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Involvement of water channel Aquaporin 5 in H_2S-induced pulmonary edema

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ABSTRACT

Acute exposure to hydrogen sulfide (H_2S) poses a significant threat to life, and the lung is one of the primary target organs of H_2S. However, the mechanisms involved in H_2S-induced acute pulmonary edema are poorly understood. This study aims to investigate the effects of H_2S on the expression of water channel aquaporin 5 (AQP5) and to elucidate the signaling pathways involved in AQP5 regulation. In an *in vivo* study, C57BL6 mice were exposed to sub-lethal concentrations of inhaled H_2S, and histological injury of the lungs and ultrastructure injury of the epithelial cells were evaluated. With real-time PCR and western blot assays, we found that H_2S exposure contributed to a significant decrease in AQP5 expression both in murine lung tissue and the A549 cell line, and the ERK1/2 and p38 MAPK signaling pathways were demonstrated to be implicated in AQP5 regulation. Therefore, adjusting AQP5 protein levels could be considered a therapeutic strategy for the treatment of APE induced by H_2S and other hazardous gases.

1. Introduction

Hydrogen sulfide (H_2S) is a colorless and toxic gas and is associated with more than 70 industries, including petroleum refineries, paper and pulp manufacturing, sewage treatment, and artificial fiber synthesis. Acute exposure to H_2S poses a significant threat to life, concentration-dependent toxicity occurs in humans following acute exposure. Exposure to moderate levels of H2S (50–100 ppm) contributes to respiratory tract irritation and olfactory fatigue. While pulmonary edema occurs following prolonged exposure to 250–500 ppm H2S (Dorman et al., 2000). However, the underlying mechanisms involving in H2S-induced pulmonary edema remain poorly understood.

The alveolar epithelium plays a crucial role in fluid transport and is thus critical for normal lung function. Accumulating evidence has revealed that the bulk of water flux across the epithelium depends on the membrane water channels called aquaporins (AQPs) (Kawedia et al., 2013). The AQPs are a family member of membrane water channels, with 13 currently known members in mammals (Jin et al., 2013), which facilitate water transport across cell membranes to respond to osmotic gradients. At least four aquaporins are expressed in the airway and lungs (Borok and Verkman, 2002). AQP1 was the first aquaporin identified in the lungs and is mainly expressed in the microvascular endothelium and macrovessels (Folkesson et al., 1994). AQP3 is expressed in large airways (Jin et al., 2013), and APQ4 is immuno-localized predominantly to the basolateral membrane of ciliated columnar cells of bronchial, tracheal, and nasopharyngeal epithelium (Nielsen et al., 1997). AQP5 is expressed at a high level in type I pneumocytes in the distal lung (Ramirez et al., 2000) and is important for regulating osmotic water permeability. It is also reported to be highly expressed on the surface of type II alveolar epithelial cells (Liu et al., 2015a,b). In the airways, AQP3 and AQP4 deletion do not impair fluid absorption in spite of their facilitation of osmotic water transport (Matsuzaki et al., 2009; Moore et al., 2000). In contrast, AQP5 deletion significantly reduced osmotic water permeability up to 15-fold in mice (Ma et al., 2000), which demonstrates the importance of AQP5 for osmotic water permeability. In addition, deletion of AQP5 raises

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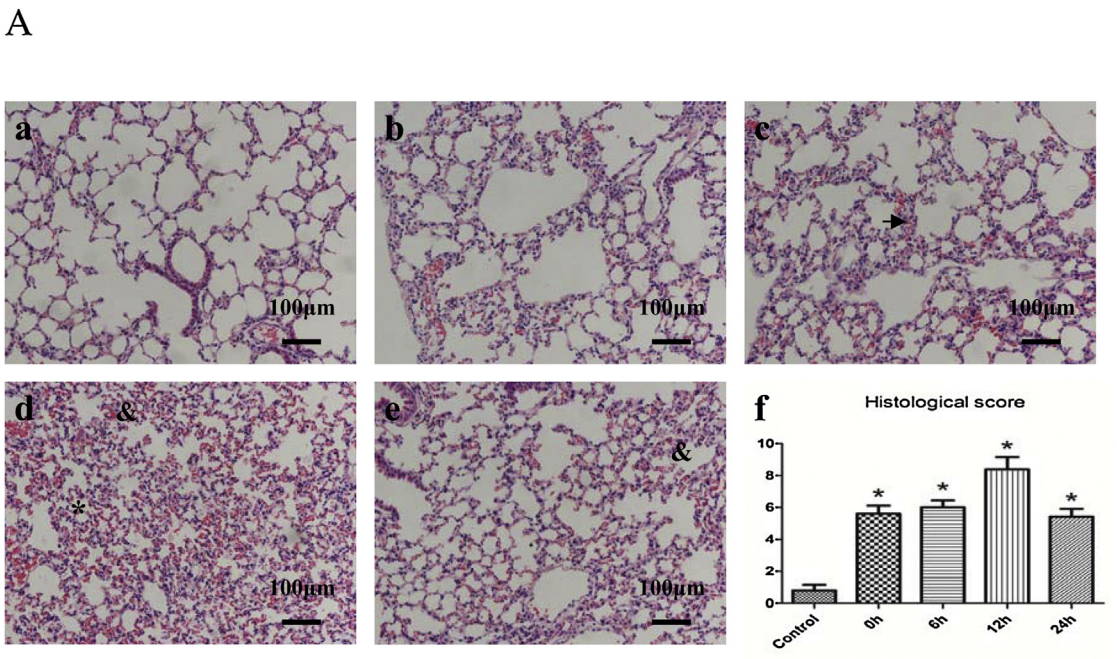

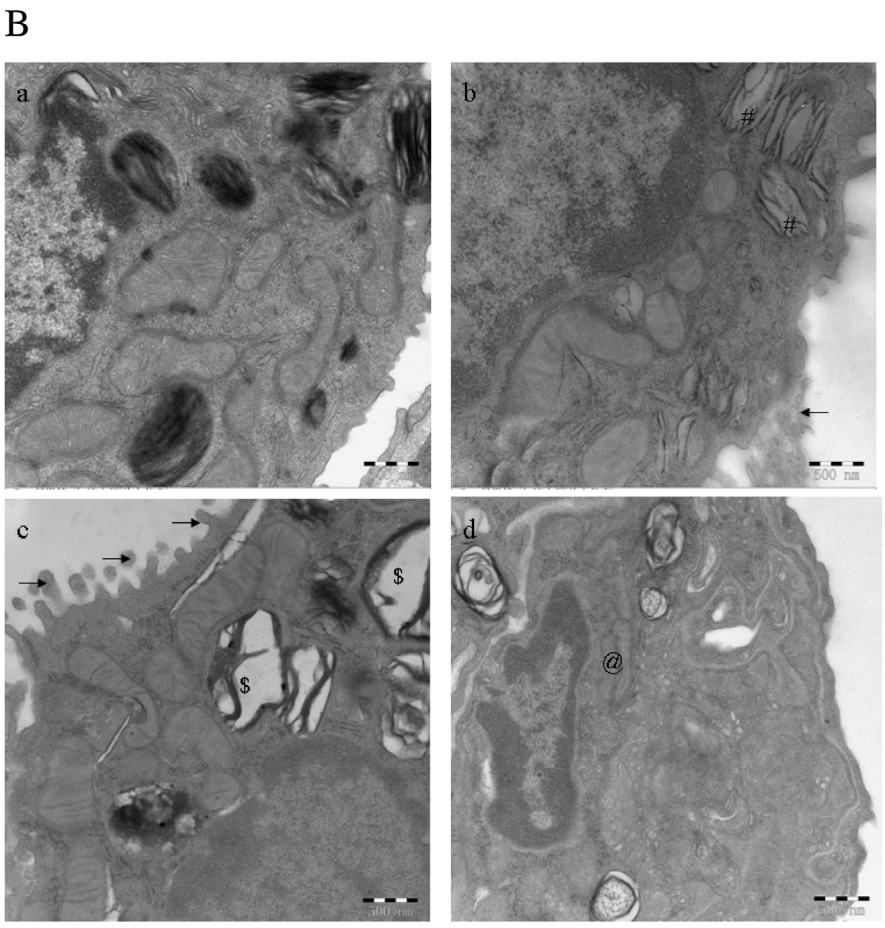

Fig. 1. Histopathological and ultra-structural changes in lung tissues after H_2S exposure.
A: Histopathological changes after H_2S exposure. (a) Control group; (b) 0 h after H_2S exposure; (c) 6 h after H_2S exposure, interlobular septal thickening (arrowheads) is seen; (d) 12 h after H_2S exposure, alveolus collapse (*), widespread alveolar wall thickness, and severe alveolar hemorrhage (&) are seen; (e) 24 h after H_2S exposure, infiltrative hemorrhage (&) is observed; (f) histological scores for all mice, data are expressed as the mean ± S.E. values for every exposure time point (n = 6 per group). Scale bar: 100 μm.
B: Ultra-structure abnormalities induced by H_2S in lung alveolar epithelial cells. (a) Control group; (b) 6 h after H_2S exposure, epithelium rupturing (arrows) and depletion of lamellar bodies (#) are observed; (c) 12 h after H_2S exposure, increased epithelium rupturing and collapsed lamellar bodies ($) are found; (d) 24 h after H_2S exposure, nuclear shrinking and apoptotic body generation (@) are present. The figure shows a representative view from each group (n = 6 per group). Magnification × 40000.