REVIEW

The overlooked benefits of hydrogen-producing bacteria

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Abstract

Intestinal bacteria can be classified into "beneficial bacteria" and "harmful bacteria." However, it is difficult to explain the mechanisms that make "beneficial bacteria" truly beneficial to human health. This issue can be addressed by focusing on hydrogen-producing bacteria in the intestines. Although it is widely known that molecular hydrogen can react with hydroxyl radicals, generated in the mitochondria, to protect cells from oxidative stress, the beneficial effects of hydrogen are not fully pervasive because it is not generally thought to be metabolized *in vivo*. In recent years, it has become clear that there is a close relationship between the amount of hydrogen produced by intestinal bacteria and various diseases, and this report discusses this relationship.

Key words: *Bacteroides*; *Firmicutes*; hydrogen; hydrogen-producing bacteria; hydroxyl radicals; IgA antibody; naked mole-rats; oxidative stress; reactive oxygen species

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Introduction

Nowadays, various foods containing lactic acid bacteria or *bifidobacteria* are consumed worldwide. In the food industry, intestinal bacteria are classified into "beneficial bacteria" and "harmful bacteria" for commercial purposes, where beneficial bacteria, such as lactic acid bacteria and *bifidobacteria*, are those that have positive effects on human health, whereas harmful bacteria are those that cause opportunistic infections and induce diseases, such as sepsis, in humans.[1] More specifically, beneficial bacteria digest dietary fibers to produce various short-chain fatty acids, which lead inhibitory T cells to maintain homeostasis in the intestinal tract.[2]

Amongst these intestinal bacteria, those that produce hydrogen, known as hydrogen-producing bacteria, are anaerobic bacteria that do not possess the enzymes to eliminate reactive oxygen species, such as superoxide dismutase and catalase, and thus cannot grow in the presence of oxygen. However, these hydrogen-producing bacteria do possess hydrogenases that allow for the production of hydrogen.[3,4] Whether or not a certain species of bacteria is hydrogen-producing can be determined by the presence of this enzyme. Hydrogenases are enzymes that reversibly catalyze the formation and decomposition of molecular hydrogen through a redox reaction.[5] Until recently, hydrogen has been long considered to be an inert gas that cannot be metabolized in the living body, and thus had been ignored by modern medicinal principles. Yet, hydrogen is a notable substance that should garner greater attention. Although some hydrogen-producing bacteria can be classified as "harmful bacteria" with pathogenic properties, its prevalence is very low in the intestines.[3] Most species of this bacteria are deemed as "Beneficial Bacteria," and in this paper, we focus on these hydrogen-producing bacteria that bring extraordinary benefits to human health.

"Super-Beneficial Bacteria" – Hydrogen-Producing Bacteria

A hydroxyl radical is an extremely toxic and highly reactive reactive oxygen species that is constantly generated in the mitochondria from birth until death. Since hydrogen is the smallest diatomic molecule, it can easily permeate mitochondrial membranes to react with these hydroxyl radicals and prevent cells from oxidative stress without any side effects.[6] Hydrogen has clinical benefits in many diseases, including neurological diseases, cardiovascular diseases, respiratory diseases, diabetes, liver and metabolic syndrome. More than 1000 papers have been published on the medical applications of hydrogen, including over 90 reports of human clinical trials. These papers confirm that hydrogen is highly effective in the treatment of a variety of diseases and that there are no safety issues.[7] Hydrogen molecules are the only species within the human body that can directly eliminate hydroxyl radicals inside mitochondria. Thus, the effects of hydrogen-producing bacteria outperform other beneficial bacteria, such as lactic acid bacteria and *bifidobacteria*, that cannot produce hydrogen. Nonetheless, hydrogen-producing bacteria have been neglected by modern medicine, even though they have these remarkable health benefits as "Super-beneficial bacteria."

Benefits of Hydrogen-Producing Bacteria: "*Bacteroides*" and "*Firmicutes*"

It is said that there are more than 100 trillion intestinal bacteria from 1000 different species in our large intestine. Among these, 70% are hydrogen-producing bacteria that possess hydrogenase, an enzyme that catalyzes the metabolism of hydrogen, as well as the ability to metabolize carbohydrates to produce acetic acid and butyric acid.[3]

According to a metagenomics survey, *Firmicutes* and *Bacteroides* are the most prevalent hydrogen-producing bacteria and account for 92% of bacterial species in the human large intestine, where 51% are *Firmicutes* and the other 41% are *Bacteroides*.[3,4] It is known that *Firmicutes* and *Bacteroides* have beneficial effects on human health, but the mechanisms by which they incite these effects are relatively unknown. As previously mentioned, given that hydrogen was considered to be an inert gas that is not metabolized in the body, little research was focused on the mechanisms of action by *Bacteroides*. Now, the core principles of these mechanisms can be explained.

Bacteroides bind to dimeric IgA antibodies to form colonies that anchor in the mucus near intestinal epithelial cells, from which they constantly produce hydrogen.[8] It is said that approximately 10 L of hydrogen are produced daily in the human intestines.[9] Hydrogen eliminates hydroxyl radicals in the intestinal epithelial cells and protects the intestinal wall from oxidative stress. Surplus hydrogen molecules penetrate the cell membrane by diffusion, and a handful of these particles circulate the entire body through the bloodstream (**Figure 1**).[10]

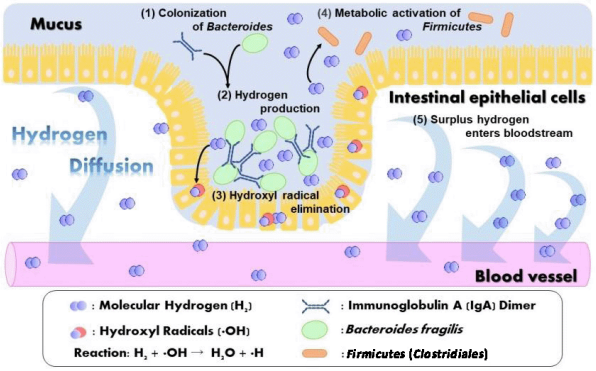

Figure 1: Dynamics of hydrogen generated by *Bacteroides* settled in the intestinal wall.

Note: (1) *Bacteroides* bound to dimeric IgA antibody form colonies in intestinal epithelial cells. (2) *Bacteroides* produce hydrogen. (3) The produced hydrogen eliminates hydroxyl radicals generated inside the intestinal epithelial cells and protects the intestinal wall from oxidative stress. (4) Hydrogen may also be involved in activating the metabolism of *Firmicutes* by colonies of *Bacteroides*. (5) Excess hydrogen diffuses across the membrane and surplus hydrogen enters the bloodstream to travel throughout the body.

Membrane permeability and diffusivity are two of the unique characteristics that separate hydrogen from other pharmaceutical agents. While the concentration of hydrogen produced by intestinal bacteria is dependent on the pH and carbohydrate content of the colon, once hydrogen enters into the bloodstream, it can circulate to the head, penetrate the blood-brain barrier, and protect brain cells from oxidative stress.[11-13] Since molecular oxygen, a larger diatomic molecule than molecular hydrogen, can penetrate the blood-brain barrier for respiration in the brain, molecular hydrogen must also be able to penetrate the blood-brain barrier. It has been reported that there are less *Bacteroides* in the intestines of patients with dementia than in healthy individuals.[14] Although this report does not explicitly mention hydrogen, we can imagine that low levels of hydrogen, due to the small number of *Bacteroides*, cause hydroxyl radical attacks on DNA, proteins, and other biological agents in brain cells, which in turn causes dementia.

The *Bacteroides* and dimeric IgA antibody colonies described above also promote the metabolic function of *Firmicutes*, another hydrogen-producing bacterium that dominates the human colon, thereby protecting against the development of enteritis.[15] *Firmicutes* are also known as butyrate-producing bacteria, and there are reports that elderly people with long, healthy lives have significantly high levels of butyric acid bacteria in their intestines.[16] Butyric acid produced by *Firmicutes* suppresses colorectal cancer via the p21 gene,[17] and it is known that the number of butyric acid bacteria is significantly lower in patients with ulcerative colitis and Crohn's disease.[18] It is possible that this is not only due to the effects of butyric acid, but also due to molecular hydrogen produced by these butyric acid bacteria. The mucus-associated functional factor, a gene with an unknown function, is thought to activate Firmicutes. If we consider that hydrogen protects against the development of enteritis, it is possible that interactions between hydrogen-producing bacteria, such as *Bacteroides* and *Firmicutes*, contribute to the maintenance of human health. In fact, there is a report that shows that by delivering hydrogen to the gastrointestinal tract via the ingestion of hydrogen water and regulating the activity of hydrogen-producing bacteria, the clinical characteristics of intestinal microflora disorders can be improved.[19]

Calico Life Sciences LLC (South San Flancisco, CA, USA), a subsidiary of Google that is conducting research and development aimed at preventing aging and its associated diseases, uses naked mole-rats (*Heterocephalus glaber*) as laboratory animals.[20-22] Naked mole-rats have a 10-fold longer lifespan than normal rodents and have greater resistance to cancer. It has been reported that *Bacteroides* and *Firmicutes* predominate the intestinal bacteria of these mice.[23] It is possible that hydrogen produced by *Bacteroides* and *Firmicutes* is involved in the longevity and cancer resistance of the naked mole-rats.

With these characteristics, hydrogen can play a key role in alleviating intractable diseases such as Parkinson's disease[24] and cancer[25,26] that are caused by oxidative stress, which is often impossible to improve by means of modern medicine and pharmaceuticals. This is another reason why hydrogen-producing bacteria are known as "super-beneficial bacteria."

Hydrogen-Producing Bacteria and Diseases – Hydrogen May Be Involved in the Gut-Brain Interaction

Comparing diseases that are caused by dysbiosis to those that have been confirmed to improve with hydrogen, it is evident that there is a clear overlap between these two groups.[27,28] For instance, diseases associated with *Bacteroides* include intractable diarrhea,[29] Crohn's disease,[30] irritable bowel syndrome,[31]

systemic inflammatory response syndrome,[32,33] inflammation,[6] Parkinson's disease,[34] rheumatism,[35] cancer,[36,37] arterial disease,[30] dementia,[13] and premature birth.[38] The diseases associated with *Firmicutes* include intractable diarrhea,[29] Crohn's disease,[30] irritable bowel syndrome,[31] systemic inflammatory response syndrome,[32] ulcerative colitis,[39] and depression.[40] The pathogenesis of diseases related to dysbiosis is associated with a decrease in the supply of hydrogen to the body due to a reduction in the number of hydrogen-producing bacteria. Diseases such as Parkinson's disease,[8,41] rheumatism,[35] cardiovascular disease,[42] and Crohn's disease[43] have been confirmed to have a clear association with a decrease in the number of hydrogen-producing gut bacteria or with a reduction in the concentration of hydrogen in exhaled air. Since the amount of antioxidant hydrogen produced by hydrogen-producing bacteria in the large intestine is significantly reduced, the possibility that biological substances in cells, such as DNA or protein, are damaged by hydroxyl radicals greatly increases. It has also been demonstrated that hydrogen in the intestines is effective against hepatitis induced by concanavalin A.[44]

As described previously, hydrogen molecules that enter the brain can protect nerve cells from oxidative stress to improve diseases caused by cranial nerve disorders, such as depression and dementia. The bidirectional relationship between the brain and the intestines is referred to as the "brain-gut interaction" or the "gut-brain axis," named by the Intestinal Microbiology Society, and hydrogen-producing gut bacteria may play a central role in this relationship.[45]

It has been reported that (1) microbiomes, (2) oxidative stress, (3) inflammation, and (4) mitochondrial dysfunction are closely related to mental disorders.[46] While the exact functions of hydrogen are not mentioned explicitly in these reports, it is easy to imagine that hydrogen plays a central role in the treatment of these diseases, considering that hydrogen produced by gut bacteria, or the "microbiome," mechanistically reduce "oxidative stress" in various parts of the body, including the brain, to suppress both "mitochondrial dysfunction" and "inflammation."

Hydrogen May Bring a Healthy Longevity

People who lack hydrogen-producing bacteria in their intestines can supply hydrogen to their bodies by inhaling hydrogen gas or by drinking hydrogen water.[47] Hydrogen-producing bacteria not only produce hydrogen, but also produce energy through the decomposition of hydrogen using hydrogenase.[3] Hydrogen-producing bacteria are also able to conserve energy by decomposing hydrogen with carbon dioxide to produce acetate and methane, or by reducing sulfate with hydrogen to generate hydrogen sulfide.[3] As such, supplying hydrogen through these methods can in fact increase the number of hydrogen-producing bacteria in the body.

In a joint study with the Osaka University School of Medicine, it was revealed that the administration of hydrogen water to sepsis-induced mice models for 7 days suppressed bacterial translocation that was causing sepsis and also increased the number of *Bacteroides* in the intestine.[48] The increasing number of hydrogen-producing bacteria consequently increases hydrogen production in the intestines and contributes to the maintenance of health.

Since a correlation between the concentration of hydrogen in exhaled air and the amount of hydrogen produced by hydrogen-producing bacteria has been reported in the past, the concentration of hydrogen in exhaled air can be used as a useful indicator of hydrocarbons metabolized by intestinal bacteria.[11] It has been reported in the past that the concentration of hydrogen in Japanese people over 100 years of age is much higher than those of the elderly diabetics with an average age of 79 years.[49] Although the concentration of hydrogen in exhaled air is affected not only by the number of hydrogen-producing bacteria in the intestinal but also the diet, the hydrogen produced by bacteria in the body may contribute to longer life spans by preventing oxidative stress. In the future, hydrogen may even contribute to immortality over healthy longevities. Hydrogen may be supplied via the inhalation of hydrogen gas without relying on hydrogen-producing bacteria. Although many people are skeptical about the medical benefits of hydrogen, it can help to improve people's health. Hence, hydrogen-producing bacteria can be seen as "super-beneficial bacteria."

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Author contributions
YI and FS designed and wrote the manuscript; SH, BS, HY, and YT supported this study by giving advice and revising the manuscript. All authors read and approved the final manuscript.

Conflicts of interest
YI, HY, SH, BS, and FS are employees of MiZ Company limited. The authors declare no conflicts of interest.

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