Effects of Valproic Acid on Ozone-Induced Inflammatory Mediator Expression 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, lipid peroxidation and lung injury. Heme oxygenase-1 (HO-1) is a marker of oxidative stress and 4-hydroxynonenal (4HNE) is a lipid peroxidation end product. 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 and inflammation 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 plexiglass chamber. This was followed by intraperitoneal injection of PBS vehicle control or VPA (300 mg/kg), 30 minutes later. A second dose of PBS or VPA was administered 24 hours later. Animals were euthanized 48 h post-exposure and lung tissue collected. Expression of HO-1 and 4HNE in the lung was determined by immunohistochemistry. 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; this was most significant in ozone exposed mice. These data suggest that VPA can decrease oxidative stress in the lung caused by ozone by downregulating HO-1 and 4HNE expression in macrophages. Supported by the American Physiological Society UGSRF Program and NIH Grants: R01ES004738, U54AR055073 and P30ES005022.