EPISODIC OZONE EXPOSURE IN INFANT RHESUS MONKEYS INDUCES NEUROPLASTICITY IN NUCLEUS TRACTUS SOLITARIUS (NTS) WHERE LUNG SENSORY FIBERS FIRST SYNAPSE. C-Y Chen, JP Joad, ES Schelegele, & AC Bonham, Center for Comparative Respiratory Biology & Medicine & California Regional Primate Center, UC Davis, CA, USA.

Exposure to ozone causes airway obstruction, chest tightness, and changes in breathing pattern, responses also caused by stimulation of lung sensory nerves via CNS reflexes. While chronic ozone exposure increases the sensitivity of lung sensory nerves, adaptation is a prominent feature of ozone-induced responses, raising the possibility that CNS processing of the primary sensory afferent signals may be altered. To address this issue, we studied the effect of episodic ozone exposure on NTS neurons where lung sensory fibers synapse. Whole-cell recordings were performed on NTS neurons in brainstem slices from infant monkeys (6/group) exposed for 22 wks to either filtered air (FA) or ozone 0.5 ppm for 8hrs/d, 5d on & 9d off (O3). We compared: 1) intrinsic neuronal properties (resting membrane potential, Vm and input resistance, $R_I$); 2) responsiveness to nonspecific excitation (# action potentials evoked by 2-s depolarizing current injections) and 3) responsiveness to sensory nerve input (threshold voltage applied to sensory nerve fibers required to evoke NTS responses and number of NTS neurons discharging action potentials at the same stimulating voltage). O3 depolarized the Vm (-54±1.3 vs. -50±0.9mV, p=0.02), increased the $R_I$ (469±30 vs. 609±38 MΩ, p=0.006), and increased the responsiveness to nonspecific excitation (p=0.04). By contrast, O3 decreased the responsiveness to sensory fiber input, as indicated by a higher threshold stimulating voltage (p=0.01) and fewer responsive neurons at the maximum voltage (p=0.001). Thus, while episodic O3 exposure increased the general level of NTS neuronal excitability, it decreased the neuronal responsiveness to sensory fiber input, findings which may explain the adaptation to repeated O3 exposure.

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**Title: PARASYMPATHETIC DOMINANCE WITH INCREASED SEVERITY OF ASTHMA: EVIDENCE FROM A PILOT STUDY**

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**Rationale:** Parasympathetic stimulation causes bronchoconstriction in asthma while the sympathetic nervous system bronchodilates. Baseline autonomic tone thus may be important in asthma. This can be measured by heart rate variability (HRV) where high frequency power (HF) signifies parasympathetic tone, low frequency power (LF) sympathetic and LF/HF ratio, sympathovagal balance.

**Methods:** We studied 6 patients with mild asthma [Beclomethasone (BDP) 0-800mcg or equivalent] (age 33± 8, 3 F), 6 with moderate/severe asthma (BDP >1000mcg or equivalent) (age 39±9, 4 F) and 6 with brittle asthma (age 40±11,4F). HF, LF and LF/HF ratio were measured both at 60° head up tilt and lying flat.

**Results:** Power in $ms^2$; expressed as mean (SD); HF, LF (but not LF/HE ratio) in log values.

| Patient type | +60° | | | FLAT | | |
|---|---|---|---|---|---|---|
| | HF | LF | LF/HF | HF | LF | LF/HF |
| Mild | 2.55 (0.36) | 2.96 (0.23) | 3.11 (2.3) | 2.82 (0.5) | 3.07 (0.2) | 3.0 (2.6) |
| Severe | 2.15 (0.59) | 2.7 (0.6) | 3.7 (0.44) | 2.56 (0.47) | 2.59 (0.51) | 1.5 (1.1) |
| Brittle | 1.63 (0.45) | 2.12 (0.44) | 4.8 (4.9) | 2.01 (0.58) | 2.19 (0.5) | 1.8 (1.2) |

**Conclusion:** At 60° LF/HF ratio increases with severity of asthma. When lying flat, LF/HF ratio falls as severity of asthma increases ($p= 0.028$ for mild vs. severe, $p= 0.046$ for mild vs. brittle) implying relative parasympathetic dominance in severe asthma. This could partly explain nocturnal symptoms in asthma. These data suggest that autonomic responses vary according to severity of asthma.

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**Respiratory-related bronchial rhythmic constriction in the dog.**

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Function of respiratory-related bronchial rhythmic constriction was analyzed in eight paralyzed dogs. The caliber of the fifth-generation bronchus was continuously measured with a balloon-tipped catheter. When the vagus nerves were intact, the bronchus rhythmically constricted in synchrony with phrenic bursts. When the vagus nerves were temporarily blocked by cooling the nerve trunks, the rhythmic constrictions disappeared. When vagus efferent fibers, i.e., distal ends of the blocked vagus nerves, were electrically stimulated with train pulses during the cold block, peak expiratory flow of mechanical ventilation significantly decreased and expiratory duration significantly prolonged. These changes were associated with a small but significant decrease in $PaCO_2$. When vagus efferent fibers were stimulated during eucapnic apnea, bronchial caliber decreased and anatomical dead space decreased as increases in stimulus intensities. We concluded that bronchial rhythmic constrictions facilitate alveolar gas change by modulating expiratory flow and anatomical dead space.

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INTERLEUKIN-1β-INDUCED AIRWAY HYPERRESPONSIVENESS (AHR) IN FERRETS ENHANCES SUBSTANCE P (SP) IN INTRINSIC AIRWAY NEURONS. Z.-X. Wu[1], B.E. Satterfield[1], J.S. Fedan[2], R.D. Dey[1]. Dept of Anatomy, West Virginia University[1] and PPRB, NIOSH[2], Morgantown, WV 26506.

Interleukin-1β (IL-1β) causes airway inflammation, enhances airway smooth muscle responsiveness and alters neurotransmitter expression in sensory, sympathetic and myenteric neurons. The aim of this study was to examine the role of intrinsic airway neurons in AHR induced by IL-1β. Ferrets were instilled intratracheally with IL-1β (0.3 μg/0.3ml) or saline (0.3 ml) once daily for 5 days. Tracheal smooth muscle contractility *in vitro* and SP expression in tracheal neurons were assessed. After IL-1β treatment, tracheal smooth muscle reactivity to acetylcholine (ACh) and methacholine (MCh) was significantly increased (EC50's: 0.91 to 0.37μM for ACh and 0.43 to 0.20 μM for MCh in control and IL-1β, respectively), as were smooth muscle contractions to electric field stimulation (EFS) at 10 Hz (from 27% to 34 % of maximal ACh contraction) and 30 Hz (37% to 44%). The IL-1β-induced AHR was maintained in tracheal segments cultured for 24 hr, a procedure shown to deplete sensory nerves while maintaining viability of intrinsic airway neurons. Pretreatment with CP-99994, a $NK_1$-receptor antagonist, attenuated the IL-1β-induced increase in reactivity to ACh and MCh and to EFS in cultured tracheal segments. In contrast, CP-99994 had no effect after saline-treatment. The number of SP-containing neurons in longitudinal trunk (LT) and innervation of superficial muscular plexus (SMP) neurons increased significantly after treatment with IL-1β. These results show that the enhanced airway smooth muscle contractile responses induced by IL-1β are mediated partly by SP and may result from increased SP-production by LT neurons and enhanced SP-innervation of SMP neurons.

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CALCITONIN GENE-RELATED PEPTIDE (CGRP) HAS MULTIPLE EFFECTS ON MEMBRANE PROPERTIES OF NEURONS IN GUINEA PIG BRONCHIAL PARASYMPATHETIC GANGLIA. Radhika Kajekar and Allen C. Myers, The Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA

Neurons in bronchial parasympathetic ganglia have membrane and synaptic properties that serve to attenuate or filter information arising from the central nervous system (Am. J. Physiol 249, L403). Substance P released from sensory nerves in airway ganglia affects this integrative function (J. Auton. Nerv. Sys. 61, 162); however, the effects of CGRP on these neurons are unknown. Using intracellular recording techniques, we determined the effects of CGRP on active, passive, and synaptic properties of principal neurons located in guinea pig bronchial parasympathetic ganglia. Bath-applied CGRP (0.001-0.1μM) hyperpolarized the resting potential -4 ± 1mV ($p<0.05$) of seven neurons; eight neurons CGRP (0.1-1.0 μM) depolarized the resting potential by 3 ± 1mV ($p<0.05$). In two neurons, the hyperpolarization response to CGRP (0.1μM) was reversed by the CGRP-1 antagonist, CGRP8-37 (1.0 μM) and subsequent application of CGRP (0.1μM) evoked a 2 mV depolarization. In three neurons, CGRP (0.01-1.0 μM) had no effect on the resting membrane potential. CGRP (0.1μM) decreased action potential accommodation in four bronchial phasic-type neurons. In addition, CGRP (0.1μM) decreased the amplitude of capsaicin-sensitive sensory nerve-evoked slow excitatory post-synaptic potentials by 53±17% (n=3). These results demonstrate that CGRP has both excitatory and inhibitory effects and may thus alter the integrative function of these neurons by several mechanisms. As CGRP is upregulated during airway inflammation, such changes may enhance its role as a neuromodulator in the inflamed airway.

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NOCICEPTIN INHIBITS CAPSAICIN-INDUCED BRONCHOCONSTRICTION IN THE GUINEA-PIG. M.R. Corboz, X. Fernandez, R.W. Egan, J.A. Hey. Allergy, Schering-Plough Research Institute, Kenilworth NJ.

*In vivo* studies were conducted in the guinea-pig to investigate the activity of the selective ORL1 receptor agonist nociceptin/orphanin FQ against capsaicin-induced bronchoconstriction, a response mediated by the release of tachykinins from pulmonary sensory nerves. Anesthetized guinea-pigs were ventilated with a rodent ventilator and placed in a whole body plethysmograph, and pulmonary resistance ($R_L$) and dynamic lung compliance ($C_{Dyn}$) were monitored. Intravenous administration of nociceptin/orphanin FQ (0.1-0.3 mg/kg) produced a dose-related inhibition of the capsaicin (1 μg/kg, intravenously)-induced bronchoconstriction. The selective nonpeptide ORL1 receptor antagonist J-113397 administered intravenously (1 mg/kg) produced a significant blockade of the inhibitory effect of nociceptin/orphanin FQ (0.3 mg/kg, intravenously) on capsaicin-induced bronchoconstriction, whereas the nonselective opioid receptor antagonist naloxone (1 mg/kg, intravenously) had no effect. On the other hand, nociceptin/Orphanin FQ (0.3 mg/kg) did not affect bronchoconstriction induced exogenously by the tachykinin $NK_2$ receptor agonist [β-ala$^8$]-neurokinin A (4-10). We conclude that nociceptin inhibits capsaicin-evoked tachykinin release from sensory nerve terminals in the guinea-pig by a prejunctional mechanism. This inhibitory action does not involve activation of opioid receptors. Schering-Plough Research Institute

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