Interface of Health Effects caused by the CardioMetabolic Syndrome and Exposures to Air Pollutant Mixtures

Jack R. Harkema
April 10, 2013
SOT Webinar
Pollution readings from the US Embassy (upper) and the local government shows hazardous levels of air pollution in Beijing on January 23, 2013. At the height of recent pollution, Beijing authorities said readings for PM2.5 -- particles small enough deeply to penetrate the lungs -- hit 993 micrograms per cubic meter, almost 40 times the World Health Organization's safe limit. (Mark Ralston/AFP/Getty Images)
This combination of photos shows the Beijing skyline during severe pollution on January 14, 2013, and the same view (click to fade) taken during clear weather on February 4, 2012. (Ed Jones/AFP/Getty Images)
Multipollutant approaches take into account that humans and ecosystems are exposed to many air pollutants at the same time.
National Public Health Burden Associated with Exposure to Ambient PM2.5 and Ozone

Fann et al. Risk Analysis. 32: 81-95, 2012
Annual PM-related deaths: 3.2 million
Annual world % of all DALY: 3.1%
CV population attributable factor: 22%

Lancet 2012; 380:2224-60
<table>
<thead>
<tr>
<th>Time</th>
<th>Pollutants</th>
<th>Health Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-2000</td>
<td>Gases ($O_3$)</td>
<td>Respiratory</td>
</tr>
<tr>
<td>2000-2010</td>
<td>Particulate Matter (PM)</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>2010 - 2020</td>
<td>Multipollutants</td>
<td>Whole Body</td>
</tr>
</tbody>
</table>
Recommendation: Address multiple pollutants in the NAAQS review and standard setting process

“Although the committee does not believe that the science has evolved to a sufficient extent to permit the development of multipollutant NAAQS, it would be scientifically prudent to begin to review and develop NAAQS for related pollutants in parallel and simultaneously”
“…discuss [the] challenges, along with opportunities and future research needs related to multipollutant approaches for the evaluation of health risks associated with exposures to air pollution.”

For the purpose of the workshop, they generally used Dan Greenbaum’s definition of multipollutant:

“a discrete and perhaps manageable set of compounds (i.e., the criteria pollutants and a subset of priority air toxics).”
Outline

• EPA-Funded, University-based Clean Air Research Centers (CLARCs)

• Interface of two global health problems — the CardioMetabolic Syndrome (CMS) and Air Pollution

• Initial results of inhalation toxicology studies from the Great Lakes Air Center for Integrated Environmental Research (GLACIER, one of the CLARCs)
Clean Air Research Centers

- Univ. Washington
- GLACIER
- SCAPE
- Harvard
- EPA - RTP

Slide from Dr. Dan Costa
Key Objectives:

• Research health effects of exposure to particulate matter (PM), ozone, and other air pollutants, both singularly and in multipollutant atmospheres.

• Take an integrated approach to their study designs.

• Consider social factors (e.g. where people live) when studying health effects to air pollution sources (e.g. traffic)
Explore and elucidate one of the most prevalent and important global health-environment interfaces:

*Inter-relationships between facets of the cardiometabolic syndrome and air pollution*
Biological pathways linking PM exposure with cardiovascular diseases

Blood
- PM or constituents in the circulation
  - UFP, soluble metals
  - Organic compounds

Vasculature
- Vasoconstriction
- Endothelial dysfunction
- PM-mediated ROS
  - ↑ BP
  - ↑ Atherosclerosis

Blood
- ↑ Platelet aggregation

Bronchioles/Alveoli
- PM and/or constituents transmitted into blood
- Pulmonary oxidative stress & inflammation
- "Systemic spill-over"

Systemic Oxidative Stress and Inflammation
- Cellular inflammatory response (↑ activated WBCs, platelets, MPO)
  - ↑ Cytokine expression/levels (↑ IL-1β, IL-6, TNF-α)
  - ↑ ET, histamine, cell microparticles, oxidized lipids; ↓ anti-oxidants

PM or constituents in the circulation

ANS imbalance
- ↑ SNS / ↓ PSNS

Vasculature
- Vasoconstriction
- Endothelial dysfunction
- Neural-mediated ROS
  - ↑ BP

Blood
- ↑ Platelet aggregation

Heart
- ↓ HRV
- ↑ Heart rate
- ↑ Arrhythmia potential

Brook RD et al. Circulation 2010;121:2331-2378
Who are susceptible to the health effects of air pollution?

- Those with chronic pre-existing diseases
  - Respiratory diseases (asthma, COPD)
  - Cardiovascular diseases (atherosclerosis)
  - Diabetes, obesity, metabolic syndrome
- Children and older adults
- Those with specific polymorphisms
- The unborn fetus
- Those with low socioeconomic status

Increased Prevalence of Obesity
The Metabolic Syndrome

• Cluster of Risk Factors for CVD and Diabetes: Central Obesity; Dyslipidemia; Hyperglycemia; Hypertension; Insulin Resistance

• Dr. Gerald Reaves, Stanford University, 1988 Banting Lecture

• Syndrome X, Insulin Resistance Syndrome, CardioMetabolic Syndrome

• Increased risk of heart attack (2X), stroke (2X), and diabetes (5X)

• 20-25% of world population
Prevalence of the MetS Across Age Groups and Gender in Various Countries

Cornier M et al. Endocrine Reviews 2008;29:777-822
Insulin Resistance in Obesity as the Underlying Cause for the Metabolic Syndrome

Our Current Research Questions

Q1. What multipollutant atmospheres in the Great Lakes Region adversely affect human health?

Q2. Does diabetes, obesity, or unhealthy diets make people more susceptible to the health effects of air pollution?
Proposed Pathogenesis

CARDIOVASCULAR EVENTS

DIABETES
- Insulin resistance and Obesity

ATHEROSCLEROSIS
- Elevated Blood Pressure
- Vascular Dysfunction
- Alterations of Lipids in the Blood
  - Impaired HDL function

CARDIOMETABOLIC SYNDROME
- Inflammation, Oxidative Stress, Autonomic Nervous System Imbalance

Air Pollution
- Ozone, PM

Lifestyle Factors
- High fat or sugar diets; Genetics
Opposing Effects of Particle Pollution, Ozone and Ambient Temperature on Arterial Blood Pressure


- **Panel study in 70 subjects with type 2 diabetes mellitus**
- Applied linear mixed models to investigate associations
- Interquartile increase in **PM** associated with **increased blood pressure**
- Interquartile increase in **Ozone** associated with **decreased blood pressure**

![Graph showing relative change in systolic blood pressure (%) for various pollutants and days](image-url)
Center Projects

PROJECT 2: Dr. Harkema
Acute CAP & O3 exposures;
Rodent models of CMS
CMS, autonomic, airway outcomes

PROJECT 3: Dr. Rajagopalan
Subchronic CAP & O3 exposure;
Murine models of CMS
CMS outcomes

PROJECT 1: Dr. Brook
Acute CAP exposures;
Human subjects: lean & obese
CMS outcomes

SHORT-TERM STUDIES

HUMAN STUDIES

ANIMAL STUDIES

Air Pollution Mixtures

Cardiometabolic Responses

Obesity Diet

PM-OBESITY/DIET INTERFACE
Interactions mediating
Susceptibility to CMS;
Synergy with PM & Ozone

LONG-TERM STUDIES

SHORT-TERM STUDIES
To provide insights into the health effects of PM, O₃, and their coexposures in a multipollutant context.
Cardio-metabolic Effects of Exposure to Differing Mixtures and Concentrations of Coarse and Fine Concentrated Ambient Particles in Obese and Lean Adults

Robert Brook, MD\textsuperscript{1}, Elif Oral, MD\textsuperscript{1} 
Marianna Kaplan, MD\textsuperscript{1} and Jesus Araujo, MD\textsuperscript{2}

\textsuperscript{1}The University of Michigan, Ann Arbor, MI
\textsuperscript{2}University of California, Los Angeles, CA
### PROJECT 1: Reduced insulin sensitivity in human subjects with 5-day ambient PM$_{2.5}$ exposure

*Sci Total Environ.* 2013 Mar 15;448:66-71

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>$\beta^*$</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN (msec) [HEART RATE VARIABILITY]</td>
<td>-13.1</td>
<td>-25.3 to -0.9</td>
<td>0.035</td>
</tr>
<tr>
<td>†HOMA-IR [METABOLIC INSULIN SENSITIVITY]</td>
<td>0.7</td>
<td>0.1 to 1.3</td>
<td>0.023</td>
</tr>
</tbody>
</table>

† Homeostasis model assessment of insulin resistance: \[\text{glucose (mg/dL)} \times \text{insulin (µU\text{•ml}^{-1})}/405\]

(Lower values denote better metabolic insulin sensitivity)

**Autonomic imbalance may be the mechanism linking PM to insulin resistance**

SDNN was inversely associated with HOMA-IR ($\beta=-0.13$ per 10 msec HRV change, $p=0.035$).

*BMI and/or age-adjusted (per 10 µg/m$^3$ of 5-day PM$_{2.5}$ average)*
Long-term Metabolic Consequences of Exposures to Multipollutant Atmospheres in the Great Lakes Region

Sanjay Rajagopalan, MD and Qinghua Sun, MD

The Ohio State University, Columbus, OH
Project 3: Aim 1

Hypothesis: Near-roadway CAP exposure promotes development of obesity and insulin resistance.

Design: C57Bl/6 model fed normal chow or high-fat chow and exposed to FA/CAP for 12 or 18 weeks. KKAy mice exposed to CAP over 8-10 weeks

- To assess effects of multi-pollutant CAP (regional vs. near-roadway) on glucose and insulin homeostasis, inflammation and insulin signaling pathways.
- To identify inflammatory chemokine mediators.
- To investigate temporal response of multi-pollutant CAP and CMS effects.

KKAy Mice = Heterozygous for the yellow spontaneous mutation (Ay). Progressively develop insulin resistance, obesity over 6-12 weeks
Effect of Regional CAP Exposure in a Model of Genetic Type II DM (KKAy Mouse Model)

EXPOSURE CONCENTRATIONS
(Columbus Regional: 12/28/2011-02/28/2012)

<table>
<thead>
<tr>
<th></th>
<th>Ambient</th>
<th>FA</th>
<th>CAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM 2.5 (µg/m³)</td>
<td>8.27</td>
<td>1.51</td>
<td>102.9</td>
</tr>
</tbody>
</table>

Enrichment Factor = 12.22

4-5 wk-old KKAy mice exposed to FA or CAP (normal diet)
Regional CAP Exposure and Insulin Resistance Measures in Genetic Type II DM (KKAy Model)

*P<0.05, **P<0.01, ***P<0.001 vs respective FA group.
Hypothesis for Air Pollution-Mediated Type 2 DM/Insulin Resistance

PM$_{2.5}$

Unhealthy Diet

Danger Signals

TLRs/NLRs

Oxidative Stress (NADPH oxidases)

Systemic Inflammation

Brain Inflammation

Liver
- Gluconeogenesis
- Lipid Deposition
- NAFLD like pathology
- ER stress

WAT
- Inflammation
- Altered adipokines

Muscle
- Glucose Uptake

Vasculation
- Endothelial dysfunction
- Inflammation vasoconstriction

BAT
- Altered mitochondrial morphology/function

UCP-1

Insulin Resistance

Liu C et al. Toxicol Pathol 2012;41:361-373
Project 2: Short-Term Animal Studies

Cardiometabolic, Autonomic, and Airway Toxicity of Acute Exposures to PM$_{2.5}$ from Multipollutant Atmospheres in the Great Lakes Region

Jack Harkema, DVM, PhD$^1$, Greg Fink, PhD$^1$
James Wagner, PhD$^1$, Masako Morishita$^2$, Tim Dvonch$^2$, Cathie Spino$^2$, and Bhramar Mukherjee$^2$

$^1$Michigan State University, East Lansing, MI
$^2$The University of Michigan, Ann Arbor, MI
Project 2: Animal Toxicology Studies

- CAPs ± O3
- ND
- HFrD

Graphs and charts showing measurements related to PM2.5 concentration and other factors.
High Fructose Diet

- Fructose has the same chemical formula as glucose ($C_6H_{12}O_6$), but with different stereochemistry.
- Metabolism of fructose differs from glucose, and is insulin independent.
- Rats on a high fructose diet develop facets of the CardioMetabolic Syndrome in 10 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Normal Diet (Teklad 22/5)</th>
<th>60% Fructose Diet (TD.89247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (% by weight)</td>
<td>22.0 %</td>
<td>18.3%</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>40.6 %</td>
<td>60.4%</td>
</tr>
<tr>
<td>Fat</td>
<td>5.5 %</td>
<td>5.2%</td>
</tr>
<tr>
<td>Kcal/g</td>
<td>3.0</td>
<td>3.6</td>
</tr>
</tbody>
</table>
High Fructose Diet-Induced CMS

Sprague Dawley Rats; 10 weeks on High Fructose Diet

Insulin Resistance

![Graph showing HOMA-IR levels for Normal Diet and High Fructose Diet.](image)

- Normal Diet: 4
- High Fructose Diet: 16

Insulin Resistance

Hypertension

![Graph showing Mean Arterial Pressure for Normal Diet and High Fructose Diet.](image)

- Normal Diet: 80
- High Fructose Diet: 110

Hypertension

Systolic Pressure

![Graph showing Systolic Pressure for Normal Diet and High Fructose Diet.](image)

- Normal Diet: 80
- High Fructose Diet: 110

Dyslipidemia

![Graph showing Serum Triglycerides (mg/dL) for Normal Diet and High Fructose Diet.](image)

- Normal Diet: 200
- High Fructose Diet: 800

Dyslipidemia

Hepatic Steatosis

- Increased hepatic triglycerides
- No weight gain
- Elevated HR
- Decreased HRV

Hepatic Steatosis
### Study 1: Dearborn Study Design

<table>
<thead>
<tr>
<th>Diet</th>
<th>Air</th>
<th>*CAPs (PM2.5)</th>
<th>O3 (0.5 ppm)</th>
<th>O3 &amp; CAPs Mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (ND)</td>
<td>8 rats</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>High Fructose (HFrD)</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

- Male rats on diet for 8 wks prior to and during exposure
- Daily 8h-exposures for two weeks (5 & 4 days/wk; 9 total exposure days)
- ~400 µg/m³ Concentrated Ambient Fine Particles (CAPs)
- Animal necropsies one day after last exposure
Urban/Industrial Exposure Site

*AirCARE 2 in Dearborn, MI

Salina Elementary School

Steel Manufacturing Plant

Michigan Department of Environmental Quality Monitoring Site
8 rats with implanted telemeters in each exposure chamber

30-second recordings every 5 minutes during daily 8-hour exposures
## Chamber Concentrations

<table>
<thead>
<tr>
<th>Air Pollutant</th>
<th>Average Daily Concentrations (Mean ± Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozone (O3)</td>
<td>0.50 ± 0.03 ppm</td>
</tr>
<tr>
<td>CAPs (PM2.5)</td>
<td>444 ± 196 µg/m3</td>
</tr>
<tr>
<td>O3 &amp; PM2.5 Mixture</td>
<td>O3: 0.49 ± 0.04 ppm</td>
</tr>
<tr>
<td></td>
<td>CAPs: 356 ± 261 µg/m3</td>
</tr>
</tbody>
</table>
Effect of Repeated Exposure of Air Pollutants on HR in HFr-fed Rats

Heart Rate (bpm) for ND group

*Horizontal lines = daily averages
Effect of Air Pollutants/Diets on SBP

Normal Diet-Fed Rats

Day 1: 7:30AM - 3:30PM

High Fructose Diet-Fed Rats

Day 1: 7:30AM - 3:30PM

Exposure
- AIR
- CAPs
- CAPs/O3
- O3
Results – Heart Rate

**Ozone**

Daily Effect of Ozone Exposure on Heart Rate
In Rats Fed Normal or High Fructose Diets

**PM2.5**

Daily Effect of CAPs Exposure on Heart Rate
In Rats Fed Normal or High Fructose Diets
Results – Heart Rate

Ozone + PM2.5

Daily Effect of Ozone+CAP Co-Exposure on Heart Rate
In Rats Fed Normal or High Fructose Diets

Change in Heart Rate (bpm)

-80 -60 -40 -20 0 20 40

Normal Diet
High Fructose Diet

Week 1
Week 2
Days of Exposure
Days of Exposure
Results – Heart Rate

Ozone

PM2.5

Ozone + PM2.5

During Exposure

Nightly Postexposure Effect of Ozone Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets

Nightly Postexposure Effect of CAP Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets

Nightly Postexposure Effect of Ozone+CAP Co-Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets

Post Exposure Evening

Nightly Postexposure Effect of Ozone Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets

Nightly Postexposure Effect of CAP Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets

Nightly Postexposure Effect of Ozone+CAP Co-Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets
Results – Blood Pressure

**Ozone**

Daily Effect of Ozone Exposure on Blood Pressure in Rats Fed Normal or High Fructose Diets

<table>
<thead>
<tr>
<th>Change in Mean Arterial Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
</tr>
<tr>
<td>-10</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

Normal Diet | High Fructose Diet

Week 1

**PM2.5**

Daily Effect of CAP Exposure on Blood Pressure in Rats Fed Normal or High Fructose Diets

<table>
<thead>
<tr>
<th>Change in Mean Arterial Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
</tr>
<tr>
<td>-10</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

Normal Diet | High Fructose Diet

Week 1

**Ozone + PM2.5**

Daily Effect of CAP+Ozone Co-Exposure on Blood Pressure in Rats Fed Normal or High Fructose Diets

<table>
<thead>
<tr>
<th>Change in Mean Arterial Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
</tr>
<tr>
<td>-10</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

Normal Diet | High Fructose Diet

Week 1

Nightly Postexposure Effect of Ozone Exposure on Blood Pressure in Rats Fed Normal or High Fructose Diets

<table>
<thead>
<tr>
<th>Change in Mean Arterial Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
</tr>
<tr>
<td>-10</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

Normal Diet | High Fructose Diet

Week 1

Nightly Post Exposure Effect of CAP Exposure on Blood Pressure in Rats Fed Normal or High Fructose Diets

<table>
<thead>
<tr>
<th>Change in Mean Arterial Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
</tr>
<tr>
<td>-10</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

Normal Diet | High Fructose Diet

Week 1

Nightly Postexposure Effect of CAP+Ozone Co-Exposure on Blood Pressure in Rats Fed Normal or High Fructose Diets

<table>
<thead>
<tr>
<th>Change in Mean Arterial Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
</tr>
<tr>
<td>-10</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

Normal Diet | High Fructose Diet

Week 1
How do air pollutants cause a drop in HR and BP?

- Trigeminocardiac reflex (TCR) causes bradycardia (increased parasympathetic activity) and is the most powerful autonomic reflex in the body.

- Irritants induce stimulation of airway sensory nerves and transient receptor potential channels (TRPs; e.g., TRPA1)

- Does O3 and/or CAPs cause a drop in HR and BP through TCR and/or TRPs?

- What are the mechanism(s) underlying HFrD enhancement of the exposure-induced bradycardia and hypotension?
Exposure-induced nasal airway inflammation and epithelial remodeling

- Neutrophils/mm basal lamina
- Epithelial cells/mm basal lamina

Comparison of different diets and exposure conditions:
- Normal Chow
- 60% High Fructose
- Air control
- CAPs
- O3
- CAPs/O3

Significance levels:
- * indicates a significant difference compared to Normal Chow
- # indicates a significant difference compared to 60% High Fructose
- & indicates a significant difference between CAPs and O3
- + indicates a significant difference between CAPs/O3 and CAPs

Histological images showing v (vasa) and e (epithelial cells) with scale bars of 50 μm.
Heart Rate Variability in Health and Disease

- **Parasympathetic Nerves**: Slows HR
- **Sympathetic Nerves**: Influenced by both sympathetic and parasympathetic input

**SDNN**: Standard Deviation of Normal to Normal Beats
- Influenced by both sympathetic and parasympathetic

**RMSSD**: Root Mean Square of Successive Differences
- Influenced predominately by vagal input
Heart Rate Variability in Health and Disease
Effects of O3 and PM2.5 Exposures on SDNN

Results: Heart Rate Variability

a = significantly different from respective group exposed to AIR
b = significantly different from respective group fed a Normal Diet
Effects of O3 and PM2.5 Exposures on RMSSD

- O3
- PM2.5
- PM2.5 + O3

a = significantly different from respective group exposed to AIR
b = significantly different from respective group fed a Normal Diet
**Results – Daily HRV**

**Ozone**

*Daily Effect of Ozone Exposure on rMSSD In Rats Fed Normal or High Fructose Diets*

<table>
<thead>
<tr>
<th>Day of Exposure</th>
<th>Normal Diet</th>
<th>High Fructose Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>Week 2</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
</tbody>
</table>

**PM2.5**

*Daily Effect of CAP Exposure on rMSSD In Rats Fed Normal or High Fructose Diets*

<table>
<thead>
<tr>
<th>Day of Exposure</th>
<th>Normal Diet</th>
<th>High Fructose Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>Week 2</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Ozone + PM2.5**

*Daily Effect of CAP+Ozone Exposure on rMSSD In Rats Fed Normal or High Fructose Diets*

<table>
<thead>
<tr>
<th>Day of Exposure</th>
<th>Normal Diet</th>
<th>High Fructose Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td>Week 2</td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
</tbody>
</table>
Central Control of Heart Rate: Hypothalamus

Paraventricular Nucleus: $\alpha_2$-adrenoceptors
Activation decreases HR and BP

High Fructose Rats:
Supersensitivity of $\alpha_2$-adrenoceptors

Central Control of Heart Rate: Hypothalamus

Exposure to concentrated PM2.5 increases production of norepinephrine in the paraventricular nucleus

Summary of Current Findings

• High fructose diet produced facets of the CMS in rats (e.g., hypertension, insulin resistance, hyperglycemia, and hepatic steatosis).

• On a normal diet, heart rate variability was enhanced with O3, decreased with CAPS, and markedly decreased with CAPs & O3.

• On a high fructose diet, changes in heart rate variability were blunted to O3, CAPs, or CAPs+O3 exposures.

• Acute exposures to O3, CAPs, or CAPs+O3 caused reductions in BP and HR that were markedly enhanced in HFrD-fed rats.

• Enhanced BP and HR responses, and blunting of HRV responses, in HFrD-fed rats suggest a diet-induced dysfunction in the autonomic nervous system.

• CAPs+O3 caused a greater decrease in BP and HR in the first few days of exposure, but a quick adaptive response with repeated exposures.
GOAL: Conduct animal CAPs exposures in different sites selected for their unique PM atmospheres: e.g., urban, rural, industrial, traffic.

### PM Characterization and Air Chemistry:

<table>
<thead>
<tr>
<th>Measurement</th>
<th>PM Property</th>
<th>Sampling Media</th>
<th>Sample Duration (hr)</th>
<th>Analytical Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEOM</td>
<td>Mass</td>
<td>-</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>APS 3320</td>
<td>Size (0.5-20 μm)</td>
<td>-</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Aethelometer</td>
<td>Black carbon</td>
<td>-</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>SMPS 3936</td>
<td>Size (0.01-0.6 μm)</td>
<td>-</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>MOI</td>
<td>Size (10 stages)/Mass &amp; Trace elements</td>
<td>Teflon</td>
<td>8</td>
<td>Gravimetric/ICP-MS</td>
</tr>
<tr>
<td>Filter (PM$_{2.5}$)</td>
<td>Trace elements</td>
<td>Teflon</td>
<td>8</td>
<td>Gravimetric/ICP-MS</td>
</tr>
<tr>
<td>Filter (PM$_{2.3}$)</td>
<td>Soluble trace elements</td>
<td>Teflon</td>
<td>8</td>
<td>Gravimetric/ICP-MS</td>
</tr>
<tr>
<td>PM2.5</td>
<td>Trace Elements, aqueous</td>
<td>30 minute</td>
<td>SEAS / ICP-MS</td>
<td></td>
</tr>
<tr>
<td>Annular Denuder-Filter Pack System</td>
<td>Acid gases &amp; aerosols and major ions</td>
<td>Teflon/Glass/denuders</td>
<td>8</td>
<td>IC/pH</td>
</tr>
<tr>
<td>Filter</td>
<td>Elemental &amp; organic carbon</td>
<td>Quartz</td>
<td>8</td>
<td>TOA</td>
</tr>
</tbody>
</table>

SEAS: Semi-continuous Elements in Aerosol Sampler
Component- and Source-associated Health Effects in Animal Studies with CAPs

RMSSD (msec)

Mo concentration (ng/m$^3$)

Fe concentration (ng/m$^3$)

S concentration (ng/m$^3$)

Selenium (ng/m$^3$)

Iron (ng/m$^3$)

Molybdenum (ng/m$^3$)
Component- and Source-associated Health Effects in Animal Studies with CAPs

**Semi-continuous HRV and Sources (30min)**

- **PM<sub>2.5</sub> concentration** (µg/m³)
- **RMSSD (msec)**

**Component and Source-**
- Unidentified
- Cement/Lime
- Coal
- Metal
- Sludge
- Motor/Diesel
- Refinery
OBJECTIVE:
We used a rat model to investigate linkages between cardiac effects of concentrated ambient particle (CAP) constituents and source factors using a unique, highly time-resolved data set.

METHODS:
Spontaneously hypertensive rats inhaled Detroit Michigan, CAPs during summer or winter (2005-2006) for 13 consecutive days. Electrocardiogram data were recorded continuously, and heart rate (HR) and heart rate variability (HRV) metrics were derived. Extensive CAP characterization, including use of a Semicontinuous Elements in Aerosol Sampler (SEAS), was performed, and positive matrix factorization was applied to investigate source factors.
Acknowledgments

• **MSU**: Drs. Katy Allen, Jim Wagner, and Greg Fink
• **UM**: Drs. Robert Brook, Tim Dvonch, Masako Morishita, Bin Nan, Cathie Spino and Bhramar Mukherjee
• **OSU**: Drs. Qinghua Sun and Sanjay Rajagopalan
• **MSU Lab**: Ryan Lewandowski, Lori Bramble, Christina Brandenberger, Ian Hotchkiss, Vanessa Hoang, Dennis Shubitowski, Daven Jackson-Humbles, Hannah Garver

This research is funded by
U.S. EPA - Science To Achieve Results (STAR) Program
Grant # RD83479701
Questions?