Hydrogen therapy may be a novel and effective treatment for COPD

Shu-Lin Liu, Kan Liu, Qiang Sun, Wen-Wu Liu, Heng-Yi Tao and Xue-Jun Sun*

Faculty of Naval Medicine, Department of Diving Medicine, Second Military Medical University, Shanghai, People’s Republic of China

*Correspondence: Xue-Jun Sun, Faculty of Naval Medicine, Department of Diving Medicine, Second Military Medical University, 800 Xiangyin Road, Shanghai 200433, People’s Republic of China. e-mail: sunxjk@hotmail.com

The protective effect of hydrogen (H₂) on ROS-induced diseases has been proved by many researches, which demonstrated that through eliminating ⋅OH and ⋅ONOO−, H₂ 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 O₂•−, ⋅OH, H₂O₂, NO•, ⋅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 (H₂), a colorless, tasteless, odorless, non-irritating, and highly flammable diatomic gas, was generally regarded as physiological inert gas in hyperbaric medicine. In 1975 and 2001, Dole et al. (1975) and Gharib et al. (2001) separately reported that H₂ 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% H₂ inhalation exhibited antioxidant and anti-apoptotic activities by selectively reducing cytotoxic oxygen radicals. The importance of H₂ 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 H₂, such as drinking H₂-saturated water, intraperitoneal and intravenous injection of H₂-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 H₂ 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 pneumo-nia (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 FEV₁ (Tashkin et al., 2003). 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 H₂O₂ 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 H₂O₂ respectively through the Haber–Weiss reaction and Fenton reaction, is also a strong toxic oxidant (Halliwell and Gutteridge, 1986, 1992). Ichinohe 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 (Ichinohe et al., 2000). Accumulating evidences support that ROS is important in the incidence and exacerbation of COPD. First, oxidative stress, such as H₂O₂ 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–anti-proteinase imbalance (Park et al., 2009).

**HYPOTHESIS**

Our hypothesis is that H₂ may be a unique, effective, and specific treatment for COPD. Given the fact that H₂ can eliminate ROS such as ‘OH and ‘ONOO⁻‘ and ROS plays an important factor in the pathogenic process in COPD, we hypothesize that H₂ may be potentially effective for COPD by preventing its occurrence, exacerbation, and slowing its process.

Compared to other oxidant scavengers, H₂ has its special advantages. First, because of its small molecular weight, H₂ can easily penetrate bio-membranes and diffuse into cytosol, mitochondria, and nucleus. Second, as H₂ selectively reacts with ‘OH and ‘ONOO⁻‘, other important ROS (e.g., H₂O₂ and O₂⁻) involved in cell signaling are not decreased, so the metabolic oxidation–reduction reactions are not disturbed. Third, the tissue compatibility of H₂ is stronger than many other oxidant scavengers. Especially, in lung the application of H₂ has some unique benefits. People have inhaled H₂ for hundreds of years in diving and it is already proved to be very safe for inhalation. Moreover, inhaled H₂ can easily reach the lung to play a therapeutic role. In addition, because of the special anatomical structure of lung, H₂ can reach lung cells easily and quickly; Furthermore, if H₂ inhalation is applied, H₂ 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 H₂ will successfully control the trend due to its potential protective effect.

**REFERENCES**

Buchholz, B. M., Kaczorowski, D. J., Sugimoto, R., Yang, R., Wang, Y., Billiar, T. R., McCurry, K. R., Bauer, A. J., and Nakao, A. (2008). Hydrogen inhalation ameliorates oxidative stress in trans-plantation induced intestinal graft injury. Am. J. Transplant. 8, 2015–2024.

Cai, J., Kang, Z., Liu, W. L., Li, R., Zhang, J. H., Luo, X., and Sun, X. (2009). Neuroprotective effects of hydrogen saline in neonatal hypoxia-ischamia rat model. Brain Res. 1256, 129–137.

Cai, J., Kang, Z., Liu, W. L., Luo, X., Qiang, S., Zhang, J. H., Ohta, S., Sun, X., Xu, W., Tao, H., and Li, R. (2008). Hydrogen therapy reduces apoptosis in neonatal hypoxia-ischamia rat model. Neurosci. Lett. 441, 167–172.

Chen, H., Sun, Y. P., Hu, F. P., Liu, W. W., Xiang, H. G., Li, Y., Yan, R. L., Su, N., Ruan, C. P., Sun, X. J., and Wang, Q. (2009). The effects of hydrogen-rich saline on the contractile and structural changes of intestine induced by ischemia-reperfusion injury. J. Surg. Res. 157, 1–7.

Dekhuijzen, P.N., Aben, K.K., Dukker, J.Aarts, I.P. Wieders, P.L., van Hervaren, C.L., and Bast, A. (1996). Increased exhalation of hydrogen peroxide in patients with stable and unstable chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 154, 813–816.

Dole, M., Wilson, F. R., and Fife, W. P. (1975). Hyperbaric hydrogen therapy: a possible treatment for cancer. Science 190, 152–154.

Drummond, M.B., Dasenbrook, E.C., Pitl, M.W., Murphy, D.J., and Fan, E. (2008). Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 300, 2407–2416.

Fukuda, K., Asoh, S., Ishikawa, M., Yamamoto, Y., Ohawa, L., and Ohita, S. (2007). Inhalation of hydrogen gas suppresses hepatic injury caused by ischemia/reperfusion through reducing oxidative stress. Biochem. Biophys. Res. Commun. 361, 670–674.

Gharib, B., Hanna, S., Abadallah, O. M., Lepidi, H., Gardette, B., and De, R. M. (2001). Anti-inflammatory properties of molecular hydrogen: investigation on type-II diabetes induced liver inflammation. C. R. Acad. Sci. III 324, 719–724.

Halliwell, B., and Gutteridge, J. M. C. (1986). Oxygen free radical and iron in relation to biology and medicine: some problems and concepts. Arch. Biochem. Biophys. 246, 501–514.

Halliwell, B., and Gutteridge, J. M. C. (1992). Biologically relevant metal ion dependent hydroxyl radical generation. FERS Lett. 307, 108–112.

Hayashida, K., Sano, M., Ohawa, I., Shimamura, K., Tamaki, K., Kimura, K., Endo, I., Kaya-Tama, K., Awamura, A., Kohsaka, S., Makino, S., Ohta, S., Ogawa, S., and Fukuda, K. (2008). Inhalation of hydrogen gas reduces infarct size in the rat model of myocardial ischemia-reperfusion injury. Biochem. Biophys. Res. Commun. 373, 30–35.

Ichinose, M., Sugira, H., Yamagata, S., Kojari, A., and Shirato, K. (2000). Increase in reactive nitrogen species production in chronic obstructive pulmonal disease airways. Am. J. Respir. Crit. Care Med. 162, 701–706.

Kanazawa, H., Shiraiishi, S., Hirata, K., and Yoshikawa, J. (2003). Imbalance between levels of nitrogen oxides and peroxynitrite inhibitory activity in chronic obstructive pulmonary disease. Zhonghua Yi Xue Za Zhi 83, 106–109.

Kawikova, I., Barnes, P. J., Takahashi, T., Tashkin, D. P., Celli, B., Senn, S., Burkhart, D., and Sun. This is an open-access article subject to a non-exclusive license between the authors and Frontiers Media SA, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and other Frontiers conditions are complied with.

Koarai, A., and Shirato, K. (2000). Effect of molecular hydrogen: investigation of H₂ has some unique benefits. People have inhaled H₂ for hundreds of years in diving and it is already proved to be very safe for inhalation. Moreover, inhaled H₂ can easily reach the lung to play a therapeutic role. In addition, because of the special anatomical structure of lung, H₂ can reach lung cells easily and quickly; Furthermore, if H₂ inhalation is applied, H₂ 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 H₂ will successfully control the trend due to its potential protective effect.