Pulmonary Effects of Inhaled Sulfur Mustard in Rats

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Sulfur mustard (SM, 2 (bis-chloroethyl) sulfide) is a cytotoxic vesicant used as a chemical warfare agent known to target the lung. Herein, we characterized the progression of SM-induced pulmonary injury in rats. Male Wistar rats were anesthetized, intratracheally intubated, and exposed to 0.4 mg/kg SM by vapor inhalation. Animals were euthanized 3, 7, 16 and 28 d later. SM inhalation resulted in necrosis of proximal bronchiole epithelium, peribronchial edema and increases in inflammatory cells 3 d post exposure. BAL levels of fibrinogen, matrix metalloproteinase (MMP)-9, receptor for advanced glycation end products (RAGE), and surfactant protein (SP)-D were also increased at 3 d, consistent with alveolar epithelial cell injury. This was correlated with increases in BAL cell number, protein content, and levels of high mobility group box (HMGB)-1. SM also induced oxidative and nitrosative stress in the lung, as measured by expression of heme oxygenase (HO)-1 and inducible nitric oxide synthase (iNOS). Lung levels of proliferating cell nuclear antigen (PCNA) and fibrinogen were also upregulated at 3 d post SM, along with tumor necrosis factor (TNF)α, cyclooxygenase (COX)-2, MMP-9, galectin (Gal)-3 and Ym1. These inflammatory changes persisted in the lung at relatively lower levels up to 16 d post SM exposure when epithelial damage and peribronchiolar inflammation were also evident in distal and respiratory bronchioles. At 28 d post SM, BAL cells and protein, as well as MMP-9, RAGE, SP-D and fibrinogen were increased to levels at or above those observed 3 d post SM. In addition, at 28 d post SM, PCNA, MMP-9, iNOS, COX-2, fibrinogen, Gal-3 and Ym1 were also upregulated. This correlated with the appearance of airway proteinaceous exudate entrapping inflammatory cells, diffuse squamous metaplasia, aberrant bronchial epithelial repair and multifocal alveolar interstitial and peribronchial fibrosis. These data demonstrate that similar pulmonary pathologic events occur in rats and humans following SM exposure and suggest that this rodent model will be useful for mechanistic studies on SM and for the identification of efficacious therapeutics for mitigating acute injury and fibrosis. *Support: NIH U54AR055073, R01ES004738, P30ES005022; EUH 778051; MSHEP 3899/H2020/2018/2.*