

808 SENSORY IRRITANT RESPONSIVENESS IN LPS-INDUCED LUNG INFLAMMATION.

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Our previous studies have shown that responsiveness to sensory irritants is enhanced in ovalbumin-induced eosinophil-rich allergic airway disease. The current study was performed to determine if a similar phenomenon occurred in neutrophil-rich airway inflammation. Toward this end, sensory irritant responsiveness was measured in female C57Bl/6J mice 1, 3 or 8 days after intranasal instillation of 20 ug lipopolysaccharide (LPS, Sigma 011:B4) or vehicle. Non-invasive plethysmography was used to assess irritant sensitivity using the induction of sensory irritation, characterized as a decreased breathing frequency due to a braking in the early phase of expiration, as a biomarker for respiratory tract sensory nerve activation. Acetic acid (80 ppm) and environmental tobacco smoke (1.7 mg/m³) were used as prototypical irritants. As assessed by lavage cellularity, neutrophilic airway inflammation was present 1 and 3 days post LPS, but had resolved by day 8. Tidal volume and peak expiratory flow to tidal volume ratio were significantly decreased from control levels on days 1 and 3 post LPS as would be expected with lung inflammation; both of these parameters had returned to control levels by day 8. At the concentrations used, both acetic acid and environmental tobacco smoke induced a mild sensory irritation response; similar irritant responsiveness was observed in both control and LPS treated mice at all time points. Thus, in contrast to ovalbumin-induced allergic airway disease, LPS-induced neutrophilic airway inflammation did not enhance irritant responsiveness, suggesting that sensory irritant hyperresponsiveness may be related to the presence of eosinophils in allergic airway disease.

809 DEPOSITION EFFICIENCY OF INHALED PARTICLES FROM 30 NM TO 10 μM IN DIFFERENT INDIVIDUAL HUMAN NASAL REPLICAS.

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Inhaled air that is filtered by the nose may prevent toxic particles from reaching the lungs. The deposition efficiency of the nose may be studied by using anatomically accurate nasal replicas. Nasal replicas were produced from magnetic resonance imaging (MRI) scans from four healthy individual humans, using a stereolithography process. In another individual with atrophic rhinitis, computed tomography (CT) scans were made pre- and post-reconstructive surgery that narrowed the nasal passages. Deposition efficiency measurements were made by producing a monodisperse aerosol and measuring particle concentration at the inlet and outlet to the nasal replica. A vibrating orifice aerosol generator was used to produce monodisperse particles from 1 to 10 μm in aerodynamic diameter. Nano-sized particles were produced using a nebulizer and differential mobility analyzer to select sizes from 30 to 100 nm. An aerodynamic particle sizer and scanning mobility particle sizer were used to count micrometer- and nanometer-sized particles, respectively. Airflow through the nasal replicas was in the inspiratory direction at a constant rate. Experimental results showed that nanoparticles around 100 nm were deposited with < 10% deposition efficiency that increased slightly as particle size decreased to 30 nm. Nanoparticle deposition efficiency did not differ significantly between the various replicas. At a particle size of 8 μm and flow rate of 20 L/min, deposition efficiency ranged from about 60% to 90% in the healthy nasal replicas. Particle deposition efficiency in the nasal replicas of pre- and post-surgical treatment for atrophic rhinitis differed significantly. Deposition in the pre-surgery nasal passages, which had a more open cross section, was much lower (about 20%) than in the narrowed post-surgery nasal passages. These studies suggest that nasal deposition efficiency and hence lung exposure may be less affected by variability in nasal passage geometry and airflow for nanoparticles than for larger-sized particles.

810 METHOD FOR EVALUATING PULMONARY DEPOSITION AND CLEARANCE OF DIFFERENT SIZED FINE-MODE PARTICLES IN A SINGLE ANIMAL.

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Over the last decade, great attention has been given to particles that are 2.5 μm in diameter or less (e.g., PM_{2.5}). While it is not uncommon for inhalation studies to involve the delivery of multiple sized particles, to trace the deposition and clearance pattern of particles of a specific size range, airborne particles generally have to be delivered in separate monodisperse aerosol applications. As a result, the deposition and clearance of different sized particles are evaluated in separate animal groups. This study describes a unique approach in which particles of varying sizes are delivered as a monodisperse aerosol and the deposition and clearance of these particles are evaluated within a single animal. Sprague Dawley rats were exposed to aerosolized 0.5, 1, and 3 μm microspheres (3hr/day, 3 consecutive days). Animals

were examined following the end of each exposure period, as well 24 and 48 hr following the last day of aerosolization. The mass concentrations of aerosolized 0.5, 1 and 3 μm microspheres were 0.3, 1.7 and 2.1 mg/m³, respectively. The deposition pattern for the different sized microspheres varied with airway pathlength, with the larger sized microspheres (3 μm) primarily depositing in the cranial lobe and the large airways. The deposition of 0.5 and 1 μm particles increased from the bronchus to the terminal bronchioles. Total particle burden (number) of 0.5 μm microspheres in the lung was observed to be 2- and 240-fold greater than the deposition of 1 and 3 μm microspheres, respectively. Significant clearance of 3 μm microspheres was noted (50% after 48 hr), whereas little clearance was found for 0.5 and 1 μm particles up to 4 days post-exposure. The retention pattern of the different sized microspheres corresponded well with known mechanisms of particle clearance. This study design could be used to assess how other air pollutants, which target different regions of the lung, may influence the total and regional pulmonary deposition and clearance patterns of different sized particles. USEPA R831714 and R832414

811 MURINE MODEL OF SO₂ EXPOSURE EFFECTS ON AIRWAY INFLAMMATORY PROCESSES.

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Oxidant air pollutants (ozone, oxides of sulfur and nitrogen, fine particulates, and aldehydes) are among the known risk factors contributing to the development of asthma and allergies. Sulfur dioxide (SO₂) is a known respiratory irritant and a major component of most PM 2.5 that induces bronchoconstriction in asthmatics, but its role as a modifier of allergic sensitization is less well understood. The generation of reactive oxygen species (ROS) may be responsible for the formation of an inflammatory profile leading to airway hypersensitivity and immunomodulation. C57/B6 mice and knock-out mice for the mast cell NADPH Oxidase (gp/91phox) gene and the epithelial NADPH oxidase gene (Duox1), were chamber exposed to both low (ambient exposure; 1 ppm) and high (accidental exposure; 50 ppm) dose SO₂. Mice were additionally sensitized to ovalbumin (Ova) by either IP injection or by nebulization. After Ova challenge, bronchoalveolar lavage (BAL) was collected for cell differentiation and cytokine profiling. Homogenized lungs were used for Bioplex cytokine measures and sulfite residue measures by fluorescent HPLC. Alternate lungs were removed and utilized for histopathology. Spleen T-cell proliferation was measured with H3-thymidine. Measurement of hypersensitivity to methacholine challenge was determined by the tracheal ring assay. High dose SO₂ induced an immunosuppressive effect, with evident damage to the epithelium, while exposure to ambient levels of SO₂ caused a Th2-type allergic response. Both exposures were dependent upon ROS production. ROS induced degranulation of mast cells appeared to be central to ambient level exposure responses, while signaling in epithelium appeared to be responsible for inflammation in the high level exposures. Ambient exposure via PM 2.5 may lead to asthma exacerbations through enhancement of allergic hypersensitivity. High concentration occupational exposure could lead to the syndrome known as occupational asthma via a chronic inflammatory state induced by ROS damage in the epithelium.

812 DIESEL PARTICLE INSTILLATION ENHANCES INFLAMMATORY AND NEUROTROPHIN RESPONSES IN THE LUNGS OF ALLERGIC BALB/C MICE.

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Neurotrophins, including nerve growth factor (NGF) mediate many features of allergic airways disease. Antibody blockade of NGF attenuates airways resistance associated with the allergen-specific airways responses in mice. Exposure to diesel exhaust particles (DEP) associated with the combustion of diesel fuel exacerbates allergic airways responses. We hypothesized that the intranasal instillation of DEP in allergic mice will increase the hallmark features of allergic airways disease including increased neurotrophin production. Ovalbumin (OVA)-sensitized and non-sensitized BALB/C mice were intranasally instilled six times over two weeks with 10 (DEP1) or 50 (DEP2) μg of the PM_{2.5} fraction of NIST SRM-2975 DEP or saline alone. The mice were then challenged with an OVA aerosol. Non-allergic mice instilled with DEP1 had a 2.7-fold increase in macrophages in the lung lining fluid one day after challenge, while those instilled with DEP2 had a 3-fold increase in macrophages and a 19-fold increase in eosinophils relative to saline instilled mice. OVA-allergic mice instilled with saline had increases in macrophages (2-fold) and eosinophils (7.1-fold) relative to non-allergic mice. DEP1 did not enhance OVA-induced responses. DEP2-exposed OVA-allergic mice had increases in macrophages (1.61-fold), eosinophils (1.45-fold), and neutrophils (1.78-fold) in the lung lining fluid one day after challenge relative to saline-instilled mice. DEP2 instillation also increased levels of the neurotrophin NT-3 (2-fold) in the lung lining fluid and serum IgE (1.4-fold) relative to saline-instilled mice. Three days after