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Hydrogen therapy may be a novel and effective treatment for COPD

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The protective effect of hydrogen (H_2) on ROS-induced diseases has been proved by many researches, which demonstrated that through eliminating $^{\cdot}OH$ and $^{\cdot}ONOO^-$, H_2 could effectively attenuate lipid and DNA peroxidation, improve cellular antioxidant capacity, and then protect cells against oxidant damage. Most of free radicals in human body are ROS, including $O_2^{\cdot-}$, $^{\cdot}OH$, H_2O_2, $NO^{\cdot}$, $^{\cdot}ONOO^-$, and so on. Under normal circumstances cells are able to maintain an adequate homeostasis between the formation and removal of ROS through particular enzymatic pathways or antioxidants. But under some pathological conditions, the balance is disturbed, leading to oxidative stress and various diseases, such as chronic obstructive pulmonary disease (COPD). Studies have shown that ROS played a pivotal role in the development of COPD and some antioxidants were effective in the protection against the damaging effects of oxidative stress. Therefore, we hypothesize that owing to its peculiarity to eliminate toxic ROS, hydrogen therapy may be a novel and effective treatment for COPD.

Keywords: hydrogen, COPD, oxidative stress, antioxidant

INTRODUCTION

Hydrogen (H_2), a colorless, tasteless, odorless, non-irritating, and highly flammable diatomic gas, was generally regarded as physiologic inert gas in hyperbaric medicine. In 1975 and 2001, Dole et al. (1975) and Gharib et al. (2001) separately reported that H_2 under a high pressure might be a therapeutic gas for cancer and parasite-induced liver inflammation by eliminating toxic ROS. In 2007, Ohsawa et al. (2007) found that 2% H_2 inhalation exhibited antioxidant and anti-apoptotic activities by selectively reducing cytotoxic oxygen radicals. The importance of H_2 immediately drew widespread concerns and it is proved to be effective for many ROS-related diseases, such as hepatic and cardiac hypoxia–ischemia injury, inflammation injury caused by small intestine transplantation and neonatal hypoxia–ischemia injury (Fukuda et al., 2007; Buchholz et al., 2008; Cai et al., 2008; Hayashida et al., 2008). Besides, other ways to administrate H_2, such as drinking H_2-saturated water, intraperitoneal and intravenous injection of H_2-saturated saline, were also effective to many disorders, such as cerebral hypoxia–ischemia injury, human type II diabetes, nephrotoxicity induced by cisplatin, Parkinson's disease and atherosclerosis in apolipoprotein (Cai et al., 2009; Chen et al., 2009; Mao et al., 2009; Sun et al., 2009; Zheng et al., 2009; Oharazawa et al., 2010). All these evidences show that molecule H_2 is effective to diseases related to oxidative stress, which may include chronic obstructive pulmonary disease (COPD).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease is a complex multifactorial disease mainly composed of chronic bronchitis and pulmonary emphysema, which is characterized by not fully reversible airflow limitation. The major feature of COPD is generally accepted as abnormal response to injury, chronic inflammation, excessive activation of macrophages, neutrophils, T lymphocytes, and fibroblasts in the lung. People even with mild COPD often manifest physiological abnormalities that lead to breathlessness and reduction in exercise tolerance, while moderate and severe COPD may remarkably affect the quality of life and mortality.

There are many treatments for COPD, such as inhalational corticosteroid (ICS) and anticholinergics, salmeterol–fluticasone combination (SFC) or tiotropium, and the prescription of antibiotics. However, until now none of them was proved to be an ideal treatment for COPD. ICS could increase the incidence of pneumonia (Drummond et al., 2008). Anticholinergics treatment showed a higher risk of cardiovascular morbidity and mortality (Singh et al., 2008). In another study, tiotropium was showed unable to reduce the decline of FEV_1 (Tashkin et al., 2008). Regarding the fact that COPD morbidity and mortality has been increasing in recent years, it would be greatly valuable to find out an effective therapy to COPD.

Oxidative stress is widely proposed as a pathogenic mechanism for COPD (Van der Vliet, 1999; Pinamonti et al., 1996; Repine et al., 1997). Many researchers found markers of oxidative stress, such as H_2O_2 and NO, in the epithelial lining fluid, breath, and urine of COPD patients (Dekhuijzen et al., 1996; Maziak et al., 1998; Praticò et al., 1998; Montuschi et al., 2000). Oxidant peroxynitrite, generated by the reaction of NO with superoxide anion, is reported to be highly correlated with COPD (Kanazawa et al., 2003). Hydroxyl radical, produced by superoxide anion and H_2O_2 respectively through the Haber–Weiss reaction and Fenton reaction, is also a strong toxic oxidant (Halliwell and Gutteridge, 1986, 1992). Ichinose found abundant nitrotyrosine positive staining cells and iNOS positive cells in induced sputum of COPD patients, indicating that oxidative stress caused by reactive nitrogen species may be exaggerated in the airways in COPD patients and overproduction of reactive nitrogen species may contribute to pathogenesis of COPD (Ichinose et al., 2000). Accumulating evidences support that ROS is important in the incidence and exacerbation of COPD. First, oxidative stress, such as H_2O_2 and isoprostane F2a-III formed by free radical peroxidation of arachidonic acid, may induce

reversible airway narrowing by constricting airway smooth muscle (Kawikova et al., 1996). Second, oxidants can promote inflammation by activating NF-kB and other pathways. Finally, oxidative stress can lead to a proteinase–antiproteinase imbalance (Park et al., 2009).

HYPOTHESIS

Our hypothesis is that H_2 may be a unique, effective, and specific treatment for COPD. Given the fact that H_2 can eliminate ROS such as $^{\cdot}OH$ and $^{\cdot}ONOO^-$ and ROS is an important factor in the pathogenic process in COPD, we hypothesize that H_2 may be potentially effective for COPD by preventing its occurrence, exacerbation, and slowing its process.

Compared to other oxidant scavengers, H_2 has its special advantages. First, because of its small molecular weight, H_2 can easily penetrate bio-membranes and diffuse into cytosol, mitochondria, and nucleus. Second, as H_2 selectively reacts with $^{\cdot}OH$ and $^{\cdot}ONOO^-$, other important ROS (e.g., H_2O_2 and O_2^-) involved in cell signaling are not decreased, so the metabolic oxidation–reduction reactions are not disturbed. Third, the tissue compatibility of H_2 is stronger than many other oxidant scavengers. Especially, in lung the application of H_2 has some unique benefits. People have inhaled H_2 for hundreds of years in diving and it is already proved to be very safe for inhalation. Moreover, inhaled H_2 can easily reach the lung to play a therapeutic role. In addition, because of the special anatomical structure of lung, H_2 can reach lung cells easily and quickly; Furthermore, if H_2 inhalation is applied as a treatment, H_2 will act on lung directly, leading to a better therapeutic effect. In conclusion, as COPD has shown an increase in mortality in recent years, we hope H_2 will successfully control the tread due to its potential protective effect.

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