Cache Valley PM2.5 Activates the Unfolded Protein Response in Human Lung Cells

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Worldwide, exposure to ambient particulate PM2.5 air pollution is associated with increases in all-cause mortality, cardiopulmonary and cardiovascular disease, stroke, diabetes, cancer, and Alzheimer’s disease. The normally picturesque Cache Valley of Northern Utah frequently experiences some of the highest PM2.5 concentrations in the United States. However, the exact mechanism(s) of Cache Valley PM2.5 (CVPM) toxicity are incompletely understood. We recently demonstrated that CVPM exposure is associated with endoplasmic reticulum (ER) stress, which triggers the unfolded protein response (UPR), a highly conserved stress-response mechanism common to many disease states. The purpose of this study was to focus on the dynamics of CVPM-induced ER stress and UPR in cultured human lung (BEAS-2B) cells exposed to CVPM (1 and 12 μg/mL; 24 h). All experiments were conducted in parallel with diesel exhaust particles (DEP) as a positive control. RNA sequencing with gene set enrichment pathway analysis confirmed significant upregulation (FDR adjusted p=0.05) in genes strongly associated with UPR activation, such as *BiP/GRP78*, *PERK*, *IRE1*, and *ATF6*. Significant cellular effects related to UPR activation were also observed, including reductions in mitochondrial membrane potential and alterations in intracellular Ca2+ homeostasis, as evidenced by a significant influx of Ca2+ in the cytosol and mitochondria, likely from the ER network. CVPM treatment also led to the release of cytochrome c oxidase from the mitochondria to the cytosol, a preliminary indicator of apoptosis. Biomarkers related production of reactive oxygen species (ROS), such as malondialdehyde and 4-hydroxynonenal, were also identified in CVPM treated lung cells, indicating ROS is likely contributing to the source of ER stress and activation of the UPR. Across most experiments, 1μg/mL DEP elicited similar results to CVPM at 12μg/mL, suggesting that CVPM is less potent than DEP. Taken together, these results support our hypothesis that a principal toxic mechanism of CVPM pollution involves ER stress and the UPR. The authors gratefully acknowledge generous support from the Marriner S. Eccles Foundation, GE Healthcare, and Utah State University.