



Inhibition of chlorine-induced lung injury by the type 4 phosphodiesterase inhibitor rolipram

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ABSTRACT

Chlorine is a highly toxic respiratory irritant that when inhaled causes epithelial cell injury, alveolar-capillary barrier disruption, airway hyperreactivity, inflammation, and pulmonary edema. Chlorine is considered a chemical threat agent, and its release through accidental or intentional means has the potential to result in mass casualties from acute lung injury. The type 4 phosphodiesterase inhibitor rolipram was investigated as a rescue treatment for chlorine-induced lung injury. Rolipram inhibits degradation of the intracellular signaling molecule cyclic AMP. Potential beneficial effects of increased cyclic AMP levels include inhibition of pulmonary edema, inflammation, and airway hyperreactivity. Mice were exposed to chlorine (whole body exposure, 228–270 ppm for 1 h) and were treated with rolipram by intraperitoneal, intranasal, or intramuscular (either aqueous or nanoemulsion formulation) delivery starting 1 h after exposure. Rolipram administered intraperitoneally or intranasally inhibited chlorine-induced pulmonary edema. Minor or no effects were observed on lavage fluid IgM (indicative of plasma protein leakage), KC (Cxcl1, neutrophil chemoattractant), and neutrophils. All routes of administration inhibited chlorine-induced airway hyperreactivity assessed 1 day after exposure. The results of the study suggest that rolipram may be an effective rescue treatment for chlorine-induced lung injury and that both systemic and targeted administration to the respiratory tract were effective routes of delivery.

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Introduction

Chlorine is a widely used industrial chemical that is highly toxic to the respiratory system. Chlorine is considered a chemical threat agent because of its respiratory toxicity, its ready availability, and its history of use in warfare. Large amounts of chlorine are produced and transported within the United States, and numerous accidental releases leading to high-level human exposures have occurred (Jones et al., 1986; Joyner and Durel, 1962; Van Sickle et al., 2009). Acute effects associated with chlorine exposure in humans include dyspnea, airway obstruction, hypoxemia, pulmonary edema, and pneumonitis (Evans, 2005; Hasan et al., 1983; Van Sickle et al., 2009). Most individuals who survive an episode of acute chlorine poisoning recover normal lung function (Jones et al., 1986), but a subset exhibits

long-term consequences of exposure, including airway obstruction and airway hyperreactivity (Hasan et al., 1983; Lemiere et al., 1997; Malo et al., 2009; Schwartz et al., 1990).

Inhaled chlorine reacts with epithelial lining fluid of the respiratory tract and possibly also directly with epithelial cells to deplete anti-oxidant defenses and produce additional toxic products (Squadrito et al., 2010). Chlorine dissolves to produce hypochlorous acid and also reacts directly with biological molecules in epithelial lining fluid including antioxidants, proteins, amino acids, and phospholipids. Many of the products of these reactions are themselves oxidizing agents that can propagate cellular damage. Low-level chlorine exposure stimulates irritant-responsive sensory nerves (Bessac et al., 2008; Gagnaire et al., 1994; Morris et al., 2005) and results primarily in airway injury characterized by inflammation, vascular leakage, and airway hyperreactivity (McGovern et al., 2010). These effects can occur in the absence of overt histological changes in the airways (McGovern et al., 2010), suggesting subtle epithelial injury and the involvement of neuronal mechanisms (Bessac and Jordt, 2010). Exposure to higher doses of chlorine causes more severe injury of the conducting airways, including the death of large numbers of epithelial cells, and also damages alveolar epithelial cells resulting in pulmonary edema (Leustik et al., 2008; Martin et al., 2003; Tian et al., 2008; Wang et al., 2004; Winternitz et al., 1920).

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