AIR POLLUTION AND THE BRAIN

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Leapfrogging Opportunities for Air Quality Improvement
Background

- Evidence from epidemiological studies demonstrated that brains of individuals (humans and dogs) living in areas with elevated levels of ambient PM exhibited inflammation and lesions. Subsequent controlled studies have supported some of these early findings.
  - Growing evidence that PM exposure increases production of inflammatory mediators and damages or kills brain cells.
  - PM exposure can affect cells that are essential for the production and metabolism of the neurotransmitter dopamine.
Ultrafine Particles are Deposited in the URT to a Great Degree

- UF Particles deposit by diffusion
- Both alveolar and nasopharyngeal regions are targeted.

Figure 5.1 Calculated mass deposition of polydisperse aerosols of unit density with various geometric standard deviations ($\sigma_g$) as a function of mass median diameter (MMD) for quiet breathing (tidal volume = 750 mL, breathing frequency = 15 min$^{-1}$). The upper panel is total deposition and the lower panel is regional deposition (NOPL = Naso-oro-pharyngo-laryngeal, TB = Tracheobronchial, A = Alveolar). The range of $\sigma_g$ values demonstrates the extremes of monodisperse to extremely polydisperse. Source: Yeh et al. (1993).
Figure 2. Inhaled fine and ultrafine particles can access the brain by translocation via the blood and also by passage along nerve cells. Below is an example of transport along olfactory nerves.\(^1\)

**Figure 3. Mn uptake in brain is active.** Mn2+ enhancement from bulb through posterior cortex over time. Z statistic maps of significant enhancement seen when comparing 6, 12, 24, 48, 72 h post-administration scans to pre-administration scans (six rats) and 5.5 days compared to pre-administration (three rats). Rows represent different coronal slices as a distance from bregma landmark according to *Paxinos and Watson, 1988*. 
Figure 6. Possible Mechanism – Mn Disrupts Fe Homeostasis in Cells and Free Fe can Produce Free Radicals via the Fenton Reaction (Zheng and Ziou, 2001)
Figure 5. Inhalation of fine and ultrafine particles injures or kills cells in the brain that make dopamine from tyrosine hydroxylase in the region called the substantia nigra. This process may be caused by activation of immune system cells that are identified using a stain for glial fibrillary acidic protein (GFAP)²

The concentrations of two factors that control gene transcription of proteins related to inflammatory responses, Nf-κB and AP-1, were increased in the brains of mice by both low (CAP 4 = ~ 30 μg/m³) and high (CAP 15 = ~100 μg/m³) concentrations of quasi-ultrafine PM.

There were some changes in the expression of mitogen activated protein kinases (MAPK) that regulate various transcription factors in the brain but a clear pattern has not yet emerged.
Both fine and ultrafine particles cause inflammatory responses in the brain which can be identified by measuring increased levels of the cytokines TNFα in the brains of CAPs-exposed mice.
Ultrafine Particle Exposure Increases Expression of AP-1 and NFkB

AP-1

NFkB

![Graphs showing AP-1 and NFkB expression levels](#)

**AP-1 Level (% Control)**
- Control: 100%
- CAP 4: 150% (∗)
- CAP 15: 150% (∗ +)

**NFκB Level (% Control)**
- Control: 100%
- CAP 4: 100%
- CAP 15: 150% (∗)
Conclusions

- Inhaled particles can cause inflammation in the brain.
- The parts of the brain that are damaged are in the same area that is related to Parkinson's Disease.
- Trace metals like Mn may be important.
- More study of ultrafine particles is needed.
Support

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Collaborators

- **Cardiovascular Project (ARB)**
  - UCI/NYU collaborative project
    - Chen, Li, Xian (Ultrasound)
    - Meacher, Gookin, Salazar, Willett (ECG, Physiology, Arterial Plaque Measurements)

- **Atherosclerosis Mechanisms**
  - SCPC Project 2 (Nel, Araujo, Kleinman, Harkema, Sioutas)

- **Direct Effects of PM on Heart**
  - EPA STAR Grant
    - GSH-Kloner and Simkovitch
    - UCI- Kleinman, Willett, Gookin, Salazar, Meacher

- **Effects on Brain**
  - California Air Resources Board
    - Western University – Arezoo Campbell
    - UCI – Kleinman, Bondy