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Hydrogen-rich pure water prevents cigarette smoke-induced pulmonary emphysema in SMP30 knockout mice

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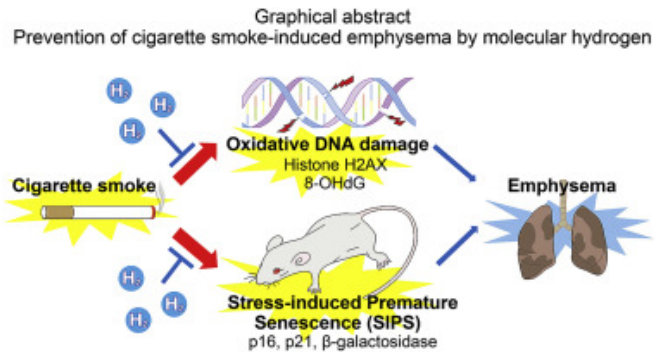
Abstract

Chronic obstructive pulmonary disease (COPD) is predominantly a cigarette smoke (CS)-triggered disease with features of chronic systemic inflammation. Oxidants derived from CS can induce DNA damage and stress-induced premature cellular senescence in the respiratory system, which play significant roles in COPD. Therefore, antioxidants should provide benefits for the treatment of COPD; however, their therapeutic potential remains limited owing to the complexity of this disease. Recently, molecular hydrogen (H_2) has been reported as a preventive and therapeutic antioxidant. Molecular H_2 can selectively reduce hydroxyl radical accumulation with no known side effects, showing potential applications in managing oxidative stress, inflammation, apoptosis, and lipid metabolism. However, there have been no reports on the efficacy of molecular H_2 in COPD patients. In the present study, we used a mouse model of COPD to investigate whether CS-induced histological damage in the lungs could be attenuated by administration of molecular H_2. We administered H_2-rich pure water to senescence marker protein 30 knockout (SMP30-KO) mice exposed to CS for 8 weeks. Administration of H_2-rich water attenuated the CS-induced lung damage in the SMP30-KO mice and reduced the mean linear intercept and destructive index of the lungs. Moreover, H_2-rich water significantly restored the static lung compliance in the CS-exposed mice compared with that in the CS-exposed H_2-untreated mice. Moreover, treatment with H_2-rich water decreased the levels of oxidative DNA damage markers such as phosphorylated histone H2AX and 8-hydroxy-2′-deoxyguanosine, and senescence markers such as cyclin-dependent kinase inhibitor 2A, cyclin-dependent kinase inhibitor 1, and β-galactosidase in the CS-exposed mice. These results demonstrated that H_2-rich pure water attenuated CS-induced emphysema in SMP30-KO mice by reducing CS-induced oxidative DNA damage and premature

cell senescence in the lungs. Our study suggests that administration of molecular H_2 may be a novel preventive and therapeutic strategy for COPD.

Graphical abstract



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Introduction

Chronic obstructive pulmonary disease (COPD) is a severe disease with a relatively high prevalence and mortality rate, and its prevalence has continuously been on the rise owing to an aging society and the cumulative effects of smoking. In 2020, COPD is projected to rank fifth in prevalence and third in cause of death [1]. COPD is characterized by chronic inflammation of peripheral airways and emphysema, represented by enlarged alveolar airspaces and destruction of the lung parenchyma [1], [2]. Cells in the respiratory system are constantly exposed to oxidants. Cigarette smoke (CS) is the most important cause of COPD as the major source of oxidants/reactive oxygen species (ROS) in the lungs and throughout the body. Oxidants derived from CS can induce DNA damage [2], [3] and stress-induced premature senescence (SIPS) [4], [5], [6] in the respiratory system during development of pulmonary emphysema. No COPD treatment has been clinically proven to restore the enlarged alveoli and destroyed lung parenchyma to date. Although antioxidants are expected to provide benefits for patients with COPD, their therapeutic potential remains limited owing to the complexity of this disease.

Molecular hydrogen (H_2) was recently reported as a preventive and therapeutic antioxidant that selectively reacts with the hydroxyl radical (▪OH), the most cytotoxic ROS generated in mitochondria, and with cytotoxic reduced oxygen radicals [7]. Molecular H_2 has also been proposed for treatment in ischemia–reperfusion injury, neurological diseases, lipid metabolism diseases, inflammation, and apoptosis, with no known side effects [8], [9]. However, there has been no report indicating that molecular H_2 is efficacious for COPD.

We previously reported that senescence marker protein 30 (SMP30), a gluconolactonase involved in vitamin C (VC) biosynthesis that decreases with aging in rats and mice, protected mouse lungs from the oxidative stress associated with aging and smoking [10], [11], [12], [13], [14]. SMP30 knockout (SMP30-KO) mice have a shorter lifespan, during which they develop emphysema within 8 weeks of exposure to CS [13], [14]. Furthermore, VC treatment successfully prevents CS-induced pulmonary emphysema in this model [15].

Accordingly, we hypothesized that H_2-rich pure water would react with CS-induced oxidants in the lungs to reduce the CS-induced DNA damage and SIPS, resulting in the attenuation of CS-induced pulmonary emphysema in the lungs. To test this hypothesis, we investigated the effects of H_2-rich pure water on lung histopathology and morphology in SMP30-KO mice after 8-week exposure to CS and explored the underlying mechanisms by evaluating the DNA damage and SIPS in the lungs.

Section snippets

Preparation of H_2-rich pure water

H_2-rich pure water was freshly prepared in cooperation with MiZ Co. Ltd. (Kamakura, Kanagawa, Japan) as previously described [9]. The concentration of H_2 in pure water was maintained at approximately 7 ppm without opening the bottle. Once the cap was opened, the H_2 concentration significantly decreased after 1 h; therefore, when feeding mice, we changed the glass water bottles twice daily until the end of the experiment.…

Mice

Male mice were maintained and bred at the Animal Facility of the Tokyo…

Effects of H_2-rich pure water on histologic and morphometric parameters of the lungs in SMP30-KO mice

Representative histologic images of the lungs from each group are shown in Fig. 1A. Chronic exposure to CS for 8 weeks generated pulmonary emphysema in SMP30-KO mice (Fig. 1A, CS) but not in air-exposed mice (Fig. 1A, Air). Lung tissues from CS+H_2 mice (Fig. 1A, CS+H_2) showed less alveolar destruction than those from CS-exposed mice without H_2 treatment. Compared with the air-exposed group, CS-exposed mice showed significantly greater airspace enlargement, based on MLI values ($p=0.0233$; Fig. 1…

Discussion

The present study demonstrated that administration of H_2-rich pure water attenuated the CS-induced lung damage in SMP30-KO mice, reducing the airspace enlargement and parenchymal destruction. Moreover, the intake of H_2-rich pure water restored the Cst in SMP30-KO mice exposed to CS. The pulmonary restoration was due, at least in part, to the attenuation of CS-induced oxidative DNA damage and premature senescence in the lungs. This is the first study to show the preventive potential of molecular …

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> ...A wide range of therapeutic interventions have been shown to ameliorate rodent lung responses to CS [327–329]. These ameliorating interventions have included N-acetylcysteine [330], SOD [331], thioredoxin [332], roflumilast [333], clarithromycin [334], MMP inhibitor [335], statins [327], TNF receptor deficient mice [317], hydrogen-rich water [29], exercise [336], and as taxanthin, a xanthophyll carotenoid [337]. It is worthy to note that many of the reported interventions have been touted as being anti-inflammatory agents or antioxidants....

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