



## Hydrogen therapy may be an effective and specific novel treatment for acute radiation syndrome

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### SUMMARY

Hydrogen is the most abundant chemical element in the universe, however, it is seldom regarded as a therapeutic gas. Recent studies show that inhaled hydrogen gas ( $H_2$ ) has antioxidant and antiapoptotic activities that protect the brain against ischemia–reperfusion injury and stroke by selectively reducing hydroxyl and peroxynitrite radicals. It is also well known that more than a half of the ionizing radiation-induced cellular damage is caused by hydroxyl radicals. Studies have shown that reducing hydroxyl radicals can significantly improve the protection of cells from radiation damage. In like manner, we hypothesize that hydrogen therapy may be an effective, specific and unique treatment for acute radiation syndrome.

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### Introduction

Hydrogen is the most abundant chemical element, constituting approximately 75% of the universe's elemental mass. It is a colorless, odorless, nonmetallic, tasteless, highly flammable diatomic gas which is mainly used in fossil fuel processing and ammonia production. Hydrogen is seldom regarded as an important agent in medical usage, especially as a therapeutic gas.

However, a recent study provided evidence that inhaled hydrogen gas ( $H_2$ ) has antioxidant and antiapoptotic properties that protect the brain against ischemia–reperfusion injury and stroke by selectively reducing  $\cdot OH$  and  $ONOO^-$  in cell-free systems [1]. This study indicates a unique function of  $H_2$  as a therapeutic gas by specifically targeting the reactive oxygen species (ROS) system.

Numerous studies have consistently demonstrated that a burst of reactive oxygen species results in a restoration of blood flow after a stroke. Reactive oxygen species (ROS) or reactive nitrogen species (RNS), such as the hydroxyl radical ( $\cdot OH$ ), superoxide anion ( $O_2^-$ ), hydrogen dioxide ( $H_2O_2$ ), nitric oxide (NO), peroxynitrite ( $ONOO^-$ ), also appear to play a critical role in cell damage of stroke, myocardial ischemia–reperfusion injury, transplantation injury and other injuries. There are now highly successful approaches for both stroke and myocardial infarction to restore blood flow to the ischemic tissue. However, we have failed to completely relieve this pathological cascade of oxidative damage after reperfusion injury [2]. The study by Ohsawa et al., is very important in showing of relieving the oxidative damage.

The idea that  $H_2$  is a therapeutic gas has also been proved by other groups in other models. The effect of hydrogen gas as a therapeutic gas has been extensively studied and researchers now find that hydrogen gas can also be effective for myocardial ischemia–reperfusion injury and transplantation injuries of other types [3–5]. However, the potential effect of hydrogen gas on another damage type which free radicals play an important role is largely ignored. That type is the acute radiation syndrome (ARS).

### Acute radiation syndrome (ARS)

Acute radiation syndrome (ARS) is the damage caused to organ tissue due to excessive exposure to ionizing radiation in a short period, though this also has occurred with long term exposure [6]. ARS, acute radiation syndrome involves partial or full destruction of the hematopoietic system (HP) and gastrointestinal tract (GI) which are often very serious and even cause death [7]. Examples of persons who suffered from acute radiation syndrome (ARS) are the survivors of the Hiroshima and Nagasaki atomic bombs, the firefighters that first responded after the Chernobyl Nuclear Power Plant event in 1986, as well as nuclear industry workers and clinical patients during their anticancer radiation therapy. Radiation therapy is now a routine treatment for certain types of cancer and over 20% of cancer patients will require radiation therapy during the treatment of their disease. Radiation itself induces damage and, therefore, the development of radioprotectants for medical and bio-defense applications are very important [7].

It is generally accepted that ionizing radiation interacts with water molecules in the biological system and thus produces a variety of active free radicals, which are capable of causing cellular damage and even cell death. It was estimated that 60–70% of the

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ionizing radiation-induced cellular damage was caused by hydroxyl radicals [8]. 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 documented [9,10].

Numerous studies have consistently shown that the ROS system, especially the hydroxyl radical and peroxynitrite mediated the main biological effects of ionizing radiation and free radicals. At present, medical researchers have tested a variety of materials with radioprotective activity, including sulfhydryl-containing chemicals, cytokines, natural products, hormones, vitamins and metal elements [11–15], and investigated the protective effects and their molecular mechanism. But so far no ideal radioprotectant has been found whose effectiveness, toxicity, selectivity and tolerance can all achieve the desired standards. The sulfhydryl compound amifostine, namely WR-2721, is the only radioprotectant registered for use in humans, and has shown good radioprotective effects [16]. But the clinical application found it had many defects such as hypertension, nausea, vomiting, and other side effects caused by the toxicity to surrounding normal tissues [17], when being administered by injection. Moreover, the poor tolerance of WR-2721 often makes it impossible to achieve sufficient drug concentration in patients, and consequently it fails to allow increased doses and improve the outcome of radiation therapy [12]. It is therefore necessary to explore new apolitical radioprotectants with high efficiency and low toxicity, which has always been one of the most important endeavors in the field of medical science and radiation protection.

In spite of the fact that radioprotective agents have been widely studied in the past decades and include several thousand agents, 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.

## Hypothesis

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

Our hypothesis is based on the theory that molecular hydrogen can selectively reduce hydroxyl radical and peroxynitrite in vitro and in vivo [1]. As hydroxyl radical and peroxynitrite are much more reactive than other ROS, it stands to reason that H<sub>2</sub> will react with only the strongest oxidants. This is advantageous for medical procedures, as it is likely that H<sub>2</sub> is mild enough not to disturb metabolic oxidation–reduction reactions or to disrupt ROS involved in cell signaling [1,2]. In addition, H<sub>2</sub> has other advantages. It can penetrate biomembranes and diffuse into the cytosol, mitochondria and nucleus. In that manner, H<sub>2</sub> can protect nuclear DNA and mitochondria and suggests that it could reduce the risk of lifestyle-related diseases and cancer.

Since 60–70% of the ionizing radiation-induced cellular damage is caused by hydroxyl radicals and hydrogen can selectively reduce hydroxyl and peroxynitrite radicals in vitro and in vivo [1], we hypothesize that hydrogen gas can be potentially effective for acute radiation syndrome by selectively reducing hydroxyl and peroxynitrite radicals. That is to say, hydrogen gas may be a prom-

ising novel radioprotectant. We believe that in vitro and in vivo work for hydrogen gas on radioprotection should commence as soon as possible. In view of the proliferation of cancer varieties and the global issues caused by terrorist threats and nuclear war, dirty bombs, or nuclear accidents, hydrogen gas may give us more hope for greater survival and fewer human casualties should a disaster occur.

## Conflict of interest statement

None declared.

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