Mechanisms of Particulate Toxicity: An Overview

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Background

- Carbon and ammonium nitrate are two of the major constituents of airborne particulate matter (PM) in California
- These types of particles have traditionally been considered to be relatively non-toxic at ambient concentrations.

Background

- The results of previous CARB-funded research in rats suggested that carbon and ammonium nitrate particles at a combined total concentration range of 250-300 μg/m^3 can induce:
  - a) proliferative changes in airway tissue (UC Davis)
  - b) changes in blood pressure and heart rate (UC Irvine)

Background

- In 1999, CARB took the unique step of funding three University of California campuses (Davis, Irvine, and San Francisco) to conduct inter-related experiments designed to further investigate how these relatively biologically inert particles might induce airway and cardiovascular toxicity in susceptible humans as well as sensitive animal models.

Mechanisms of Particulate Toxicity: UC Davis-UC Irvine-UCSF

- UC Davis: ovalbumin-sensitized Brown Norway rat exposed to aerosolized ovalbumin (a model of allergic airway inflammation that has some features of human asthma).
- UC Irvine: senescent Fischer 344N rat (a model relevant to elderly humans).
- UCSF: allergic asthmatic individuals

Mechanisms of Particulate Toxicity: UC Davis

- Four Brown Norway rat experiments:
  - 1) development of model of allergic airway inflammation
  - 2) development of protocol to optimize conditions of exposure to aerosolized ovalbumin (OVA)
  - 3) effects of PM (150 $\mu g/m^3$ ammonium nitrate and 100 $\mu g/m^3$ carbon) exposure for 2 days in “optimum” model of OVA sensitization and exposure
  - 4) effects of PM exposure for 3 and 6 days in the model
- *In vitro* culture of bronchial tissue specimens from UCSF human subjects with asthma

Mechanisms of Particulate Toxicity: UC Davis

- In Experiment 1, a reasonable model of allergic airway inflammation was developed.
- In Experiment 2, a single OVA challenge 2 wks after sensitization appeared to be the best protocol for subsequent PM experiments.
- In Experiment 3, a 2-day exposure to PM caused **no** increase in airway responsiveness, mucin production, or airway eosinophils (features of human asthma) beyond the effects of OVA challenge, but did induce increased airway epithelial cell proliferation in the sensitized/challenged animals.

Mechanisms of Particulate Toxicity: UC Davis

- In Experiment 4, neither 3 or 6-day exposure to PM caused an increase in airway eosinophils or airway epithelial cell proliferation beyond the effects of OVA; 3-day exposure caused an increase in mRNA for IL-4 (a cytokine involved in allergic inflammation), but this increase was absent after 6-day exposure.
- The results of the *in vitro* human tissue work will be discussed with the UCSF experiments.

Mechanisms of Particulate Toxicity: UC Irvine

- Senescent Fisher 344N rats were exposed to PM (150 μg/m^3 ammonium nitrate and 100 μg/m^3 carbon) with and without ozone (0.2 ppm) for 4 hrs and monitored for blood pressure (BP) and electrocardiographic data.
- In a second experiment, the effects of 3 consecutive days of 4-hr exposures to PM were compared to those of 3 days of filtered air (FA).

Mechanisms of Particulate Toxicity: UC Irvine

- In the single-day experiment, there was no effect of either PM or PM/ozone on BP or heart rate (HR).
- In the 3-day experiment, there were significantly greater falls in systolic BP across the PM exposures on days 1 and 3 compared to FA; there were no PM-related changes in HR; there was a PM-related decrease in HR variability (consistent with human epi. data).

Mechanisms of Particulate Toxicity: UCSF

- Allergic asthmatic subjects were exposed to PM (150 $\mu g/m^3$ ammonium nitrate and 150 $\mu g/m^3$ carbon) with and without ozone (0.2 ppm) for 4 hrs as well as to 3 consecutive days of 4-hr exposures to PM.
- Lung function and heart rate variability (HRV) were measured across/during the exposures and bronchoscopy was performed 6 hrs after the 1-day and the 3rd of the 3-day consecutive exposures to assess airway inflammation.

Mechanisms of Particulate Toxicity: UCSF

- Airway inflammatory changes in bronchoalveolar lavage fluid were confined to the PM/ozone exposures.
- 4-hr exposure to PM was associated with a small, but significant decrease in one measure of lung function, FEF_{25-75}.
- 4-hr exposure to PM/ozone, but not PM alone, was associated with significant changes in HRV.

Mechanisms of Particulate Toxicity: UCSF

- *In vitro* culture of bronchial tissue specimens from the UCSF subjects was performed at UC Davis.
- The tissue specimens were cultured with and without treatment with specific allergen (i.e., an allergen to which the subject was sensitized).
- mRNA expression of multiple cytokines was measured and there was evidence of both PM and ozone effects for certain cytokines.

Mechanisms of Particulate Toxicity: UC Davis-UC Irvine-UCSF

- Key findings
  - No enhancement of allergic airway inflammation by carbon and ammonium nitrate particles in BN rats
  - These particles did induce airway epithelial cell proliferation, confirming the previous UC Davis findings.
  - 4-hr exposures on 3 consecutive days induced decreases in both BP and HRV in senescent rats.
  - PM/ozone but not PM alone induced decreased HRV in young asthmatic individuals.

Mechanisms of Particulate Toxicity: UC Davis-UC Irvine-UCSF

- Taken together, the results of the experiments at the three UC campuses suggest that exposure to carbon and ammonium nitrate particles at concentrations approximately an order of magnitude higher than ambient air can induce adverse effects in animal models of allergic airway inflammation and the elderly as well as, in combination with a high-ambient exposure to ozone, in allergic asthmatic humans.
- Future research should address the mechanisms of epithelial cell proliferative and decreased HRV effects.