

Valproic Acid Decreases Ozone-Induced Oxidative Stress in Mice

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Ozone is an air pollutant which causes lung injury and oxidative stress. We previously demonstrated that macrophages accumulating in the lung in response to ozone-induced injury, contribute to toxicity by releasing cytotoxic reactive oxygen species (ROS) and reactive nitrogen species (RNS). This promotes oxidative stress and lipid peroxidation, which can be detected by measuring expression of the antioxidant enzyme, heme oxygenase-1 (HO-1), and the lipid peroxidation end product, 4-hydroxynonenal (4HNE), respectively. Surfactant protein-D (SP-D) is a pulmonary collectin with anti-inflammatory activity in a normal lung. After injury, reactive nitrogen species disrupt dodecameric SP-D structure, resulting in the release of dimers and trimers which promote inflammation and oxidative stress. Valproic acid (VPA) is a histone deacetylase (HDAC) inhibitor which has been shown to exert anti-inflammatory and antioxidant activity. We hypothesized that VPA would decrease ozone-induced oxidative stress, resulting in reduced toxicity. To test our hypothesis, female C57Bl6/J mice (18-22 g; 13-14 weeks) were exposed to air or ozone (0.8 ppm, 3 h) in a whole-body Plexiglas chamber. This was followed by intraperitoneal injection of VPA (300 mg/kg), 30 minutes later. A second dose of VPA was administered 24 hours later. Animals were euthanized 48 h post-exposure and lung tissue collected. Exposure of animals to ozone resulted in increased expression of HO-1 and 4HNE in alveolar macrophages when compared to air exposed control mice. Treatment of animals with VPA downregulated alveolar macrophage expression of HO-1 and 4HNE. Mice exposed to ozone showed increased expression and altered structure of SP-D, when compared to control mice. VPA decreased ozone-induced increases in SP-D expression and conformational changes. These data suggest that VPA can decrease oxidative stress in the lung caused by ozone and may act through surfactant pathways. Supported by the Rutgers Summer Undergraduate Research Fellowship and NIH Grants: ES004738, R25ES020721, AR055073 and ES005022.

