

Valproic Acid Blunts Lung Injury, Oxidative Stress, Inflammation, and Altered Pulmonary Mechanics Induced by Inhaled Ozone

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Ozone is an air pollutant known to cause oxidative stress and inflammation in the lung. This can contribute to lung injury and aberrant pulmonary functioning. In the present studies we assessed the effects of valproic acid (VPA), a histone deacetylase inhibitor with antioxidant and antiinflammatory 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 0.5 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, surfactant protein-D (SP-D), IgM and cells in BAL, indicative of lung injury and inflammation. Ozone also caused oxidative stress as measured by disruption of SP-D structure, and increases in lung heme oxygenase-1 (HO-1) and 4-hydroxynonenal (4HNE)-modified proteins. Treatment of mice with VPA significantly reduced ozone-induced increases in BAL SP-D levels and blunted alterations in SP-D structure; HO-1 and 4HNE modified protein expression was also decreased. Flow cytometric analysis of BAL lung cells showed that ozone-induced injury and oxidative stress were associated with increases in proinflammatory macrophages in the lung. These cells expressed ARL11 and TNF α , 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 central resistance and elastance; this was abrogated by VPA. Taken together, our data demonstrate that VPA is effective in reducing ozone-induced lung injury, inflammation and oxidative stress, and mechanical dysfunction. These findings may be useful in the development of therapeutics to treat oxidant induced lung injury. *Supported by Rutgers SURF/ASPET, NIH ES004738, AR055073, and ES005022.*

