Realizing brain therapy with "smart medicine": mechanism and case report of molecular hydrogen inhalation for Parkinson's disease

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Abstract

The Michael J. Fox Foundation has been funding research on Parkinson's disease for 35 years, but has yet to find a cure. This is due to a problem with the philosophy behind the development of modern medical treatments. In this paper, we will introduce "smart medicine" with a substance that can solve all the problems of central nervous system drugs. The substance is the smallest diatomic molecule, the hydrogen molecule. Due to their size, hydrogen molecules can easily penetrate the cell membrane and enter the brain. In the midbrain of Parkinson's disease patients, hydroxyl radicals generated by the Fenton reaction cause a chain reaction of oxidation of dopamine, but hydrogen entering the midbrain can convert the hydroxyl radicals into water molecules and inhibit the oxidation of dopamine. In this paper, we focus on the etiology of neurological diseases, especially Parkinson's disease, and present a case in which hydrogen inhalation improves the symptoms of Parkinson's disease, such as body bending and hand tremor. And we confidently state that if Michael J. Fox encountered "smart medicine" that could be realized with molecular hydrogen, he would not be a "lucky man" but a "super-lucky man."

Key words: dopamine; Fenton reaction; hydrogen; hydroxyl radicals; hydrogen-producing bacteria; oxidative stress; Parkinson's disease; reactive oxygen species

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Introduction

In the 1966 science fiction movie "Fantastic Voyage," written by Isaac Asimov, the submarine "Proteus" carries a medical team that was miniaturized and sent into a patient to reach the brain through blood vessels and successfully burn off the hematoma of a cerebral hemorrhage with a laser. Not only was there a time limit of only 60 minutes for Proteus to be miniaturized and reach the brain, it also had to go through the ordeal of protecting itself from platelets and white blood cells.

In 2016, half a century after the release of "Fantastic Voyage," Elon Musk, the founder of TESLA and SPACE X, founded Neuralink in San Francisco, CA, USA. Neuralink is attempting science fiction by implanting electrodes in the brain, an approach that is an invasion of the head and raises ethical issues.[1] Kernel, a Los Angeles, CA, USA-based company also founded in 2016, has been working since its inception to implant microchips in the hippocampus to treat neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. However, the company decided that it would be very difficult to achieve this goal and froze the project for ethical and regulatory reasons.[2]

Since the brain is the central organ that controls life, a protective blood-brain barrier exists to prevent substances from having unrestricted access to the brain.[3] When developing drugs for use in the central nervous system, the challenge is to penetrate the blood-brain barrier. This challenge includes limitations in the molecular weight of the drug, the need to assess blood-brain barrier permeability, and the need for safety and minimal side effects.[4,5]

We present here "smart medicine," which can easily solve all of the problems associated with brain therapy, suppress chronic inflammation in the brain without any invasion or side effects, and improve diseases for which there is no cure, such as Parkinson's disease, schizophrenia, and Alzheimer's disease. The star of "smart medicine" is hydrogen, the smallest diatomic molecule. The purpose of this paper is to describe the use of hydrogen in the treatment of neurological disorders, which we call "smart medicine" because it could easily overcome the limitations of modern medicine, which originated with Hippocrates in ancient Greece.

The Root of Brain Cell Damage

The problem with the association between neurological diseases and abnormalities in metal metabolism is not the lack of metal ions, but the excessive deposition of metal ions in the brain.[6,7] Although the brain weighs only 2–3% of the adult body mass, it accounts for 15% of blood flow and 20% of oxygen consumption.[8] Because the brain metabolizes large amounts of oxygen, it contains a large number of hemoproteins with porphyrin-iron complexes as complement molecules. The supply of iron ions to the brain is carried out through the blood-brain barrier by endocytosis via transferrin receptors in the blood, and the discharge of iron ions returns to the circulatory system via the cerebrospinal fluid. Once in the brain, iron

is supplemented by ferritin, an iron storage protein found in cells and mitochondria. The iron ions supplemented by ferritin remain stable within the ferritin without causing cellular damage.[9] However, if metal metabolism in the brain is disrupted for some reason and there are too many iron ions in the brain for ferritin to supplement, the iron ions are released into brain cells and mitochondria.[6,10] When the released iron ions react with endogenous hydrogen peroxide, hydroxyl radicals with strong oxidizing power are produced (Fenton reaction; equation 1).[11] The hydroxyl radicals react with lipids, proteins, and DNA, resulting in cellular and mitochondrial damage. Since the brain is a particularly oxygen-consuming organ, iron ion deposition results in hydroxyl radicals constantly attacking brain cells and their mitochondria.[11]

$$H_2O_2 + Fe^{2+} \rightarrow \cdot OH + OH^- + Fe^{3+} \quad (1)$$

Parkinson's disease, Alzheimer's disease, and age-related dementia are all associated with neuronal death in the brain.[12] Neuronal death is preceded by the degeneration of neuronal processes where synapses are located. Neurite degeneration is induced by oxidation of the cell membrane. It has been confirmed that neurite damage is induced by the addition of hydrogen peroxide to the cell culture medium. The hydroxyl radicals produced by the Fenton reaction deprive the lipids that make up the cell membrane of electrons to produce lipid peroxides, resulting in the loss of fluidity of the cell membrane and consequently cell damage. Thus, the degeneration of neuronal processes that occurs prior to neuronal cell death is triggered by hydroxyl radicals.

The denaturation of neurites *in vitro* caused by hydrogen peroxide to the medium can be inhibited by vitamin E, an antioxidant, because hydrogen peroxide acts from outside the cell to inside the cell.[13] However, hydroxyl radicals that generate hydroxyl radicals are usually produced inside the mitochondria of the cell, and fat-soluble vitamins such as vitamin E cannot reach the inside of the mitochondria, which allows hydroxyl radicals generated inside the cell to attack the mitochondrial membrane.[14]

Parkinson's Disease – Dopamine Chain Oxidation by Fenton Reaction

In the midbrain of able-bodied person, dopaminergic nerves where dopamine is biosynthesized are densely packed. These dopaminergic nerves are called the midbrain substantia nigra, because they contain neuromelanin pigment, a polymer of dopamine, and are black in color.[15] Patients with Parkinson's disease have dopaminergic degeneration or dropout in the midbrain substantia nigra, and the neuromelanin pigment in the same region is significantly reduced.[16] This means that the degradation of dopamine is accelerated in the midbrain substantia nigra of Parkinson's disease patients. The degradation of dopamine is catalyzed by monoamine oxidase in the outer mitochondrial membrane, which generates hydrogen peroxide.[17] Hydrogen peroxide generates hydroxyl radicals through the Fenton reaction, which oxidizes dopamine to 6-hydroxydopamine (6-OHDA).[18] Because injection of 6-OHDA into the ventricles of mice causes marked dopaminergic cell loss and progressive substantia nigra degeneration, 6-OHDA has been used in mouse models of Parkinson's disease due to its neurotoxic effects.[19] 6-OHDA reacts with molecular oxygen to form superoxide, which is then supplied with hydrogen ions and electrons to form hydrogen peroxide.[18] The generated hydrogen peroxide oxidizes dopamine again to produce 6-OHDA, starting an endless chain reaction (**Figure 1**). Especially in Parkinson's disease patients, the amount of ferritin in the brain is low, and iron ions are free in the substantia nigra, making them susceptible to the Fenton reaction.[20] The hydroxyl radicals produced by the Fenton reaction decrease not only the level of dopamine but also the level of glutathione, a peripheral antioxidant.[21,22] The hydroxyl radicals also denature the protein α-synuclein.[17]

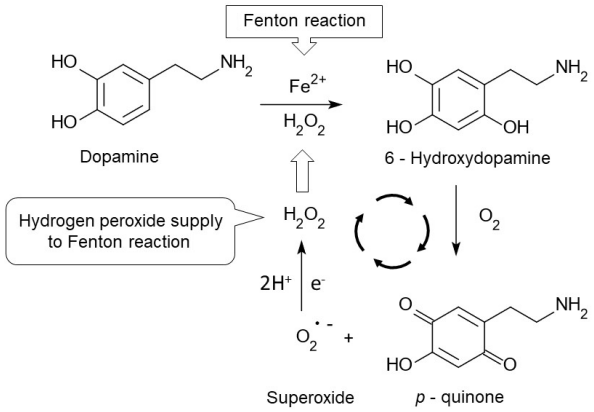

Figure 1: Chain oxidation of dopamine initiated by the Fenton reaction in the substantia nigra of the midbrain of Parkinson's disease patients.

Since the chain oxidation of dopamine occurs in the outer mitochondrial membrane of dopaminergic cells in the substantia nigra of the midbrain, therapies should aim to deliver antioxidants to this location to stop the chain oxidation reaction based on the Fenton reaction.

The Reality of Brain Drug Development – Four Challenges That are Difficult to Overcome

In order to inhibit the cell membrane oxidation of brain cells and the chain oxidation reaction of dopamine in the substantia nigra of the midbrain in Parkinson's disease, it is necessary to stop the Fenton reaction in the brain and compensate for the lack of dopamine. The substantia nigra of the midbrain, which is responsible for Parkinson's disease, is located deep in the center of the brain. However, there are at least four major barriers to get through in order to target the substantia nigrato deliver of drugs and dopamine: passage through the blood-brain barrier, targeting the mitochondria, the elimination of drug metabolites, and limitations of the drug itself.

Blood-brain barrier

The first difficulty in drug discovery for the central nervous system is to pass the blood-brain barrier. Capillary endothelial cells in the brain are composed of tight junctions that connect the cells to each other.[23] This structure prevents the indiscriminate entry of drugs from the blood into the intercellular

fluid of the brain. Transporters and receptors with various substrate specificities are expressed in the blood-brain barrier, controlling the movement of selective substances, and drugs that can pass into the brain are limited in terms of physical properties.[24,25] Recently, it has become clear that the onset and pathogenesis of Alzheimer's disease cause changes in cell adhesion and in the transporters that make up the blood-brain barrier, resulting in a barrier function that is different from that of normal cells, making it extremely difficult to develop drugs for the central nervous system.[4] Drugs can be directly injected into the brain, but this approach is invasive.[5]

Drug delivery to the mitochondria

Once a drug has successfully crossed the blood-brain barrier, the next difficulty is delivering the drug to the mitochondria of brain cells. Mitochondria have a double membrane structure (inner and outer membranes). While the outer membrane of mitochondria can nonspecifically permeate low-molecular-weight substances of up to 5 kDa, the inner membrane of mitochondria has an extremely high resistance to drug permeation, making drug delivery very difficult.[26,27] In order to achieve drug delivery to mitochondria, this high barrier must be overcome. Attempts have been made to selectively deliver antioxidants into the mitochondria, but this has not yet resulted in an effective disease treatment.[14,27]

Expulsion of drug metabolites

Just as the submarine Proteus escaped from the brain and returned to the outside of the body after its mission in the Fantastic Voyage was completed, the metabolites of the drug that complete its mission must also be discharged from the body. This is because even when the drug reaches the mitochondria safely, if the metabolites of the drug are not discharged outside the mitochondria, they may accumulate inside the mitochondria and cause unpredictable side effects.

A transport system that actively discharges metabolites exists at the blood-brain barrier. However, for drug metabolites that reach the brain, they must be discharged from the mitochondria to the outside of the cell and then from the brain to the blood stream.[28] This requires a drug discovery concept that is the exact opposite of drug delivery to the mitochondria, and it is extremely difficult to achieve both drug delivery and discharge.

Limitations of drug efficacy

Levodopa, the precursor of dopamine, is currently an effective drug in the treatment of Parkinson's disease, but it is a treatment that only inhibits progression. It also has a short half-life in the blood, meaning it hardly reaches the brain.[29] In the book "*Awakening*" by Oliver Sacks, a patient who developed Parkinson's disease after encephalitis was given levodopa to awaken him, but the effect waned due to drug resistance.[30] This drug tolerance was depicted as a wearing-off phenomenon, where the time for the drug to work was shortened and the drug dose had to be increased. Another possibility is the on-and-off phenomenon, where the symptoms suddenly get better or worse regardless of when the drug is taken, but eventually get worse. This is a limitation of modern medicine.[29]

Super Lucky Man

The conventional approach to drug discovery, which is to create a single drug for a single brain disease, is difficult because of the many issues that must be overcome. Molecular hydrogen can solve all of these problems.[30] Because of its excellent diffusivity, hydrogen can penetrate the cell membranes that make up the blood-brain barrier, enter the brain, reach the dopamine cells in the substantia nigra of the midbrain, and scavenge the hydroxyl radicals that are constantly being generated inside the mitochondria of the dopamine cells.[31] Furthermore, molecular hydrogen would stop the vicious cycle of the chain reaction of dopamine by converting the hydroxyl radicals inside the brain mitochondria into water molecules. Since the reaction products of hydrogen and hydroxyl radicals are also only water molecules, the drug metabolites, which are foreign to the brain like pharmaceuticals, will not remain in the brain. The excess molecular hydrogen is naturally expelled from the brain by diffusion. Only molecular hydrogen can convert hydroxyl radicals, which are the cause of almost all neurodegenerative diseases, into water molecules in the brain (equation 2). If the oxidation reaction of dopamine can be inhibited, the symptoms of Parkinson's disease will be improved by the accumulation of dopamine due to the inherent dopaminergic capacity of dopamine cells. In fact, the onset and progression of substantia nigra degeneration were effectively suppressed in a Parkinson's disease mouse in which 6-OHDA was injected into the brain to induce substantia nigra degeneration, and the mice were given 50% saturated hydrogen water to drink freely.[19] This is thought to be due to the fact that the hydrogen molecules ingested by drinking the water reached the brain and suppressed the dopamine chain oxidation reaction by the Fenton reaction as described above.

$$H_2 + 2{\cdot}OH \rightarrow 2H_2O \quad (2)$$

In fact, in animal experiments, Parkinson's disease has been improved by inhaling hydrogen gas and drinking hydrogen water.[31] Because the brain size of small animals, such as mice and rats, differs from that of humans, it is necessary to inhale a larger amount of hydrogen in order to have a significant effect on Parkinson's disease in humans. However, since hydrogen has no side effects, if people could inhale it all day long in a facility like a hydrogen room, for example, hydrogen could stop the progression of Parkinson's disease and perhaps even lead to improvement. In his book "*Lucky Man*," Michael J. Fox, a Parkinson's disease patient, became interested in research on embryonic stem cells and the transplantation of dopaminergic cells, which can produce dopamine, into the substantia nigra of Parkinson's disease patients.[32-34] However, even if dopaminergic cells are transplanted into the substantia nigra of the midbrain, dopamine will continue to be destroyed unless the hydroxyl radicals generated by the Fenton reaction catalyzed by iron ions accumulated in the midbrain of Parkinson's disease patients are stopped. Hydrogen is the only substance that can convert hydroxyl radicals in the brain into water molecules and stop the chain oxidation of dopamine by the Fenton reaction. Hydrogen inhalation therapy is non-invasive, so there is no need to drill into the skull and implant a

chip that provides electrical stimulation to the brain. If patients suffering from neurological disorders, including Parkinson's disease and post-traumatic stress disorder, were treated with hydrogen, they would all be "super lucky."

Report on The Improvement of Parkinson's Disease by Hydrogen Inhalation

There have been reports of improvement in Parkinson's disease by drinking hydrogen water.[30] However, when drinking hydrogen water, the amount of hydrogen intake is limited to the amount of hydrogen water that the patient can drink. With hydrogen gas inhalation, patients can consume more hydrogen without filling up their stomachs with water. Therefore, we recruited Japanese patients diagnosed with Parkinson's disease to monitor the effects of hydrogen gas inhalation on their health. After informed consent, they all used a hydrogen gas inhaler manufactured by MiZ Company Limited (Kanagawa, Japan), which controls the concentration of hydrogen to 10% by volume without the risk of hydrogen explosion.[35]

Case 1

A Parkinson's disease patient (67-year-old male, medical history: about 8 years) inhaled a mixed gas of hydrogen and air using a gaseous hydrogen inhalation apparatus (MHG-2000α; MiZ Company Limited) for about 90 minutes per day over about 2 months. Here, the mixed gas was inhaled at first every 2 or 3 days over about 3 weeks, and then every day over about the subsequent 5 weeks. The hydrogen concentration in MHG-2000α was 6.0% to 7.0% by volume (hydrogen generation rate: about 140 mL/min). Before undergoing the inhalation of hydrogen gas, the patient had undergone drug therapy and rehabilitation, but had not exhibited any sign of improvement in Parkinson's disease symptoms (particularly, slow movement, shaking of limbs, forward-bending posture, etc.).

As a result of inhaling the hydrogen gas over about 2 months, the patient improved to be almost comparable to a healthy person in complexion, voice, movement, gait, etc. In addition, when hydrogen gas was inhaled for 90 minutes for the first time, shaking of hands stopped about 30 minutes after the start of inhalation, shaking under the jaw stopped about 40 minutes after the start of inhalation, and the posture forward-bending in a dogleg shape improved to midway between the upright state and the dogleg shape state 90 minutes after the start of inhalation.

Case 2

A Parkinson's disease patient (72-year-old male, medical history: about 6 years) inhaled a mixed gas of hydrogen and air using a gaseous hydrogen inhalation apparatus for 90 or 120 minutes per day. Here, the mixed gas was inhaled every day over about 4.5 months. The hydrogen concentration in MHG-2000α is 6.0% to 7.0% by volume (hydrogen generation rate: about 140 mL/min).

In the patient, the waist had bent in a dogleg shape and the hands and the mouth had been considerably shaking before starting to inhale hydrogen gas. When hydrogen gas was inhaled for the first time, shaking of the hands stopped about 45 minutes after the start of inhalation of hydrogen gas, shaking of the mouth stopped about 55 minutes after the start of inhalation of hydrogen gas, and bending of the waist improved about 90 minutes after the start of inhalation of hydrogen gas compared to before inhalation of hydrogen gas. In the patient, the hands and legs did not shake, or shook slightly, the mouth shook slightly, and the forward-bending posture improved to a reasonably upright state, although the posture was not completely upright, immediately after the hydrogen gas had been inhaled for 90 or 120 minutes per day for about 1 month. The next day, however, the hands, the mouth and the legs were observed to shake often, but as described above, after inhalation of hydrogen gas there was no shaking or little shaking, and it was observed that the symptoms tended to be significantly improved. Such a state was observed over about 3 months after the start of inhalation of hydrogen gas, and during this period, the patient also ingested hydrogen water (hydrogen concentration: 1.6 ppm) about 30 times. Marked improvement was observed about 4 months after the start of inhalation of hydrogen gas, shaking of the hands and the mouth was too small to be recognized unless under careful observation, bending of the spine was reduced compared to the symptom in the early stages, and the spine had straightened. In addition, the time taken for fastening buttons of clothing and the time taken for changing clothes were markedly shortened, it became possible to raise the arms, the body became flexible as a whole, and the voice became lively.

Case 3

A Parkinson's disease patient (46-year-old male), who had been affected about 3 years earlier, took 0.375 mg of Pramipexol LA Tablet (Sawai Pharmaceutical Co., Ltd., Osaka, Japan), 2.5 mg of FP Tablet OD (FP Co., Ltd., Osaka, Japan) and 100 mg of Carcopa Formulated Tablet L (Kyowa Pharmaceutical Industry Co., Ltd., Toyama, Japan) every day, and underwent glutathione infusion once every week. However, because symptoms specific to Parkinson's disease, such as slow movement, shaking of limbs and a tiny step gait, had not sufficiently improved, hydrogen gas was inhaled using hydrogen gas inhalation equipment (hydrogen concentration: about 4% by volume) for about 20 minutes every day over 3 months.

The patient's symptoms of action tremors, slowness of movement and tiny step gait were measured by visual analog scale (**Figure 2**). After the start of inhalation, it was observed that all of the symptoms evidently improved compared to the symptoms before inhalation of hydrogen gas.

Case 4

A Parkinson's disease patient (60-year-old male), who had been affected about 4 years earlier, took three drugs. The patient had symptoms such as slowness of movement, bending of the back in a dogleg shape, and shaking of a hand handling chopsticks. Thus, hydrogen gas was inhaled using a gaseous hydrogen inhalation apparatus (hydrogen concentration: 6.0% to 7.0% by volume (hydrogen generation rate: about 140 mL/min) for 1 to 3 hours every day over 3 months.

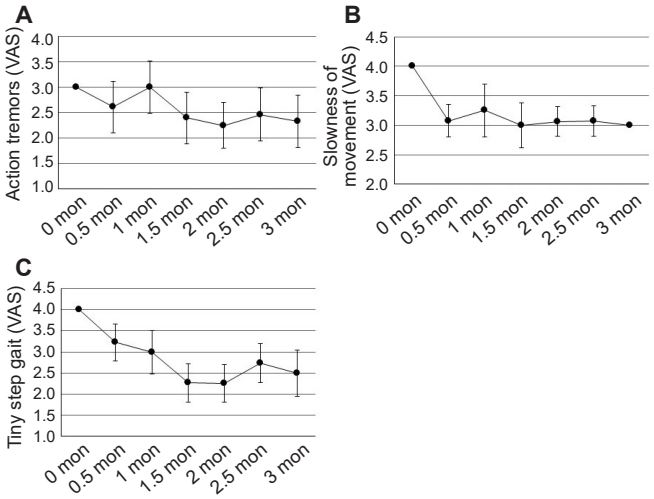

Figure 2: Symptoms of a 46-year-old male patient with Parkinson's disease over 3 months after starting to inhale hydrogen gas.
Note: (A–C) The improvements in the symptoms of action tremors, slowness of movement and tiny step gait, respectively. A greater VAS value indicates a worse condition. Values are expressed as the mean ± SD. VAS: Visual analog scale.

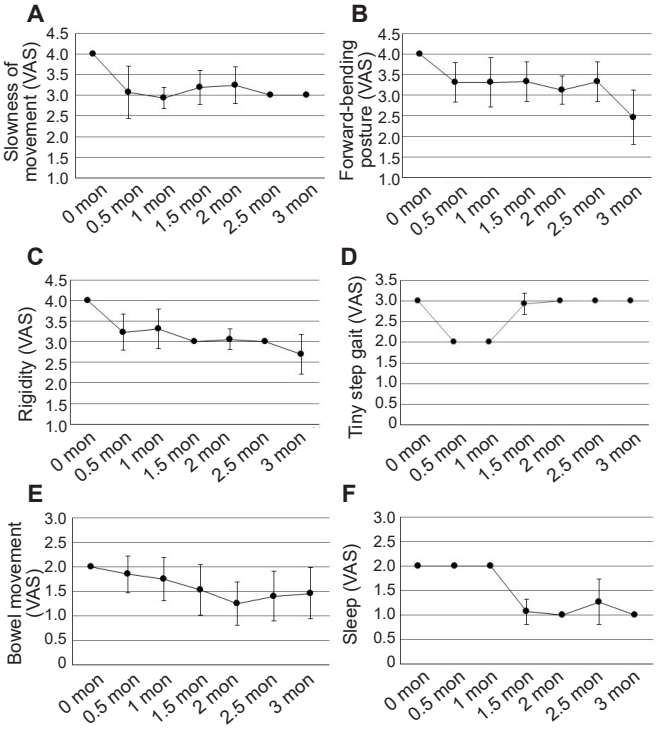

Figure 3: Symptoms of a 60-year-old male patient with Parkinson's disease over 3 months after starting to inhale hydrogen gas.
Note: (A–F) The improvements in the symptoms of slowness of movement, forward-bending posture, rigidity, tiny step gait, bowel movements (constipation) and sleep (insomnia), respectively. A greater VAS value indicates a worse condition. Values are expressed the mean ± SD. VAS: Visual analog scale.

The symptoms of slowness of movement, forward-bending posture, rigidity, tiny step gait, bowel movements (constipation) and sleep (insomnia) of the patient were measured by the visual analog scale (**Figure 3**). After the start of inhalation, it was observed that slowness of movement, forward-bending posture, rigidity, bowel movements (constipation) and sleep (insomnia) evidently improved compared to the symptoms before inhalation of hydrogen gas.

Hydrogen-Producing Bacteria Protect Our Brain

There has been a great deal of studies on the relationship between gut microbiota and brain immunity. These studies have reported that metabolites produced by endobacteria, such as intestinal short-chain fatty acids, gamma-aminobutyric acid, serotonin, and trimethylamine, have an effect on the brain, but these effects are often unclear.[36,37]

For example, *Bacteroides fragilis*, the predominant intestinal bacterium in humans and mice, has an extracellular polysaccharide, polysaccharide A.[37] Polysaccharide A suppresses experimental autoimmune encephalomyelitis by inducing regulatory T cells.[37] Bacteroides, on the other hand, are decreased in patients with dementia, suggesting that they may have some effects on dementia.[37] However, dementia is a brain disease, and it is not clear how Bacteroides, which reside in the intestine and are far from the brain, act. The solution to this problem is hydrogen.[38] Bacteroides are a hydrogen-producing bacterium with hydrogenase, an enzyme that produces hydrogen. The hydrogen produced by Bacteroides not only suppresses inflammation in the intestines, but some of it also travels through the bloodstream to the brain. Since hydrogen has excellent diffusivity and can penetrate cell membranes, it can pass through the blood-brain barrier and enter the brain. The hydrogen that enters the brain also penetrates the mitochondrial membranes of brain cells, enters the brain cell mitochondria, scavenges hydroxyl radicals, which are the causative agents of inflammation, and protects the brain from damage from hydroxyl radicals. When the number of Bacteroides is low, the amount of hydrogen produced by Bacteroides is also reduced, thus weakening the brain's defenses against hydrogen, which is thought to be the cause of dementia (**Figure 4**). Bacteroides, a hydrogen-producing bacterium, was significantly lower in patients with Parkinson's disease and dementia, suggesting that hydrogen produced by hydrogen-producing bacteria in the intestines may contribute to the prevention of neurological diseases such as Parkinson's disease.[39,40] To improve Parkinson's disease once it has developed, the amount of hydrogen produced by hydrogen-producing bacteria in the intestines will not be enough, and more active inhalation of hydrogen will be important. Although many cases of hydrogen improving neurological disorders of the brain have been reported, the ameliorative effect of hydrogen on Parkinson's disease has not been stable, which is thought to be due to the fact that the amount of hydrogen inhaled is too small.[19] Since the midbrain, where Parkinson's disease is located, is in the center of the brain, it is important to send more hydrogen into the brain through prolonged hydrogen inhalation to ensure that it reaches the midbrain.

Alkahest, a company in San Carlos, CA, USA acquired by a Spanish manufacturer of plasma products, is conducting trials for the treatment of Parkinson's disease and dementia. It is also looking for target molecules in the blood of elderly people and developing relevant drugs. However, molecular hydrogen in the blood is not one of these molecules. Molecular hydrogen is a very light molecule and is quickly released from the blood and into the atmosphere. We are excited to learn their reaction when they detect the presence of molecular hydrogen.

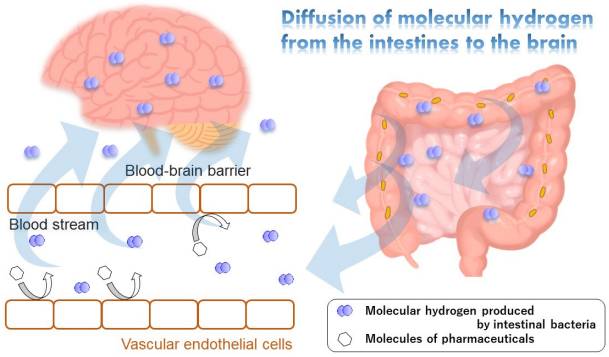

Figure 4: Molecular hydrogen produced by hydrogen-producing bacteria in the intestines reaches the brain and protects it against hydroxyl radical damage.
Note: Created with Microsoft PowerPoint.

Conclusion

The therapeutic effect of hydrogen on the brain has been introduced in this paper. Since hydrogen can reach not only the brain but also the whole body due to its diffusivity, it is also effective against diseases of organs other than the brain. Above all, since hydrogen therapy requires only inhalation, it is available to all people, regardless of social status.[41] The ever-increasing cost of medical care in the face of an aging society is a concern for many countries around the world. The "smart medicine" discussed in this paper could be a new treatment method to solve most of the problems of modern medicine without relying on national medical costs, doctors, or drugs.

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

Conflicts of interest
YI, SB, SH and FS are employed by MiZ Company Limited. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement
No additional data are available.

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