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Short Communication

# Antioxidant Bioactivity of Molecular Hydrogen Gas Produced by Intestinal Bacteria with Undigested Carbohydrates

**Yuji Aoki***

*Department of Internal Medicine, National Hospital Organization Matsumoto Medical Center, Japan*

***Corresponding Author:** Yuji Aoki, Department of Internal Medicine, National Hospital Organization Matsumoto Medical Center, Japan.

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## Abstract

In the previous report, it was found that exhaled breath hydrogen gas was increased in Japanese centenarians, suggesting an association of their longevity with hydrogen gas produced by intestinal bacteria with undigested carbohydrates. As a preliminary study to assess its antioxidant effects, breath hydrogen gas and urine biomarkers of oxidative stress were measured in seven healthy controls (3 males, 4 females; age, 35 ± 11 (mean ± SD) years; body mass index, 20.5 ± 2.3). The breath hydrogen gas negatively correlated with urine 8-iso-prostaglandin F2α (rs = -0.750, p = 0.052; Spearman's correlation), but did not correlate with urine 8-hydroxydeoxyguanosine (rs = 0.476, p = 0.280). It is odd but there was a significant negative correlation between 8-hydroxydeoxyguanosine and 8-iso-prostaglandin F2α (rs = -0.884, p = 0.008). Taken together with the relevant literature, it is presumed that hydrogen gas would rather protect lipids from oxidative stress. A question is raised whether hydrogen gas in the body can efficiently scavenge hydroxyl radical and peroxynitrite. But a possibility is also raised that molecular hydrogen gas can be involved in various antioxidant mechanisms including the Nrf2 signaling pathway, partially contributing to healthy longevity.

**Keywords:** Molecular Hydrogen Gas; Intestinal Bacteria; Antioxidant Bioactivity; Healthy Longevity

In the previous report [1], it was found that exhaled breath hydrogen gas was increased in Japanese centenarians, suggesting the association of hydrogen gas with their longevity. Molecular hydrogen gas is composed of two protons and two electrons, and highly combustible with activation energy such as an electric spark. Hydrogen gas is generally considered to be physiologically inert, similar to nitrogen gas, in human bodies. There is no source for hydrogen gas in humans other than bacterial metabolism of carbohydrates in the intestine. Hydrogen gas produced by intestinal bacteria with undigested carbohydrates is quickly absorbed into the portal circulation and partially excreted by the lungs. Hydrogen breath tests are commonly used to reveal functional gastrointestinal disorders, including carbohydrate malabsorption and small intestinal bacterial overgrowth [2]. Since it was demonstrated that 2 - 4% hydrogen gas could act as an antioxidant by selectively reducing cytotoxic oxygen radicals [3], beneficial effects of hydrogen gas have been evaluated in experimental and clinical studies [4-10]. Molecular hydrogen can mitigate tissue oxidation induced by hydroxyl radical and peroxynitrite, which are strong enough to react with inert hydrogen gas. In other words, hydrogen gas is mild enough neither to disturb metabolic redox reactions nor to affect reactive oxygen species that function in cellular signaling, which would be of some importance for antioxidant therapeutic strategies [11].

As a preliminary study to assess antioxidant effects of hydrogen gas in the body, breath hydrogen gas and urine biomarkers of oxidative stress were measured in seven healthy controls (3 males, 4 females; age, 35 ± 11 (mean ± SD) years; body mass index, 20.5 ± 2.3). Because the inter-individual variations of breath hydrogen gas concentrations were found to be larger in the post-absorption period after a breakfast meal, breath hydrogen concentrations were measured using a portable breath hydrogen gas analyzer (HYDlyzer, TAIYO, Osaka, Japan) between 11:00 and 18:00, or more than 4 hours after breakfast [1]. Spot urine samples were collected to measure oxidative products excreted into urine.

Urine 8-iso-prostaglandin F2α (8-iso-PGF2α) and 8-hydroxydeoxyguanosine (8-OHdG) are products of oxidative damaged lipid and DNA, respectively, which were measured by a referee laboratory (SRL, Inc., Tokyo, Japan). As shown in Figure 1, breath hydrogen gas concentration negatively correlated with urine 8-iso-PGF2α (rs = -0.750, p = 0.052; Spearman's correlation, borderline significance), but did not correlate with urine 8-OHdG (rs = 0.476, p = 0.280). It is odd but there was a significant negative correlation between urine 8-iso-PGF2α and 8-OHdG (rs = -0.884, p = 0.008). These suggest that molecular hydrogen gas circulating in the body potentially functions as an antioxidant, but that biomolecules are not uniformly affected by oxidative stress.

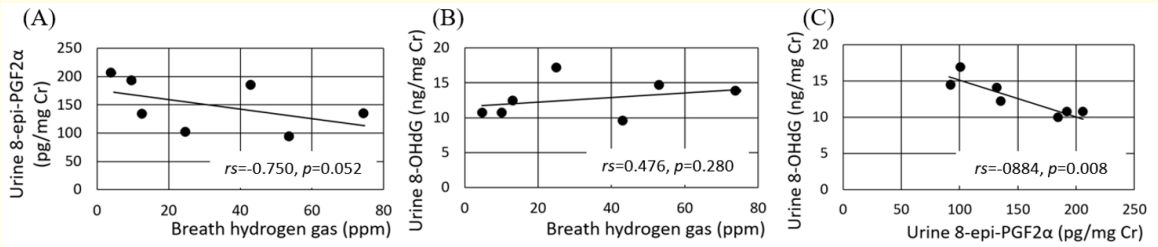


**Figure 1:** Correlations of breath hydrogen gas concentration with urine 8-epi-prostaglandin F2α (8-epi-PGF2α) (A) or 8-hydroxydeoxyguanosine (8-OHdG) (B) and between urine 8-epi-PGF2α and 8-OHdG (C) in 7 healthy controls.

In a study, drinking hydrogen-rich water was demonstrated to briefly increase breath hydrogen gas concentrations [4], which were within the range of daily intra- or inter-individual variations [1,12]. The study [4] demonstrated that urine 8-iso-PGF2α (or 8-isoprostane), but not urine 8-OHdG, was significantly reduced by drinking 900 mL of hydrogen-rich water per day for 8 weeks. Another study [5] demonstrated that urine thiobarbituric acid reactive substances (lipid peroxidation products), but not 8-OHdG or 8-isoprostane, were significantly reduced by drinking 1.5 - 2L of hydrogen-rich water per day for 8 weeks. Taken together, it is presumed that hydrogen gas would rather protect lipids from oxidative stress. As demonstrated in Japanese centenarians [1], limited but some antioxidant effects of hydrogen gas produced by intestinal bacteria might contribute to people's longevity by partially preventing age-related deleterious diseases.

Hydrogen gas is not easily dissolved in water, and 100%-saturated hydrogen water contains 1.6 ppm or 0.8 mM hydrogen at room temperature, which would be much less than that produced by intestinal bacteria in total (~12L of hydrogen gas per day) [13]. The breath hydrogen gas concentrations (ppm) were detected at the end of exhaled breath, approaching to its alveolar concentrations. For example, as alveolar concentrations of oxygen are % and the solubility coefficient of hydrogen is smaller than that of oxygen, it would be easy to understand that hydrogen gas dissolved in the blood is far less than oxygen gas. A question is raised whether hydrogen gas in the body can efficiently scavenge hydroxyl radical and peroxynitrite, which are continuously generated in normal and disease states [11]. But a possibility is also raised that molecular hydrogen gas can be involved in various antioxidant mechanisms including the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway [11]. In an animal model, it was demonstrated that hydrogen gas could activate the Nrf2-antioxidant response element (ARE) pathway that transcriptionally regulates various antioxidant and cytoprotective proteins [14]. It is also suggested that the pulsatile increase, but not continuous increase, of hydrogen concentrations could be involved in exerting its beneficial effects as a gaseous signaling modulator [7].

Thus, increased breath hydrogen gas concentrations, depending on the presence of undigested carbohydrates and hydrogen-producing bacteria in the intestine, could partially contribute to healthy longevity through antioxidant mechanisms including the Nrf2-ARE pathway. Such increase of hydrogen gas might be attributable to the traditional foods and gut microbiome in Japan [15,16], a country that is known for the longevity of its population.

## Conflict of Interest Statement

The author has indicated no potential conflict of interest.

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