Systemic vascular effects caused by inhaled toxicants, especially particulate matter

Matthew Campen, PhD
Regents' Professor, Department of Pharmaceutical Sciences
Director, UNM Environmental Health Signature Program
Many Health Consequences of Air Pollution Exposure Occur Beyond the Lungs

• Air pollution exposure has been associated with:
  • Pulmonary Disease (NEJM 2015; 372:905-913)
  • Metabolic Disease (Circulation. 2009;119:538-546)
  • Maternal-fetal health effects (NTP, 2019)
  • Cardiovascular Disease (JACC 2018, 72:2054-2070)
  • Neurological Disease (EHP 2016, 124:23–29)
    • Neurodegenerative and developmental

https://www.epa.gov/climate-indicators/climate-change-indicators-wildfires
General Concept for Pulmonary-Derived, Pathologic circulating factors

Mostovenko et al., ToxSci, 182:107-119, 2021
Implications of a “bioactive” circulation

- The serum/plasma comes in contact with endothelial cells throughout the body
- Endothelial cells have a major homeostatic role for all organ systems
- Thus, endothelial cells are often involved in any disease pathogenesis
Study 1: CALIFORNIA FIRES, 2020

A. Study site location map showing the areas affected by the California fires in 2020.

B. Setup of scientific equipment and personnel collecting data.

C. Control and PM-exposed groups for studying microglial activation.

D. Graph comparing microglial activation between Control and PM-exposed groups, showing increased activation in the PM-exposed group.
Real-World Exposure

- Mobile laboratory located on the Pueblo of Laguna, NM (AirCARE1, on loan from Michigan State)
- 20 days, 4h/d
- C57BL/6 mice, male 8 wks
- Average for all 4h periods was 104 µg/m³
- Meteorological conditions varied, but at least 5 days included a high component of wildfire smoke, assessed by levoglucosan and climate modeling

Scieszka et al., Toxicol Sci, 2020
Microglial Activation

A. ZO1/GFAP/IBA1/ALB

B. Microglial Frequency

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<tr>
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<td>All CD45+ cells (%)</td>
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<td>CD45 Fluorescence</td>
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Microglial CD45

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Microglial CCL2

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Microglial TNFα

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Microglial iNOS

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Microglial ICAM-1

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<td>ICAM-1* (%)</td>
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Scieszka et al., Toxicol Sci, 2020

Dr. Shahani Noor

David Scieszka
More anti-inflammatory endothelial cells after 20d woodsmoke exposure

Scieszka et al., Toxicol Sci, 2020
Lab-Based Woodsmoke Mouse Exposure Chamber

Ed Barr
Is Advanced Age a Risk Factor?
Interactions between lung spillover and senescence-associated secretory proteins
Drug groups:
Veh = Vehicle
Resv + NMN = resveratrol + nicotinamide mononucleotide
D+Q = senolytics (Dasatinib + Quercetin)
Exposure Concentrations: PM$_{2.5}$ and Gases

**B. Exposure Concentrations for PM**

- Average (mg/m$^3$): Total 0.448
- 24 hour: 0.037

**C. CO and NOX**

- Average Conc. (PPM):
  - CO: XYZ
  - NO$_x$: ABC
Cardiac Function is impacted by Woodsmoke and Aging
• Cardiac Metabolomic Response to woodsmoke is greater in older mice

• Sustained effect > 10 weeks after exposure
• Sustained cardiac metabolomic response appears reduced by interventions

• Resveratrol + Nicotinamide Mononucleotide is the best overall recovery
WS exposure reduces Serotonin, which is rescued by each drug intervention.

**Serotonin**

- **18 mo**
- **21 mo Veh**
- **21 mo R+NMN**
- **21 mo D+Q**
- **21 mo RNDQ**

**Bar Chart:**
- **% Change**
- **0.0534**
- **1.00**
- **1.50**
- **2.00**

**Line Graph:**
- **Time Mobile (%)**
- **Exposure Timepoint**
- **P=0.0527**
- **P=0.006**

**Additional Graph:**
- **Grip Strength (N)**
- **Exposure Timepoint**
Conclusions

• Wildfire smoke has the potential to impact health beyond the lungs
  • Study 1 – naturally occurring PM from wildfires 1000km away induced neuroinflammation, altered brain metabolites, and serum peptides
    • Not shown, neuroinflammation evolved and resolved over a 28-day period
  • Study 2 – In older mice, sustained impacts on cardiac metabolites, largely resolved by several interventions
    • Persistent neurometabolic concerns exist as well

• Our data raises concerns about cardiac and neurological issues that may be long-lasting beyond the end of exposure
• Epidemiological studies on the relationship between wildland fire smoke exposure and depression should be undertaken to assess whether firefighters or impacted communities may be at risk
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Questions?