Dietary DHA Mitigates Ozone Induced Pulmonary Inflammation and Reductions in Specialized Pro-Resolving Mediators

Kymberly M. Goddy1, B. Kilburg-Basnyat1, S.W. Reece1, M. Hodge1, E. Browder1, C. Psaltis1, J. Manke2, M.L. Armstrong2, N. Reisendorph2, R. Tighe3, S.R. Shalik4
1Department of Pharmacology and Toxicology, East Carolina University; 2School of Pharmacy, University of Colorado, Denver, Denver, CO; 3Department of Medicine, Duke University Medical Center, Durham, NC; 4Department of Nutrition, University of North Carolina Chapel Hill, Chapel Hill, NC.

Background

- Pulmonary exposure to air pollutants, such as ozone (O3), leads to enhanced pulmonary and cardiovascular morbidity and mortality (Altararo-Moreno et al., 2007; Nawrot et al., 2006; Pope et al., 2002).
- O3 exposure has been reported to induce pulmonary inflammation and alter systemic lipid metabolism in rodent and human models (Robertson et al., 2013; Peter et al., 2004).
- During resolution of inflammation, the immune system switches from pro-inflammatory lipid mediator production to the production of specialized pro-resolving mediators (SPMs).
- Previously, we have shown that O3 exposure reduces pulmonary SPM levels are decreased including docosahexaenoic acid (DHA)-derived 17-hydroxydocosahexaenoic acid (17-HDHA), resolvins D1 precursor and protectin D1 (FDB). (Kilburg-Basnyat et al., 2018).

Hypothesis

Dietary supplementation with the parenteral fatty acid DHA mitigates O3-induced pulmonary inflammation by increasing pulmonary levels of DHA-derived SPMs.

Murine model of ozone exposure

Figure 1. DHA supplementation increases pulmonary SPMs.

- Western diet (defined as a diet containing high intake of saturated fats) has been associated with increased respiratory symptoms and lower lung function in multiple lung diseases (Brigham et al., 2018).
- DHA is a n-3 polyunsaturated fatty acid (n-3 PUFA) that is poorly consumed in the western diet (Caldier et al., 2012).
- Dietary DHA intake has been associated reduced infection in infectious and non-infectious lung diseases (Farjadian et al., 2016; Bates et al., 2018; Kosaraju et al., 2017).
- Recently, n-3 PUFA intake has been linked with decreased exacerbation of pollution driven lung diseases (Brigham et al., 2019).
- It is currently unknown if dietary intake of DHA decreases O3-induced pulmonary inflammation and injury and mitigates reductions in DHA-derived SPMs.

Figure 2. Dietary DHA supplementation reduces O3-induced cellular inflammation in the airspace.

- Male wildtype (WT) mice were fed normal chow (NC) or normal chow supplemented with 2% DHA (DHA) diet for 6 weeks. After 6 weeks of diet, mice were exposed to filtered air (FA) or 1 ppm of O3 for 3 hrs. Mice were necropsied 24 hrs after exposure and lung tissue was harvested and analyzed for cytokines and chemokines expression by real time PCR. *p < 0.05, **p < 0.01.

Figure 3. DHA supplementation reduces select O3-induced cyto/chemokine expression in the lung.

- Male wildtype (WT) mice were fed normal chow (NC) or normal chow supplemented with 2% DHA (DHA) diet for 6 weeks. After 6 weeks of diet, mice were exposed to filtered air (FA) or 1 ppm of O3 for 3 hrs. Mice were necropsied 24 hrs after exposure and lung tissue was harvested and analyzed for cytokines and chemokines expression by real time PCR. *p < 0.05, **p < 0.01, ***p < 0.001.

Conclusions and Future Directions

- Ozone exposure reduces SPM levels in lung while increasing inflammation.
- Dietary DHA increase pulmonary SPM levels.
- Dietary DHA mitigates ozone induced lung inflammation by:
  - decreasing BAL macrophages and neutrophils.
  - decreasing pro-inflammatory cytokine IL-6, monocyte chemoattractant CCL2, and neutrophil chemotactant CXCL2.
- Total protein was increased in BAL fluid in all diet groups exposed to O3.
- Circulating immune cells were unaltered with dietary DHA supplementation.

Future directions:

- Determine if a DHA-supplemented diet alters TLR4 driven inflammation in the lung in the lung after O3 exposure.
- Examine if O3 exposure decreases SPM concentrations in specific pulmonary immune cell subsets (alveolar, interstitial, exudative macrophages).
- Evaluate whether or not SPM signaling is decreased in the lung during O3 exposure, driving pulmonary inflammation and injury.

Acknowledgements

This research was supported by the Health Effects Institute Walter A. Rosenbloom Award (to K.M.G.), the National Center for Complementary and Integrative Health NIH R01AT008375 (to S.R.S), and NIEHS CH/HE (P30ES025225). We would also like to thank Anita Coburn and Courtney Silliman for help with GBCs.