Despite the vast number of various strategies available, no single tactic has proven sufficient to completely abolish spinal cord IRI. Hydrogen gas may be effective in reducing oxidative stress after cardiac arrest, and is now potentially effective against spinal cord IRI.[1] The ability to potentially have a universal, safe, and easily applied technique to avoid the devastating results of spinal cord IRI is a very exciting prospect, and the results of this study conducted by Kimura and colleagues[1] indicate the possible clinical usefulness of hydrogen gas and also open up new avenues for further research.

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Commentary: Hydrogen: Lightweight molecule takes on a heavyweight problem

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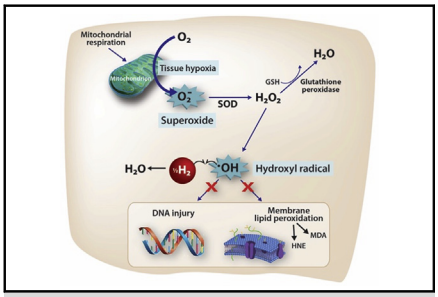
Diatomic hydrogen (H_2) is the lightest and most abundant molecule in the universe. Hydrogen's reactivity with oxygen is well recognized as a thermodynamically favorable redox reaction that forms water. H_2's small size results in unsurpassed diffusivity (even diffusing through steel), enabling it to reach therapeutic targets effectively even in low-flow states. In vivo, inhaled H_2 undergoes solubilized transport to the tissues and undergoes redox reactions with reactive oxygen species (ROS) within the mitochondrion, resulting in a substantial arteriovenous difference in dissolved H_2 content (~10 ng/mL).[1] Shown in Figure 1, H_2 is an ideal therapy for ischemia and reperfusion, where the underlying pathophysiology is mitochondrial oxygen deprivation leading to the subsequent formation of ROS. Unreduced ROS initiate a complex cascade that leads to oxidation of DNA, lipid membranes, and other structures culminating in apoptosis.



Effect of H_2 in neutralizing damage induced by reactive oxygen species following ischemia.

CENTRAL MESSAGE

Reperfusion following ischemia produces reactive oxygen species O_2-•, H_2O_2, and •OH. These species react with DNA, lipids, and proteins, resulting in cellular injury and death. H_2 reduces •OH to H_2O.

In this issue of the *Journal*, Kimura and colleagues[2] describe a series of well-controlled experiments demonstrating that H_2 attenuates the effects of experimental spinal ischemia in a dose-dependent fashion with improved motor function, reduced histopathologic injury, and reduced cerebrospinal fluid glutamate and hydroxyperoxide concentrations. These findings are consistent with a preponderance of evidence that H_2's primary effect is related to reactivity with and chemical reduction of oxygen species. In addition to glutamate, mitigation of this central pathology has been

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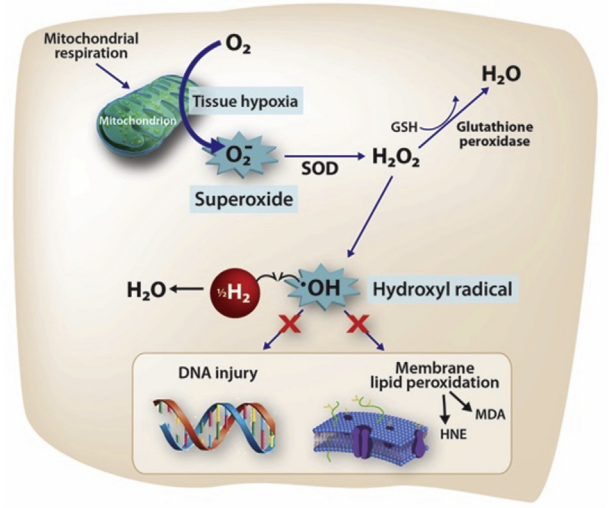

FIGURE 1. Reperfusion of ischemic organs results in the production of reactive oxygen species, including the superoxide anion radical (O_2-•), hydrogen peroxide (H_2O2), and the hydroxyl radical (•OH). These oxidant species, particularly •OH, react with DNA, lipids, and proteins, resulting in cellular injury and death when present in high concentrations. H_2 has been shown to reduce •OH to H_2O. *SOD*, Superoxide dismutase; *HNE*, 4-hydroxynonenal; *MDA*, malondialdehyde.

shown to alter various signal transduction pathways and gene expression, including calcium-dependent signaling pathways such as nuclear factor of activated T cells,[3] nuclear factor kappa-B,[4] Nrf2, and others.[5] Importantly, H_2 has shown clinically beneficial effects in a number of preclinical models, including circulatory arrest,[6] cardiac arrest,[7,8] stroke,[1] sepsis,[9] and transplantation.[10]

Over the past several years, several groups have described the administration of H_2 to patients with cardiac arrest,[11,12] stroke,[13] myocardial infarction,[14] and asthma,[15] and several trials are ongoing in the setting of coronavirus disease 2019−related respiratory illnesses. Combining results of these studies and preclinical data,[16] H_2 appears to have a favorable safety profile in a diverse range of clinical settings. Perhaps most important is the environmental safety of handling hydrogen gas mixtures, since mixtures containing an excess of 4% H_2 exceed the lower flammability limit and pose a substantial hazard in a clinical setting. This can be overcome through the use of commercially produced, certified, nonflammable hydrogen mixtures that contain less than 4% H_2. Specifically, we have shown that 2.4% H_2 mixtures with air, oxygen, and oxygen−carbon dioxide mixtures can be attached to the gas inlets of standard ventilators, anesthesia machines, and membrane oxygenators (for cardiopulmonary bypass sweep gases) even in the surgical setting.[6] When so arranged, administered H_2 concentration remains constant independent of inspired oxygen fraction or cardiopulmonary bypass or ECMO flow rates, and the environmental hazards are eliminated.

Work to determine whether H_2 will prove efficacious in the clinical setting is underway. Our group has recently embarked on a phase I Investigational New Drug trial examining the clinical safety and feasibility of H_2 inhalation in healthy adults (NCT04046211). This is the first step in determining whether H_2 becomes an important therapeutic in the treatment of clinical conditions in which ischemia and reperfusion play a central role.

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