448.9

A NOVEL ROLE FOR EPITHELIAL CHLORIDE CURRENTS AS A KEY STEP IN EPITHELIUM-DEPENDENT AIRWAY RELAXATION.
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The airway epithelium is the first surface exposed to inhaled compounds and may play a major role in determining the airway response to various stimuli. One important function of the epithelium may be to release relaxing factors to maintain patent airways. To study epithelial function in intact airways, we developed an apparatus to simultaneously measure the transepithelial voltage and the resistance to flow in isolated, perfused mouse tracheas. We previously used a similar system to demonstrate epithelium-dependent relaxation of constricted airways in response to substance P (SP) (Am. J. Physiol. 277: L264-70). Since SP is known to stimulate transepithelial chloride secretion in cultured epithelial monolayers, we tested the hypothesis that epithelium-dependent relaxation of mouse trachea depends on activation of epithelial chloride currents. Measurements of transepithelial voltage and airway resistance showed that the chloride currents preceded relaxation. Blocking chloride currents with chloride channel inhibitors or anion replacement abolished both the transepithelial voltage change and the relaxation to SP. We also found that increasing the driving force for chloride secretion increased the relaxation to SP. These data suggest that airway epithelial chloride currents may represent an important early step in the release of an epithelium-derived relaxing factor in response to SP. This new finding may lead to important new insights regarding the progression of airway diseases such as cystic fibrosis where impaired epithelial chloride currents may affect the release of epithelium-derived factors.

448.10

THE ROLE OF AIRWAY NEURONS IN IN O_3-INDUCED AIRWAY HYPER-RESPONSIVENESS (AHR) IN FERRET TRACHEA
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Exposure to O_3 is frequently associated with AHR. Release of substance P (SP) from sensory C-fibers may contribute to AHR, but SP levels are increased in intrinsic airway ganglia after O_3 exposure. The aim of this study is to examine the role of intrinsic neurons in AHR. Ferrets were exposed to 2 ppm O_3 or air for 1 h. Tracheas were removed and maintained in organotypic culture for 24 h (± 10 μM capsaicin). Previous studies have shown that sensory nerves degenerate during culture, but that innervation of smooth muscle by intrinsic airway neurons maintains intact. Responses of tracheal smooth muscle to acetylcholine (ACh), methacholine (MCh) and electrical field stimulation (EFS) were measured in isolated strips. Reactivity to ACh and MCh were elevated significantly after O_3-exposure (respective EC50's: for ACh, from 1.69 to 0.65 μM for air and O3; for MCh, from 1.41 to 0.59 μM for air and O_3), as were contractions to EFS at 10 and 30 Hz. Capsaicin-treatment partially abolished the O_3-induced increase in reactivity to ACh, MCh, and EFS. In contrast, capsaicin had no effect on these responses after air-treatment. These results suggest that sensory nerves and intrinsic airway neurons may contribute to O_3-induced AHR by enhanced neuropeptide release. (Supported by NIH HL 35812).

448.11

HUMAN LARYNX, TONGUE, PHARYNX AND ESOPHAGUS MUSCLES CONTAIN SLOW AND α-CARDIAC MYOSIN
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We examined human upper airway muscles for the presence of slow tonic (STMF) or α-cardiac muscle (ACMF) using specific antibodies against myosin heavy chain (MHC) isoforms. **Methods:** Unfixed human autopsy specimens were cryosectioned and incubated with monoclonal antibodies including: HB-76 against α-cardiac MHC and ALD-19 and/or ALD-58, specific for slow tonic MHC. **Results:** *In the larynx* STMF were found in the thyroarytenoid muscle (N=9), cricothyroid (N=5), and lateral cricoarytenoid muscles (N=2). *In the tongue (N=2)*, STMF and ACMF were present in all intrinsic muscles in proportions ranging from 15-33%. STMF were rare or absent from the extrinsic tongue muscles. *In the pharyngeal and upper esophageal muscles (N=2)*, both STMF and ACMF were found at high concentrations in the cricopharyngeus muscle. In the inferior constrictor muscle STMF were present but no ACMF. **Comment:** These results show that most muscles in the human upper airway contain STMF and ACMF. In all locations the exact distribution of each MHC was different, suggesting a specific functional role for these MHCs. In some locations the MHCs appear to be specific to humans.

448.12

THE MECHANICAL STATE OF HIGHLY SHORTENED SMOOTH MUSCLE AFTER FORCED LENGTH OSCILLATIONS.
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Smooth muscle tissues that are capable of extreme shortening show a marked increase in stiffness at their shortest length. The "radial constraint hypothesis" (*J. Appl. Physiol.* 86(1):5-15, 1999) suggests that this is the result of an internal force balance between force generators (crossbridges) and radially-oriented connective tissue. Disruption of either of these elements in actively shortened tissue should result in predictable dimensional changes; in particular, detaching crossbridges should result in a forced lengthening of the tissue. When large length oscillations (33 Hz for 1 sec, and up to 50% of the prevailing muscle length) were applied to electrically stimulated canine tracheal muscle, the tissue elongated rapidly, even in the absence of external distending forces. Immediately after oscillation, the tissue stiffness (as measured by high-frequency (80 Hz) length perturbations) was also reduced, in proportion to the oscillation amplitude. The distensibility of the tissue, measured by its length change in response to force steps, also increased. While the stimulus was maintained, the stiffness and muscle length recovered towards their pre-oscillation values. These results indicate that the length oscillation disrupted attached crossbridges and permitted passive tissue forces to re-extend the muscle, a behavior consistent with the radial constraint hypothesis. *Supported by the Department of OB/GYN, Indiana University School of Medicine.*

MECHANISMS OF LUNG INJURY (449.1-449.2)

449.1

PROLONGED MECHANICAL VENTILATION AFTER PREMATURE BIRTH INHIBITS MICROVASCULAR FORMATION IN LUNGS OF PRETERM LAMBS.
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Lambs that are born prematurely and mechanically ventilated for 3-4 wks have persistently elevated pulmonary vascular resistance (PVR) and muscularized small pulmonary arteries (Chest 114:6S, 1998). We hypothesized that preterm birth followed by longterm mechanical ventilation also inhibits formation of lung microvessels. We counted precapillary and postcapillary "corner" microvessels (15-20 mm in diam) per unit area of lung tissue, and estimated capillary surface density by intersection counting, in lung tissue sections from preterm lambs mechanically ventilated for 3-4 wks and term lambs of similar gestational age (term, 1 d old) or postnatal age (term, 3 wks old). The preterm lambs and fetal control lambs were delivered at ~125 d gestation (term ~147 d).
Preterm and fetal lambs had significantly (*) fewer microvessels and less capillary surface density than term lambs had. We conclude that preterm birth followed by longterm mechanical ventilation inhibits lung microvascular formation which in turn contributes to increased PVR.

Lamb Group	Microvessels/100 μm^2	Capillary Surface Density (cm^{-1})
Fetus (n=5)	5.4 ± 1.3* (mean ± SD)	177 ± 45*
Term, 1 day (n=5)	9.7 ± 2.1	401 ± 122
Term, 3 weeks (n=5)	9.3 ± 2.1	529 ± 158
Preterm, (n=10)	7.0 ± 1.8*	261 ± 80*

449.2

DEXAMETHASONE TREATMENT REDUCES EXPRESSION OF PDGF α AND β RECEPTORS AND VEGF RECEPTOR KDR/FLK-1 IN THE LUNGS OF NEWBORN RATS
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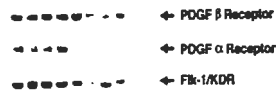
Previous studies have suggested that PDGF and VEGF play important roles in lung development. The formation of secondary septae, essential for alveolarization, has been shown to be PDGF-dependent and may involve signaling through the PDGF α-receptor on alveolar myofibroblasts. Angiogenesis, also important for postnatal alveogenesis, is dependent on PDGF β-receptors and the VEGF receptor KDR/Flk-1. Dexamethasone (Dex) treatment of newborn rats inhibits alveolarization and causes persistent lung hypoplasia. The aim of this study was to determine if Dex treatment reduces expression of the PDGF and VEGF receptors in the lungs of newborn rats. Three day old Sprague Dawley rats were injected daily with 0.25ug of Dex for 3 days. Control littermates were injected with the vehicle (20ul ethanol). Western blot analysis for PDGF α- and β-receptors and VEGF receptor KDR/Flk-1 was performed on lung tissue from 6 day old control and Dex-treated rats. Dex-treated rats showed reductions in PDGF α- and β-receptors (14-fold and 3-fold; $P<0.05$) and KDR/Flk-1 (3-fold; $P<0.05$) compared to controls. We conclude that Dex treatment reduces expression of PDGF α- and β-receptors and VEGF receptor KDR/Flk-1 in the lungs of newborn rats during the critical period of postnatal alveolarization. We speculate that reductions in PDGF α- and β-receptors and KDR/Flk-1 contribute to Dex induced lung hypoplasia.



Supported by American Heart Association Scientist Development Award to TDLC and Grant-In-Aid to SHA.

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Experimental Biology 2000®
San Diego, California
April 15-18, 2000

ABSTRACTS

Abstracts 1.1-565.7

Official Publication of the Federation of American Societies for Experimental Biology
Volume 14, Number 4, March 15, 2000