**Title**: Nanoparticulate matter exposure causes a time-dependent activation of inflammatory microglia with associated white matter damage in a mouse model

**Authors**: Michelle Connor, Hans Baertsch, Kristina Shkirkova, Ashley Knebel, Krista Lamori-Foote, Qinghai Liu, Constantinos Sioutas, William Mack

**Introduction**

Exposure to ambient air pollution, specifically the nano-scale subfraction (nPM; particles <200nm diameter), is associated with white matter damage and neurocognitive decline in both experimental and human studies. The histopathology and cognitive correlates are similar to those observed in vascular dementia and small vessel ischemic disease. nPM-associated white matter damage involves microglial activation. However, the microglial phenotype and time course of white matter damage remain uncharacterized. This study examines myelin injury and microglia activation in the corpus callosum of mice exposed to 3 weeks (45 hours) and 10 weeks (150 hours) of nPM.

**Methods**

Air pollution consisting primarily of traffic-related emissions was collected from an urban area in Los Angeles; nPM was isolated and stored. Mice were exposed to either re-aerosolized nPM or filtered air for 3 weeks (45 hours) or 10 weeks (150 hours) (n=18/group). Activated microglia were characterized by immunohistochemical staining of Iba-1+iNOS to identify M1 pro-inflammatory cells, and Iba-1+Arg to identify M2 anti-inflammatory cells. Myelin injury was assessed by immunohistochemical staining of myelin associated glycoprotein (MAG), a marker of normal myelin; and degraded myelin basic protein (dMBP), specific for myelin degradation.

**Results**

M1 pro-inflammatory microglia were significantly increased in the corpus callosum of mice exposed 10 weeks of nPM compared to filtered air (p<0.05). This was accompanied by a significant decrease in MAG (p<0.05), and increase in dMBP (p<0.05) immunofluorescent density. Mice exposed to 3 weeks of nPM did not demonstrate any differences in microglia activation or white matter injury, compared to mice exposed to filtered air (p=NS).

**Conclusion**

10 week, but not 3 week, exposure to nPM results in inflammatory microglia activation and myelin injury in the corpus callosum of mice. M1 pro-inflammatory microglia release inflammatory cytokines and reactive oxygen/ nitrogen species, which may contribute to the white matter damage observed in this model.

Funding: NIA P01AG051521, NIEHS R01ES024936