Editorial

Will the hydrogen therapy be approved shortly?

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Ischemia-reperfusion injury is a critical issue in surgical fields

Ischemia-reperfusion is characterized by a restriction of blood supply to multiple organs, followed by the subsequent reperfusion with accompanying re-oxygenation. Ischemia-reperfusion injury causes serious damages in a wide range of conditions by inducing strong oxidative stress. For example, cardiac or cerebral infarction, cardiac arrest, organ translation, and liver resection cause ischemia-reperfusion injury in multiple organs when blood flow is recovered (1). Because most surgical treatments are associated with ischemia-reperfusion injury, to overcome this damage is one of critical issues in surgery.

Recently, Malý *et al.* reported that inhalation of hydrogen gas (H_2 as the chemical formula or molecular hydrogen) prevented ischemia-reperfusion liver damage during major liver resection using 12 domestic pigs. H_2 treatment reduced oxidative stress, resulting in the mitigation of damages caused by ischemia-reperfusion (2). Because liver resection is one of the high-risk surgeries that often cause fatal complications, H_2 inhalation is awaiting approval as a possible actual therapy.

Hydrogen has emerged as a safe medical gas

Biological effects by several medical gases are experimentally accepted in preventive and therapeutic interventions. Carbon monoxide (CO), hydrogen sulfide (H_2S), and nitric oxide (·NO) play important roles as signaling molecules at lower levels; however, they are highly toxic molecules at higher concentrations. In contrast, H_2 is advantageous in having no cytotoxicity (3).

H_2 was considered as a non-functional and inert gas at body temperature in mammalian cells for a long time. In fact, in the absence of catalysts, H_2 does not react with any biological compounds, including the oxygen molecule, at body temperature. On the other hand, in some bacteria, H_2 can be metabolized by a kind of enzymes termed hydrogenase. In contrast, mammals do not have any functional hydrogenase genes. Thus, this is why H_2 was believed to be non-functional in our cells.

This concept was overturned by a publication in 2007 describing that H_2 acted as a preventive and therapeutic antioxidant through reducing highly reactive oxidants such as hydroxyl radical (.OH) and peroxynitrite ($ONOO^-$) in cultured cells, and moreover that H_2 exhibited cytoprotective effects against strong oxidative stress in a model animal (4). Subsequently, a large number of studies have revealed the preventive and therapeutic effects of H_2. These publications exhibited efficient beneficial effects against oxidative stress in most organs (3). Moreover, it has been revealed that H_2 has multiple functions, including anti-inflammatory, anti-allergic, and anti-apoptotic effects, and regulation of autophagy in most tissues of model animals (3). In turn, H_2 stimulates energy metabolism (5).

H_2 has great advantages because of no or little toxicity (6): H_2 has experimentally no cytotoxicity even at high concentrations (3,7). Importantly for an actual application, the biological safety of H_2 was revealed by the inhalation of an extremely high concentration of H_2

gas in an exotic breathing gas mixture, Hydreliox, which is composed of 49% H_2, 50% helium and 1% O_2. This mixed gas is used to prevent decompression sickness and nitrogen narcosis during deep diving (7). Inhalation of H_2 gas of the range between 1–4% exhibits excellent efficacy (4,8), and there is no risk of fire or explosion when the H_2 concentration is less than 4%.

Molecular hydrogen can be ingested by various ways

There are various methods to ingest H_2 into the body. Inhalation of H_2 gas is a straightforward therapeutic method through a ventilator circuit, facemask, or nasal cannula. Because inhaled H_2 gas defuses rapidly and is incorporated into the whole body, the inhalation is considered as the most suitable method against acute oxidative stress.

H_2 is dissolved in water up to 0.8 mM (1.6 mg/L) at atmospheric pressure and room temperature and does not change pH. Solubilized H_2 (H_2 infused in water; termed H_2-water) may be convenient in potable, and can be administered by a safe way by drinking H_2-water (5).

Alternatively, H_2 can be injected intravenously or intraperitoneally as H_2-saline (H_2 dissolved in saline). This method allows more delivery of H_2 with great efficacy than drinking H_2-water (9). Additionally, H_2-loaded eye drop is applicable by dissolving H_2 in saline and by directly administering to the ocular surface (10).

During cold preservation, H_2 can be delivered to cardiac grafts using an H_2-infused water bath, and efficiently mitigated myocardial injury caused by cold ischemia-reperfusion. This device to saturate organs with H_2 during cold storage may have a merit for actual therapeutic and preventative uses during transplantation (11).

Molecular hydrogen exhibits great efficacy against ischemia-reperfusion injury

Because ischemia-reperfusion induces strong oxidative stress, to overcome the ischemia-reperfusion injuries should be one of the serious issues in many clinical treatments. As an acute rat model, oxidative stress damage was induced by the focal brain infarction followed by reperfusion. The inhalation of H_2 gas markedly mitigated the brain damage by decreasing oxidative stress. Thus, H_2 may be applicable as an effective antioxidant therapy. By the ability to rapidly diffuse across membranes and the blood brain barrier, H_2 can reach any regions in any cells, and react with cytotoxic reactive oxygen species. Thus, H_2 is considered to protect cells against oxidative damage.

Subsequently, inhalation of H_2 gas improved ischemia-reperfusion injuries in myocardial infarction (8,12). H_2-saline protected against renal ischemia-reperfusion injury. H_2 gas inhalation exhibited great improvement in survival and the neurological deficit score in a rat model with post cardiac arrest syndrome (13). H_2 also mitigated damage during the transplantation of various organs by inhalation (14).

For translational research, the efficacies of H_2 should be examined using large laboratory animals. In dogs, H_2 exerted cardioprotection through the involvements of ATP-dependent K^+-channels and permeability transition pores of mitochondria (12). In swines, H_2 gas inhalation, perioperatively, diminishes neurologic injury following experimental circulatory arrest (15). A recent publication demonstrated the reduction of oxidative stress induced by ischemia-reperfusion in resection of the liver using domestic pigs (2).

Pilot clinical studies have been performed in cerebral infarction, cardiac infarction and cardiac arrest syndrome (16-18).

Twenty-five patients with acute cerebral infarction inhaled H_2 gas with no significant adverse effects, and were improved in oxygen saturation in comparison with 25 blinded control patients. The H_2 gas therapy significantly improved the relative signal intensity of magnetic resonance imaging in the sever infarction site. NIH Stroke Score was used to evaluate the clinically quantifying stroke severity, and the Barthel Index was used for physical therapy evaluation. These scores were significantly improved by H_2 inhalation in comparison with the control group. These results suggested a potential for widespread and general application of H_2 gas (16).

A prospective, open-label clinical pilot study was designed for 20 patients experiencing ST-elevated myocardial infarction. H_2 inhalation during percutaneous coronary intervention was safe and feasible, and promoted left ventricular reverse remodeling at 6 months after ST-elevated myocardial infarction (17). Five patients with post-cardiac arrest syndrome underwent H_2 gas therapy with accompanying target temperature management. No adverse effects attributable to H_2 inhalation were observed, and 4 patients survived at least 90 days with favorable neurological outcomes (18).

The Japanese Minister of Health, Labour and Welfare received H_2 inhalation therapy as an advanced therapy B for post-cardiac arrest syndrome. This advanced therapy B

is expected to receive approval for the actual application of H_2 therapy. The study protocol for a randomized controlled trial was published as "Efficacy of inhaled HYdrogen on neurological outcome following BRain Ischemia During post-cardiac arrest care (HYBRID II trial)" (19).

Molecular mechanism to exert multiple functions including anti-oxidative stress against ischemia-reperfusion

In the latest knowledge, H_2 can react with only the molecules having extremely oxidative reactivity including .OH and $ONOO^-$ in the absence of a catalyst in biological conditions. According to the reaction rate of H_2 with ·OH, which was obtained in homogeneous aqueous solution, it may be difficult for H_2 to overcome competition with other cellular anti-oxidants; however, the living cell structure is complicated with various microenvironments. The conventional kinetics obtained in homogeneous aqueous conditions cannot be applied to consider the molecular mechanism of H_2.

Experimentally, H_2 decreased the level of cellular ·OH and the subsequent production of lipid peroxides because ·OH triggers a lipid free-radical chain reaction, resulting in the accumulation of lipid peroxides (20).

Severe lipid peroxidation initiates ferroptosis, which was emerged as a new type of cell death, and characterized by condensed mitochondrial membrane densities as well as the diminished amounts or loss of mitochondria crista and outer membrane rupture. Thus, H_2 may protect cells against cell death, such as ferroptosis, in ischemia-reperfusion.

Lipid peroxides are non-enzymatically resolved into end products, some of which function as signal mediators, such as 4-hydroxynonenal (HNE). In turn, HNE modulates Akt/FoxO1 signaling. Because H_2 decreases the level of lipid peroxides, H_2 indirectly may modulate the Akt/FoxO1 signaling pathway (21).

Alternatively, to exert multiple functions in addition to anti-oxidative function, H_2 can regulate various signal transduction pathways and the expression of various genes. As a mechanism, H_2 interferes in the lipid free-radical chain reaction and modifies lipid mediators that function as antagonists of various receptors to modulate signal transduction. For example, a modified oxidized phospholipid suppresses a Ca^{2+} channel, and subsequently inactivates the Ca^{2+}-dependent transcription factor NFAT. Because NFAT transcribes several inflammatory cytokines, including TNF-α and IL-6. In fact, after 2 hours of ischemia-reperfusion, H_2 suppressed the increase in inflammatory cytokines to calm inflammation (13).

Hydrogen therapy may be useful in the treatment of advanced cancers

H_2 was first reported as a ·OH scavenger in 2007, and subsequently the beneficial effects of H_2 were reported in more than 170 disease models and 70 human diseases including ischemia-reperfusion injury, inflammation, metabolic syndrome, and cancer (3).

Recent studies have investigated the application of H_2 gas therapy for patients with advanced cancer.

In Japan, patients with stage IV colorectal cancer inhaled H_2 gas for 3 h/day in their own homes and received chemotherapy. H_2 gas improved progression-free survival and overall survival times, accompanied by a decrease in the abundance of exhausted terminal $PD1^+$ $CD8^+$ T cells and an increase in active terminal PD1 $CD8^+$ T cells (22).

In China, 82 patients with stage III and IV cancer were prospectively followed-up, after treatment with H_2 inhalation. No sever hematological toxicity was observed. H_2 Inhalation of H_2 gas induced complete and partial remission in tumors of the 80 patients at 21–80 days (median 55 days). In patients with advanced cancer, inhaled H_2 can improve patients' quality-of-life and control cancer progression (23,24).

Inhalation of H_2 gas may be a simple and low-cost treatment with no or little adverse effect, and will require further investigation as a strategy to cure or improve patients with advanced cancer.

Concluding remarks

H_2 has strong potential for actual applications in various medical fields, including ischemia-reperfusion injury, advanced stage cancer, dementia, and metabolic syndrome. H_2 should be very unusual from the viewpoint of conventional medicine because of its absence of cytotoxicity and its multiple functions to overcome severe diseases from chronic to acute stages. Thus, to receive public approval is critical for the application of the H_2 treatment.

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Footnote

Conflicts of Interest: The author holds a right of patents involved in H_2 therapy for ischemia-reperfusion injury.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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