Cardiovascular Diseases, Susceptibility to Oxidative Injury and Compensatory Mechanisms: Insights from Rodent Models

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Issue:

- Individuals with cardiovascular disease (CVD) may suffer greater injury from air pollution exposure than healthy individuals.
- One of the reasons is that the body's ability to produce antioxidants is greatly reduced in diseased people.
- However, not all individuals with CVD would be expected to have similar susceptibility to environmental exposures.
- Better understanding of the variations in susceptibility allow one to make accurate estimates of risk and develop targeted therapeutic approaches.

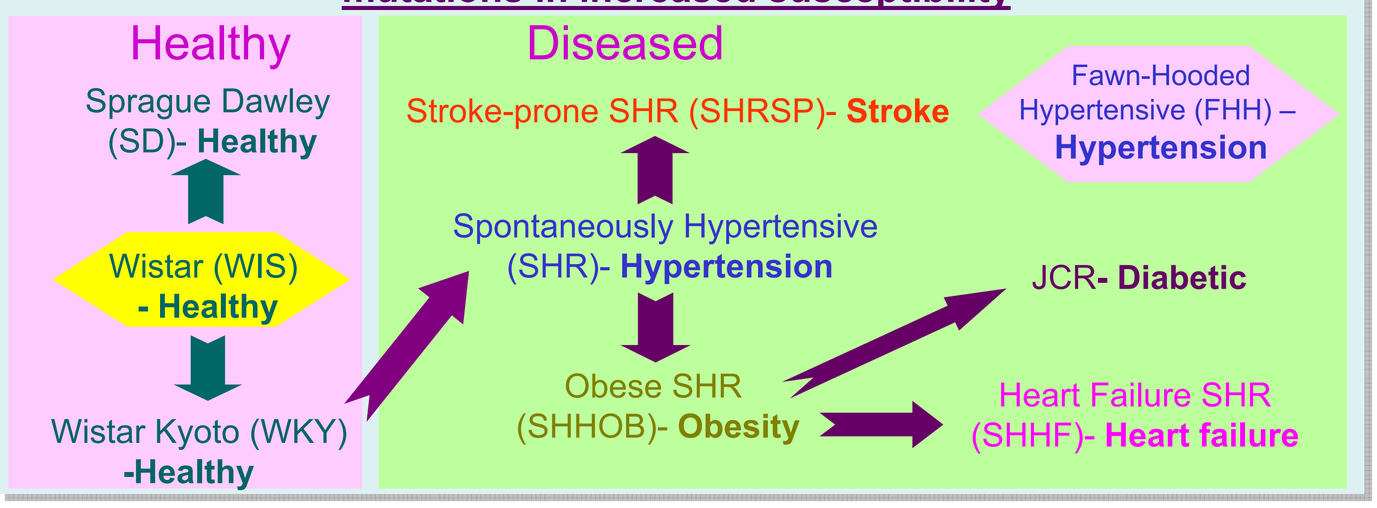
Questions:

- Are rat strains that demonstrate various forms of CVD more susceptible to acute ozone-induced oxidative injury?
- Does their antioxidant status predict greater susceptibility to ozone-induced injury?
- Are there links between susceptibilities to injury by ozone, antioxidants, and gene regulation?

Approach:

Expose healthy and CVD rat models to an environmental oxidant (ozone) and evaluate toxicity to the lung and levels of antioxidants such as glutathione and ascorbate. Evaluate gene expression patterns to identify biomarkers that can be linked to differences in susceptibility.

Use of healthy and naturally occurring polygenetic rat disease models helps in understanding the influence of disease and genetic mutations in increased susceptibility



Experiment Protocol

Healthy and CVD rat models

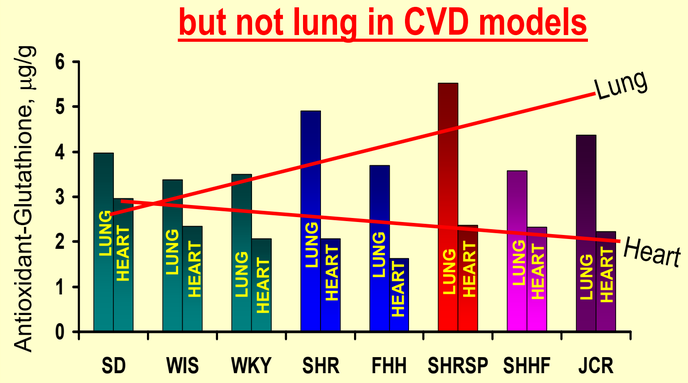
Air or 0.25, 0.5, 1.0 ppm Ozone exposure for 4 hours

Immediately or 1-day after ozone exposure

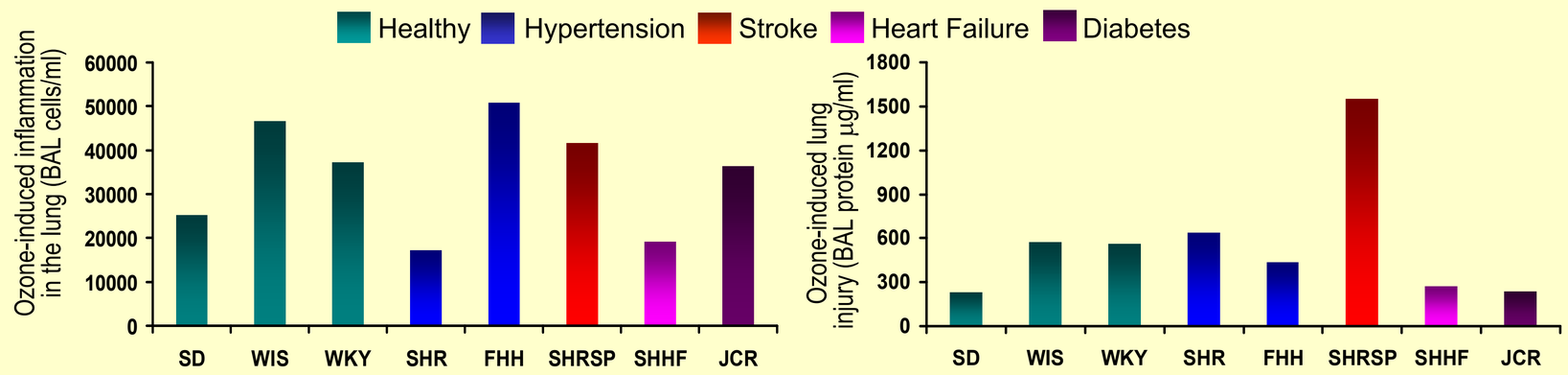
Analysis of:

- Bronchoalveolar lavage (BAL) markers of lung injury and inflammation
- Lung, and heart glutathione and ascorbate
- Protein and gene expression analysis
- Global gene expression profiling
- Single nuecleotide polymorphisms

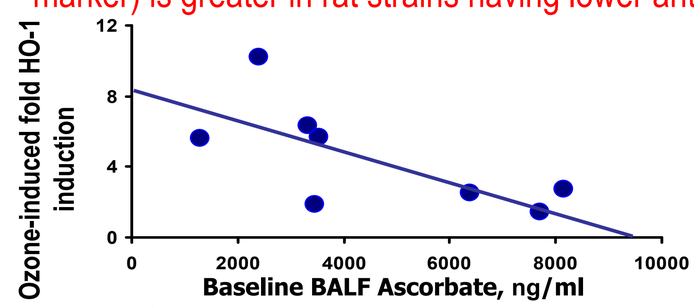
Antioxidant deficiency in the heart but not lung in CVD models



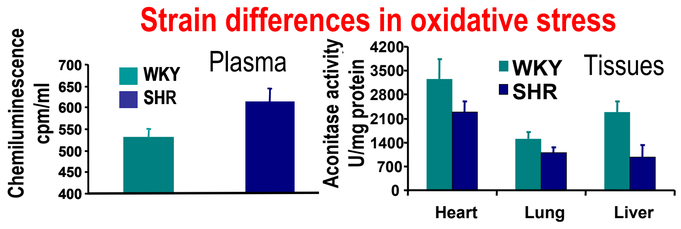
Ozone-induced lung inflammation and injury depend on the animal model of CVD



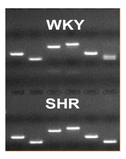
However, ozone-induced oxidative stress (HO-1 as a marker) is greater in rat strains having lower antioxidants



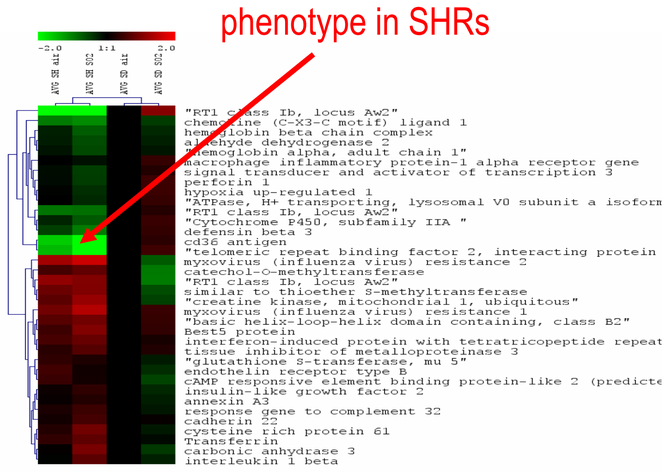
Strain differences in oxidative stress



Analysis of NRF-2 promoter single nucleotide polymorphism in WKY and SHR rats



Strain differences in gene expression pattern demonstrate obese-metabolic syndrome phenotype in SHRs



Greater oxidative stress in SHRs as determined by measurement of blood and tissue markers.

However, there are no differences in the NRF2-promoter sequence, which have been shown to produce oxidative stress in mice

Impact:

- Our results demonstrate that not all rat strains having CVD are more susceptible to ozone-induced injury.
- Study results provide an example of the complexities in relating chronic diseases, oxidative stress, genetic background, and antioxidant compensation.
- Redundancy in biological mechanisms, epigenetic controls, and genetic differences may all play a role in determining susceptibility to environmental stressors.
- Unraveling these complex relationships should provide a mechanistic understanding of susceptibility, and lead to efficient strategies for protecting the most vulnerable individuals.

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