Abrogation of Ozone-induced Oxidative Stress, Inflammation, and Aberrant Pulmonary Mechanics by Valproic Acid

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Acute exposure to inhaled ozone causes oxidative stress, inflammation, and impaired pulmonary mechanics. This is associated with an accumulation of inflammatory macrophages in the lung that contribute to toxicity by releasing reactive intermediates and pro-inflammatory mediators. In the present studies we assessed the effects of valproic acid (VPA), a histone deacetylase inhibitor with antioxidant and anti-inflammatory activity, on ozone-induced pulmonary toxicity. Female C57B16/J mice (18-22 g) were exposed to air or ozone (0.8 ppm, 3 h) in whole body chambers. This was followed 30 min and 24 h later by i.p. administration of PBS control or VPA (300 mg/kg). Mice were euthanized 48 h later and bronchoalveolar lavage (BAL) and tissue collected. Ozone-exposure resulted in increased levels of protein, IgM and cells in BAL, indicative of lung injury and inflammation. Ozone also caused oxidative stress as measured by increases in lung hemeoxygenase (HO)-1 and 4-hydroxynonenal (4HNE) modified proteins. Treatment of mice with VPA significantly reduced ozone-induced increases in expression of HO-1 and 4HNE modified proteins. Flow cytometric analysis of BAL lung cells showed that ozone-induced injury and oxidative stress were associated with increases in pro-inflammatory macrophages in the lung. These cells expressed ARL11 and TNFα, demonstrating that they are activated. VPA treatment reduced the number of activated macrophages accumulating in the lung in response to ozone; VPA also suppressed the accumulation of monocytic and granulocytic myeloid-derived suppressor cells (MDSC). Ozone-exposure caused alterations in pulmonary function, including increases in resistance and decreases in tissue elastance; these changes were blunted by VPA. Taken together, our data demonstrate that VPA is effective in reducing ozone-induced inflammation, oxidative stress, and mechanical dysfunction. These findings may be useful in the development of therapeutics to treat oxidant induced lung injury.

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