

Inhalation of particulates and gases and systemic inflammatory effects: Modification of circulating components promotes cerebrovascular endothelial inflammation and dysfunction

○ **Matthew J. CAMPEN¹, Mario ARAGON¹, Lauren TOPPER¹, Andrew OTTENS², Aaron ERDELY³**

¹University of New Mexico, USA, ²Virginia Commonwealth University, USA,

³National Institute of Occupational Safety and Health, USA

Epidemiological studies indicate a strong link between inhaled particulate matter (PM) and cardiovascular and neurological disorders. Additionally, there is evidence that certain gases, such as ozone, and mixed gas-PM exposures may have similar effect beyond the lung. Therefore, we have explored the role of serum components in driving cerebrovascular endothelial inflammatory responses and dysfunction that result from exposure to a wide array of PM and gas mixtures. Using multiwalled carbon nanotubes (MWCNT) via pulmonary delivery in mice, we observed acute deficits in blood brain barrier, activation of astrocytes, and induction of cortical CCL5 and interleukin-6 (IL6) mRNA that were abrogated by coadministration of a rho kinase inhibitor that improves endothelial barrier integrity. This outcome was replicated in a rat model of inhaled ozone, suggesting pathways common to both gases and PM. We further explored the bioactivity of serum from exposed rodents, in terms of the ability to induce inflammatory responses in cerebrovascular endothelial cells in vitro, and found that, again, both MWCNT and ozone exposures led to compositional changes that elicited transcriptional changes and surface receptor expression of inflammatory adhesion molecules, and also diminished regrowth of cerebrovascular endothelial cells. Serum proteomic analysis reveals <1,000 high confidence peaks induced by ozone and peptide sequencing suggests that many of these peaks reflect fragmented or oxidatively modified endogenous peptides, rather than synthesis or secretion of new proteins. Similar serum alterations were noted following exposure to MWCNT. Using myographic approaches, we subsequently confirmed that the fraction of serum components <10 kDa could reduce ex vivo vasorelaxation responses and that this serum bioactivity was absent in matrix metalloproteinase-9-deficient mice, suggesting a role for protease activity in generating pathological circulating constituents. These studies provide mechanistic evidence for a role for circulating components to drive the systemic vascular effects of inhaled pollutants, but further characterization of the serum compositional changes is needed to fully understand this phenomenon.