HEI

STATEMENT

Synopsis of Research Report 198

HEALTH EFFECTS INSTITUTE

Understanding the Early Biological Effects of Isoprene-Derived Particulate Matter Enhanced by Anthropogenic Pollutants

BACKGROUND

In this study Dr. Jason Surratt, who was a recipient of HEI's Walter A. Rosenblith New Investigator Award, and his colleagues characterized and compared the oxidative property and biological responses of laboratory-generated secondary organic aerosol (SOA) derived from the photochemical oxidation of isoprene in the presence of oxygen radicals or the condensation of key intermediates of isoprene oxidation. Isoprene was chosen because it is an abundant volatile organic compound derived from biogenic sources (i.e., certain types of vegetation) for which there is limited mechanistic information. Work has shown that the oxidation of isoprene follows two main pathways depending on the level of nitrogen oxides. At high levels, it leads to the formation of methacrolein (MACR), which is further oxidized to methacrylic acid epoxide (MAE). At low levels, isoprene is converted to isoprene hydroxyhydroperoxide (ISOPOOH) and subsequently to isoprene epoxydiols (IEPOX).

APPROACH

The aim of the study was to examine the oxidative potential and the effect on cellular toxicity and gene expression of SOA derived from either isoprene or one of its metabolites, which were synthesized in the author's laboratory. Oxidative potential was measured using the dithiothreitol (DTT) assay of extracts of SOA collected on filters, which assesses the ability of the SOA extracts to oxidize DTT in a test tube. Two types of cellular experiments were conducted: (1) exposure by resuspension to each SOA extract for 9 hours, at which time the extracellular medium was collected for analysis, and (2) a 1-hour direct exposure of the cells to the isoprene-derived SOA (in the aerosol state) followed by incubation in fresh medium for 9 hours, at which time the extracellular medium was collected for analysis.

The biological endpoints measured included:

- lactate dehydrogenase, used as a marker of cell toxicity;
- expression of specific inflammation- and oxidative stress–related genes (interleukin-8 [*IL-8*], prostaglandin-endoperoxide synthase 2 [*PTGS2*], and heme oxygenase 1; and
- expression of multiple genes using two separate panels of genes (a panel of 84 human oxidative stress–associated genes and a panel of 249 human inflammation–associated genes).

What This Study Adds

- The study provides a thorough evaluation of oxidative potential and effects on gene expression of SOA derived from isoprene (an abundant organic compound that is released by vegetation), which contributes to ambient particulate matter levels.
- The results show that isoprene-derived SOA has some oxidative potential and induces genes that regulate antioxidant defenses, suggesting that this SOA leads to an increase in cellular oxidant burden.
- The study also tested SOAs derived from intermediate products of isoprene oxidation and showed that NO_x levels can mediate SOA formation reaction pathways and may ultimately affect the SOA oxidative activity.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Jason Surratt at the University of North Carolina, Chapel Hill, and colleagues. The complete report, *Understanding the Early Biological Effects of Isoprene-Derived Particulate Matter Enhanced by Anthropogenic Pollutants* (© 2019 Health Effects Institute), can be obtained from HEI or our website (see next page).

MAIN RESULTS AND INTERPRETATION

All SOA samples showed some DTT activity. ISOPOOH-derived SOA had the highest DTT response followed by MACR- and isoprene-derived SOA, which had similar oxidative potential.

There was no increase in lactate dehydrogenase in any of the experiments using either direct SOA exposure or resuspension exposure.

Both direct exposure and resuspension exposure to isoprene-derived SOA increased the expression of PTGS2 and IL-8. Resuspension exposure to IEPOX- and MAE-derived SOA also increased the expression of PTGS2 (IL-8 was not measured), but exposure to ISOPOOH-derived SOA did not. MACR was not tested.

The expression profiles of the two gene panels showed that direct exposure to isoprene-derived SOA induced the differential expression of the largest number of genes (22 total) versus 2, 13, and 4 genes for IEPOX-, MAE-, and ISOPOOH-derived SOA, respectively. Given the different exposure protocols, it is not clear whether the results are a consequence of the different experimental conditions or of different activities of the SOA.

The investigators analyzed for enrichment of the affected genes within biological pathways and found that the pathway that appeared to be consistently enriched across the various experiments was the one for Nrf2-mediated oxidative stress (i.e., nuclear factor [erythroid-derived 2]-like 2).

There was no clear relationship between DTT activity and the number of altered oxidative stress–related genes. Because the assays measure different oxidative pathways, they are not expected to be correlated.

CONCLUSIONS

This project has shed some light on an important area of research on particulate matter and health, namely, that oxides of nitrogen can mediate SOA formation reactions and thereby affect the oxidative activity of the resulting SOA. In addition, the study has shown that direct exposure of cells to isoprene-derived SOA in the aerosol state increased the expression of genes in the Nrf2 pathway, which regulates antioxidant defenses, and suggests that this SOA can lead to an increase in cellular oxidant burden. Overall, the results indicate that the endpoints selected respond to chemical differences in the SOA precursors and suggest novel approaches for studying the effects of SOA.

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