Chronic Cardiopulmonary Diseases Enhance Susceptibility to Environmental Exposures

Sensitive Sub-Populations

Urmila P. Kodavanti, Mette C. Schladweiler, Allen D. Ledbetter, William P. Watkinson, Srikanth S. Nadadur, Robert C. MacPhail, MaryJane Selgrade, Daniel L. Costa
Experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, ORD, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, 27711.

Environmental Issue

Cardiovascular and chronic pulmonary diseases rank number 1 and number 4, respectively, in causation of human mortality world wide. As humans age, nearly 40% experience hypertension, a precursor for the development of cardiovascular disease. Thus, the health and economic impacts of cardiovascular diseases are enormous. A variety of environmental factors interact with genetics in the expression of these diseases. While genetic polymorphisms associated with susceptibility to develop cardiovascular diseases are being rapidly investigated, environmental factors such as life style, diet, and unnatural environmental exposures have been linked to cardiovascular diseases for decades. Tobacco smoke-related risk for developing atherosclerosis is a well established example of how inhaled pollutants increase the risk of cardiovascular disease. Recently, increases in air pollution have been linked to a risk of exacerbating myocardial infarction. Thus, the effects of environmental exposures have been more readily apparent in individuals with preexisting cardiovascular and other diseases (the susceptible subgroups).

Why humans are variably susceptible to environmental exposures

Genetic Make-up
Monogenic/polygenic
-Disease sensitivity
-Species/strain
-Gender

Environmental Factors
-Exposures
-Infections
-Personal habitats
-Nutrition

Susceptibility to develop a disease is determined by genetic make-up and its interaction with environmental factors. Further, due to genetics and modified host physiology, individuals with diseases are even more susceptible to subsequent environmental exposures such as air pollution.

How variability can be accounted for in determining risk

Healthy Animal → Diseased Animal
Healthy Human → Diseased Human

Toxicological Paradigm: The use of susceptible disease models in extrapolation to diseased humans

Objectives

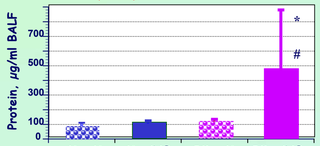
- Develop/identify animal models representing humans with cardiovascular and pulmonary diseases
- Determine relative susceptibility of disease models and investigate pathobiological mechanisms to aid in reducing uncertainty

Which animal models of human cardiovascular and pulmonary diseases are employed in air pollution health effects studies?

- Chronic Bronchitis
- Chronic Obstructive Pulmonary Disease (COPD)
- Pulmonary Hypertension
- Systemic Hypertension/Congestive Heart Failure

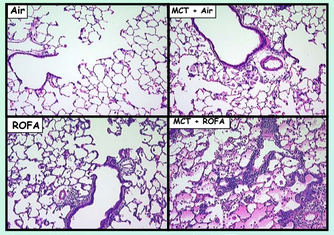
What happens when susceptible animals are exposed to air pollution?

Bronchitic but not healthy rats demonstrate inflammatory response to real-time ambient PM

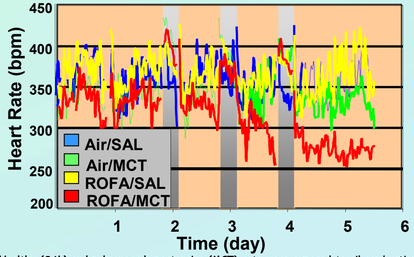


Rats were made bronchitic and then exposed to real-time concentrated ambient PM (CAPs, ~650 µg/m3, 6 h/d, 2d). Pulmonary injury was assessed by determination of protein in their lung washings (BALF).

Lung pathology and heart rate changes are greatly exacerbated following combustion PM exposure in pulmonary hypertensive rats

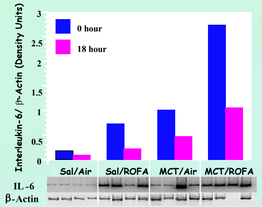


Healthy (air) and pulmonary hypertensive (MCT) rats were exposed to oil combustion PM (ROFA) by inhalation (15 mg/m3x6h/dx3d) and lung pathology was determined.



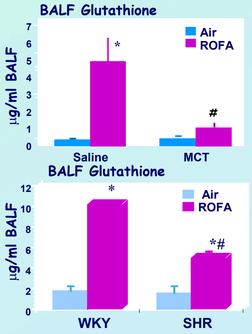
Healthy (SAL) and pulmonary hypertensive (MCT) rats were exposed to oil combustion PM (ROFA) by intratracheal instillation and heart rates were determined by radiotelemetry.

Exacerbated gene expressions in diseased animals following PM exposure provide insight into the mechanism of susceptibility



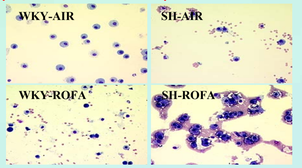
Healthy (Sal) and pulmonary hypertensive (MCT) rats were exposed to oil combustion PM (ROFA) by inhalation (15 mg/m3x6h/dx3d) and lung interleukin-6 expression was determined using polymerase chain reaction.

Like healthy rats, pulmonary and systemically hypertensive rats cannot increase their antioxidant compensation in response to PM-induced injury



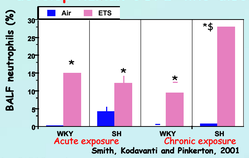
Healthy (Saline) and pulmonary hypertensive (MCT) (upper) or healthy (WKY) and systemically hypertensive (SHR) rats (lower) were exposed to oil combustion PM (ROFA) by inhalation (15 mg/m3x6h/ dx3d) and lung glutathione,an antioxidant was measured in lung washings

Hypertensive rats have a greater hemorrhagic response to combustion particles inhalation



Healthy (WKY) and systemically hypertensive (SH) rats were exposed to oil combustion PM (ROFA) by inhalation (15 mg/m3x6h/ dx3d) and the presence of red blood cells was visualized in their lung washings

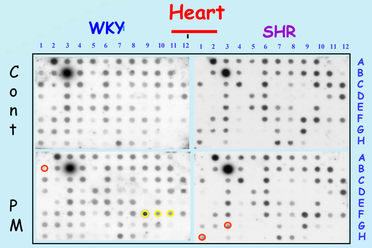
Susceptible rats exposed to tobacco smoke develop human COPD-like disease



Smith, Kodavanti and Pinkerton, 2001

Healthy (WKY) and systemically hypertensive (SH) rats were exposed to tobacco smoke (85mg/m3x6h/dx2d) and the presence of inflammatory neutrophils was determined in their lung washings.

We use state-of-the-art gene array technology to understand biological mechanisms of susceptibility. Pulmonary exposure to PM can cause gene expression changes in the hearts of hypertensive rats.



Healthy (WKY) and systemically hypertensive (SH) rats were exposed to residual oil fly ash by intratracheal instillation and lung RNA was isolated and used for gene expression analysis using gene array approach.

Summary and Conlcusions

- Rats exhibiting cardiovascular and chronic pulmonary diseases are more vulnerable to adverse PM health effects
- Preexisting vascular disease/injury results in greater susceptibility to cardiovascular effects of PM
- Animal models with pulmonary and systemic hypertension have reduced ability to compensate by increasing antioxidants
- Genetically predisposed rats when exposed to cigarette smoke develop pulmonary injury/ inflammation similar to that of humans

Impact

The use of animal models mimicking human chronic cardiopulmonary diseases allows one to investigate the mechanism/s and the levels of susceptibility, which through extrapolation can then be used to determine variation in human susceptibility to air pollution.

Building the scientific foundation for sound environmental decisions