

# Conventional drug acts as a “rifle gun” while hydrogen as a “machine gun”

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## Abstract

Most of the drugs used in modern medical treatments are symptomatic treatments and are far from being a cure for the diseases. The adverse effects are unavoidable in the drugs in modern medical treatments. Molecular hydrogen ( $H_2$ ) has a remarkable therapeutic effect on various diseases, and many clinical studies have reported that  $H_2$  has no adverse effects. Therefore,  $H_2$  is a novel medical gas that is outside the concept of modern medical treatment.  $H_2$ , unlike drugs, works on the root of many diseases by scavenging the two kinds of strong reactive oxygen species, hydroxyl radical ( $\cdot OH$ ) and peroxynitrite ( $ONOO^-$ ). Since the  $H_2$  alleviates the root of diseases and can treat many diseases at the same time, the medical application of  $H_2$  may be called “machine gun therapy.” In this review, we demonstrated that the root of many diseases is based on  $\cdot OH$ -induced oxidative stress in the mitochondria, and at the same time, the root of chronic inflammation is also attributed to  $\cdot OH$ .

**Key words:** chronic inflammation; elemental reductionist approach; hydroxyl radical; machine gun therapy; mitochondria; modern medicine; molecular hydrogen; NLRP3; reactive oxygen species

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## INTRODUCTION

Most conventional drugs used in modern medicine act on each target. The drugs are symptomatic treatments and are far from being a cure for the diseases. Modern medical treatment can control acute inflammatory diseases, but not chronic inflammatory diseases. In contrast, molecular hydrogen ( $H_2$ ) acts on the root of many diseases and has various therapeutic and preventive effects.  $H_2$  taken into the body is distributed throughout the body by its diffusing effect. And since  $H_2$ , unlike drugs, has no adverse effects, the dosage of  $H_2$  can be increased. Recently, we demonstrated that  $H_2$  is promising for medical applications.<sup>1</sup>

Jones<sup>2</sup> has demonstrated that  $H_2$  is the safest reducing agent and that it could be a promising anti-inflammatory agent. In this review, expanding on the hypothesis of Jones’ paper,<sup>2</sup> we present the perspective for  $H_2$  medicine by discussing why  $H_2$  is effective against many diseases.

## PROBLEMS IN MODERN MEDICINE

Based on the World Health Organization’s Statistical Classification and Related Health Problems, the number of diseases should be from 30,000 to 40,000.<sup>3</sup> However, pharmacopeia such as U.S. and British Pharmacopeia illustrates approximately 20,000 drugs registered.<sup>4,5</sup> The registered drugs with a variety of dosages are duplicated so that only several thousand drugs exist in our society. Modern medicine views the human body as an aggregation of organs and conducts a microscopic analysis of organs as objects. These methods of modern medicine are called the “elemental reductionist approach.”<sup>1,6,7</sup> It subdivides the object of study from organ to cell, then to

molecule, and finally to gene to identify the factors that most affect diseases. Drugs are designed to act on a single factor (e.g., enzymes, receptors, and genes) in order to ameliorate the diseases.<sup>1,6,7</sup> In modern medicine, it is also said that there is a “one-to-one relationship” between the cause of a disease and its treatment.<sup>1,6,7</sup> However, many diseases are not caused by a single factor alone, but by multiple factors and a wide variety of mechanisms.<sup>1,6,7</sup> Therefore, modern medicine may be called “rifle gun therapy” because it can target a single shot.

## HYDROXY RADICAL AS A ROOT OF MANY DISEASES

The human adult consumes large amounts of oxygen per day at rest. However, various reactive oxygen species (ROS) are formed by an imbalance between free radical and reactive metabolic production. ROS are products of oxygen-derived small molecules involved in normal cellular metabolism, including superoxide anion ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), and hydroxyl radical ( $\cdot OH$ ).<sup>8</sup> Among the ROS, the  $\cdot OH$  has greater oxidation power than  $O_2^-$  and oxidizes intranuclear DNA, while  $O_2^-$  and  $H_2O_2$  do not have sufficient oxidation power to oxidize the DNA directly. In addition, mitochondria, the source of these ROS, are constantly exposed to high levels of  $\cdot OH$ , which cause mitochondrial DNA damage and cellular apoptosis.<sup>8</sup>

Therapeutic applications of  $H_2$  were first described in 1975.<sup>9</sup> Dole et al.<sup>9</sup> reported that hyperbaric hydrogen showed marked antitumor effects in mice. However, the potential of  $H_2$  in medical applications has not been widely reported. In 2007,  $H_2$  was indicated by Ohsawa et al.<sup>8</sup> as a therapeutic antioxidant that could selectively scavenge two kinds of strong ROS,  $\cdot OH$



and peroxy nitrite (ONOO<sup>-</sup>).

H<sub>2</sub> diffuses into the cytosol, mitochondria, and nucleus in relation to its distribution characteristics.<sup>8</sup> H<sub>2</sub> is an inactive molecule that has no metabolic system in mammalian cells and does not interact with biological substances, but it is a molecule that reacts with ·OH, which occurs inside mitochondria.<sup>6</sup> In addition, because the reaction product of H<sub>2</sub> and ·OH is a water molecule, and the production of H<sub>2</sub> in the intestine,<sup>6</sup> adverse effects caused by H<sub>2</sub> have not been observed in many clinical studies. Indeed, the clinical efficacy and safety of H<sub>2</sub> were reported in more than 100 papers.<sup>10-13</sup> H<sub>2</sub> has become a novel antioxidant due to its antiapoptotic, antioxidant, and anti-inflammatory effects.

## INVOLVEMENT OF HYDROXYL RADICAL IN CHRONIC INFLAMMATION

Chronic inflammation is the root cause of many diseases. It is no exaggeration to say that "chronic inflammation is the treatment source of all disease". Modern medical treatment can control acute inflammatory diseases, but it cannot control chronic inflammatory diseases. Inflammation is induced by releasing inflammatory cytokines produced by macrophages and neutrophils. Minor but prolonged inflammation can damage the living body and induce chronic inflammation. Recent studies have shown that mitochondria play an important role in producing cytokines.<sup>7,14-16</sup> It has also been reported that mitochondria-related ROS activates the nucleotide-binding and oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, and its stimulation triggers producing inflammatory cytokines.<sup>17-19</sup>

In a normal condition, the NLRP3 activity is tightly restrained by ubiquitination. However, stimulation of cells with lipopolysaccharide and adenosine triphosphate can trigger NLRP3 deubiquitination and can abolish this constraint, resulting in the activation of NLRP3 inflammasome.<sup>20</sup> Lipopolysaccharide and adenosine triphosphate can elicit vigorous production of proinflammatory cytokines via the transmembrane Toll-like receptor 4 and P2X purinoceptor 7 receptors, respectively. This process is dependent on mitochondrial ROS production. In addition, oxidized mitochondrial DNA, the ROS-oxidized product released from mitochondria, is capable of binding and activating NLRP3.<sup>21</sup> NLRP3 inflammasome activation by inhibiting mitochondrial ROS-dependent NLRP3 deubiquitination and by suppressing the generation of oxidized mitochondrial DNA may be blocked by mitochondria-targeted antioxidants such as H<sub>2</sub>.

It has been shown by some literature that H<sub>2</sub> in the various animal models of inflammation could be based on the mechanisms by inhibitions of mitochondrial oxidation and NLRP3 inflammasome activation.<sup>22-30</sup> Therefore, the mitochondrial selective ·OH scavenger such as H<sub>2</sub> can block the cascade leading to the activation of the NLRP3 inflammasome. H<sub>2</sub> may be able to aim for "machine gun therapy" because it works on the root of many diseases including chronic inflammatory diseases by scavenging ·OH and ONOO<sup>-</sup>. H<sub>2</sub> is a novel medical gas that is outside the concept of modern medical treatment.

Non-steroidal anti-inflammatory drugs, steroids, and biological products such as anti-interleukin-6 monoclonal antibody

and antitumor necrosis factor-α monoclonal antibody have been applied clinically as anti-inflammatory drugs. However, these drugs have less effects and adverse effects, indicating that H<sub>2</sub> is an ideal antioxidant with potent anti-inflammatory effects and without adverse effects.

In Japan, although H<sub>2</sub> gas has been approved by the Ministry of Health, Labor, and Welfare as an advanced medical treatment B, the pharmaceutical approval of H<sub>2</sub> as a medical gas is not obtained. Therefore, clinicians have used the H<sub>2</sub> at their own discretion or in clinical research. We are trying to develop an H<sub>2</sub> gas inhaler as a medical device. The day will come when H<sub>2</sub> gas inhalers will be used in the market as a medical device in the near future.

## CONCLUSION

In this paper, we demonstrate that the root of many diseases is based on ·OH-induced oxidative stress in the mitochondria, and at the same time, the root of chronic inflammation is also attributed to ·OH. And we have also shown that H<sub>2</sub> medicine is a new treatment that can be replaced by modern medicine. Since the H<sub>2</sub> alleviates the root of disease and subsequently treats many diseases, the medical application of H<sub>2</sub> truly may be called "machine gun therapy."

### Author contributions

SH collected the literature and drafted the initial manuscript. SH, IY, SB, TY, and SF revised the manuscript and edited the language. All authors read and approved the final manuscript.

### Conflicts of interest

HS, IY, SB, SF are employees of MiZ Company Limited, Japan.

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