ORIGINAL ARTICLES

The Hypothesis of an Effective Safe and Novel Radioprotective Agent Hydrogen-rich Solution

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ABSTRACT

Most ionizing radiation-induced damage is caused by radical oxygen species (ROS). Some radioprotectors, such as amifostine, exert radioprotective effects by scavenging radical oxygen species. Recent studies show that hydrogen (H_2) has antioxidant activities that protect the brain and intestine against ischaemia-reperfusion injury and stroke by selectively reducing hydroxyl and peroxynitrite radicals. However, it is seldom regarded as a radioprotective agent. In like manner, we hypothesize that hydrogen may be an effective, specific and novel radioprotective agent. But H_2 is explosive, while hydrogen-rich solution (solution such as physiological saline saturated with molecular hydrogen) is safer.

Keywords: Hydrogen, ionizing radiation, radioprotection

La Hipótesis de una Solución rica en Hidrógeno como Agente Radioprotector Novedoso, Seguro y Efectivo

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RESUMEN

La mayor parte de los efectos dañinos inducidos por la radiación ionizante, son causados por especies radicales de oxígeno (ROS). Algunos radioprotectores, tales como la amifostina, ejercen efectos radioprotectores mediante el rescate de especies radicales de oxígeno. Estudios recientes muestran que el hidrógeno (H_2) posee una actividad antioxidante que protege el cerebro y el intestino contra las lesiones por repercusión isquémica y accidente cerebrovascular, mediante la reducción selectiva de radicales de hidroxilo y peroxinitrito. Sin embargo, raramente se le considera como un agente radioprotector. De manera similar, planteamos la hipótesis de que el hidrógeno puede ser un agente radioprotector efectivo, específico y novedoso. Pero el H2 es explosivo, mientras que la solución rica en hidrógeno (como es el caso del suero fisiológico saturado con hidrógeno molecular) es más segura.

Palabras claves: Hidrógeno, radiación ionizante, radioprotección

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INTRODUCTION

Hydrogen is the most abundant chemical element. It is a colourless, odorless, nonmetallic, tasteless and highly flammable diatomic gas which was considered as a physiological inert gas. Hydrogen is seldom regarded as an important agent in medical usage. However, Ohsawa *et al* (1) found that molecular hydrogen could selectively reduce cytotoxic reactive oxygen species, such as •OH and ONOO− *in-vitro* and exert therapeutic antioxidant activity in a rat middle cerebral artery occlusion model.

Reactive oxygen species (ROS) or reactive nitrogen species (RNS), such as the hydroxyl radical (•OH), superoxide anion (O_2-), hydrogen dioxide (H2O2), nitric oxide (NO) and peroxynitrite (ONOO-) appear to play a critical

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role in cerebral, myocardial and hepatic ischaemia-reperfusion injuries, transplantation injury and other injuries. It also has been demonstrated that H_2 is effective in the prevention of these injuries (2–4). However, the potential effect of hydrogen gas on another damage type which free radicals play an important role in is largely ignored. That type is the damage induced by irradiation.

Hypothesis

Radiation therapy is a routine treatment for certain types of cancer and some cancer patients will require radiation therapy during the treatment. Radiation itself induces damage and therefore the development of radioprotectors for medical and bio-defense applications are very important (5). The protection of nuclear industry workers is also very necessary.

Exposure to ionizing radiation (IR) can produce severe health impairments due to injury and failure to susceptible organs. Detrimental effects of IR on biological tissues are, in major part, mediated *via* increased production of hydroxyl radical. Hydroxyl radical produced during radiolysis of water can trigger oxidation of lipids, amino acids and saccharides leading to formation of various secondary free radicals (6, 7). These free radicals can produce severe health impairments due to injury and failure to susceptible cells and organs. Therefore, timely elimination of radiation-induced free radicals would presumably protect normal tissues from the damaging effects of radiation. In fact, the effect of free radical scavengers to ameliorate the oxidative injuries due to ionizing radiation has been considerably reported (8, 9).

Various radioprotective strategies have been explored including thiol compounds that can scavenge free radicals (10). At present, thiol compounds are the most effective class of radioprotectors; however, they have significant shortcomings including relatively high toxicity and unfavourable routes of administration which negatively affect their application and efficacy (11).

In spite of the fact that numerous radioprotective agents have been widely studied in the past decades, no agent comprehensively conforms to the criteria of an optimal radioprotectant. Radiobiologists have long been interested in identifying novel, nontoxic, effective and convenient compounds to protect humans against radiation induced normal tissue injuries. Therefore, there is a need for safer and even more effective radioprotective treatments. Hydrogen is continuously produced by colonic bacteria in the body and normally circulates in the blood (12), so it is physiologically safe for humans to inhale hydrogen at a relatively low concentration. It is also a highly diffusible gas and reacts with hydroxyl radical to produce water (13). Dissolving H_2 in solvent such as PBS physiological saline or medium is easy to apply and safe. Therefore, it may have great potential for clinical use.

Our hypothesis is that hydrogen–rich solution may be a promising, effective and safe radioprotective agent. This theory is unique because it proposes a clinical use for hydrogen gas and goes beyond the view that hydrogen gas can only be used for energy production.

This hypothesis is based on four generally well-accepted premises. Firstly, molecular hydrogen can selectively reduce hydroxyl radical and peroxynitrite *in vitro* and *in vivo* (1). As hydroxyl and peroxynitrite are much more reactive than other ROS, it stands to reason that H_2 will react with only the strongest oxidants. Secondly, 60–70% of the ionizing radiation-induced cellular damage is caused by hydroxyl radicals (10) while molecular hydrogen can selectively reduce hydroxyl radical (1). This is to say, H_2 can specifically alleviate the injury induced by irradiation. Thirdly, H_2 is an explosive gas. It is very dangerous to use it directly in radiation protection. If it is dissolved in solutions such as PBS physiological saline or pure water, it will be safer and more convenient. The saturation of H_2 in these solutions could reach 0.6 mmol/L. Fourthly, it is physiologically safe for humans to receive hydrogen because it is continuously produced by colonic bacteria in the body and normally circulates in the blood (12). Conversely, the sulfhydryl compound amifostine, named WR-2721, which is the only radioprotectant registered for using in human, has shown good radioprotective effects (14). But it has many side effects which include hypertension, nausea and vomiting and thus would limit its clinical use (15).

CONCLUSION

The novelty of the hypothesis comes in viewing H_2 as a promising novel radioprotectant. Dissolving it in solution make it safer and more convenient to use in clinic. We believe that the work for hydrogen on radioprotection *in vitro* and *in vivo* should commence as soon as possible. Because of the proliferation of cancer varieties and the global issues caused by terrorist threats and nuclear weapons, or nuclear accidents, an effective, specific and novel radioprotective agent is required. We believe that hydrogen gas especially hydrogen-rich solution may give us more hope for greater protection from irradiation.

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REFERENCES

1. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata et al, Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med 2007; **13:** 688–94.
2. Hayashida K, Sano M, Ohsawa I, Shinmura K, Tamaki K, Kimura K et al, Inhalation of hydrogen gas reduces infarct size in the rat model of myocardial ischaemia-reperfusion injury. Biochem Biophys Res Commun 2008; **373:** 30–5.
3. Buchholz BM, Kaczorowski DJ, Sugimoto R, Yang R, Wang Y, Billiar T et al. Hydrogen inhalation ameliorates oxidative stress in transplantation induced intestinal graft injury. Am J Transplant 2008; **8:** 2015–24.

4. Abraini JH, Gardette-Chauffour MC, Martinez E, Rostain JC, Lemaire C. Psychophysiological reactions in humans during an open sea dive to 500 m with a hydrogen-helium-oxygen mixture. J Appl Physiol 1994; **76:** 1113–8.
5. Damron TA, Spadaro JA, Horton JA, Margulies BS, Strauss JA, Farnum CE. Novel radioprotectant drugs for sparing radiation-induced damage to the physis. Int J Radiat Biol 2004; **80:** 217–28.
6. Stadtman ER. Oxidation of free amino acids and amino acid residues in proteins by radiolysis and by metal-catalyzed reactions. Annu Rev Biochem1993; **62:** 797–21.
7. Fan X. Ionizing radiation induces formation of malondialdehyde, formaldehyde, and acetaldehyde from carbohydrates and organic acid. J Agric Food Chem 2003; **51:** 5946–9.
8. Shirazi A, Ghobadi G., Ghazi-Khansari M. A radiobiological review on melatonin: a novel radioprotector. J Radiat Res (Tokyo) 2007; **48:** 263–72.
9. Yan SX, Hong XY, Hu Y, Liao KH. Tempol, one of nitroxides, is a novel ultraviolet-A1 radiation protector for human dermal fibroblasts. J Dermatol Sci 2005; **37:** 137–43.
10. Vijayalaxmi Reiter RJ, Tan DX, Herman TS, Thomas CR Jr. Melatonin as a radioprotective agent: a review. Int J Radiat Oncol Biol Phys 2004; **59:** 639–53.
11. Maisin JR. Bacq and Alexander Award lecture-chemical radio-protection: past, present, and future prospects. Int J Radiat Biol 1998; **73:** 443–50.
12. Reth M. Hydrogen peroxide as second messenger in lymphocyte activation. Nat Immuno *l*2002; **3:** 1129–34.
13. Labiche LA, Grotta JC. Clinical trials for cytoprotection in stroke. NeuroRx 2004; **1:** 46–70.
14. Gosselin TK, Mautner B. Amifostine as a radioprotectant. Clin J Oncol Nurs 2002; **6:** 175–6, 180.
15. Genvresse I, Lange C, Schanz J, Schweigert M, Harder H, Possinger K et al, Tolerability of the cytoprotective agent amifostine in elderly patients receiving chemotherapy: a comparative study. Anticancer Drugs 2001; **12:** 345–9.