test was used for correlations.

RESULTS

A successful N-PD measurement and sodium transport quantification was possible in all infants within 4 hours of birth (range, 1 to 4 hours; median, 2.0 hours) and in 16 infants at 21 to 48 hours of birth (median, 26.5 hours). Recording of N-PD lasted for 6.2 (±0.5) minutes; prolongation of the measurement often induced restlessness in the infants. Accordingly, measurement of N-PD during perfusion of the chloride-free solution was possible in 11 infants within 4 hours and 9 infants within 21 to 48 hours. The lung compliance measurement was possible in 19 and 20 infants, respectively.

The maximal stable N-PD was −15.4 (±1.5) mV and −14.4 (±1.5) mV (n = 36, NS) during perfusion with saline. At the initial <4-hour time point after birth, amiloride in the perfusion solution reduced the potential difference by 44.0% (±4.2) (Table, P < .0001 vs saline). The N-PD response was similar at 21 to 48 hours after birth, as amiloride in the perfusion solution reduced the potential difference by 43.4% (±3.7) (P < .0001 vs saline; P = .90 between the two time points). Replacement of the physiologic saline solution with a Cl^- free solution significantly increased N-PD from the amiloride-inhibited nadir, demonstrating active Cl^- secretion in the human perinatal airway epithelium. No difference in the magnitude of Cl^- secretion existed at <4-hour and 21- to 48-hour time points.

The initial lung compliance at <4 hours was significantly increased by 48 hours after birth (Table). The lung compliance of the 11 subjects with sleep phase determination under visual control was not different from the value obtained from the infants under polysomnography (19.7 ± 2.5 and 19.9 ± 1.6 mL/kPa per kilogram for polysomnography and visual, respectively), suggesting that these preselected variables can be used to determine the sleep phase of the newborn infant.

A significant correlation existed between amiloride-sensitive potential difference at <4 hours and lung compliance at 21 to 48 hours after birth (r^2 = 0.40, P < .003; Figure). Importantly, a correlation existed between the initial amiloride-sensitive nasal potential and the change in lung compliance between the two time points (r^2 = 0.31, P = .013; n = 19). The 6 newborn infants with the highest initial amiloride-sensitive sodium transport had lung compliance of 27.3 (±3.2) mL/kPa per kilogram at 21 to 48 hours after birth,