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EDITORIAL

Unravelling the potential of hydrogen in biological systems

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Molecular hydrogen (H_2) and oxyhydrogen (66% H_2/ 33% O_2) gases have been demonstrated to remediate the effects of numerous diseases in adults[1-4]. By acting as an anti-inflammatory and antioxidative agent, it is reported that H_2 can improve recovery through mitigating hyperinflammatory responses and reducing oxidative stress[5-7]. As the precise mechanisms of H_2 activity are currently undefined, the lack of primary target identification, coupled with difficulties regarding administration methods (e.g., dosage and dosage frequencies, and long-term effects of treatments), there is a requirement for H_2 research to evidence how it can reasonably and effectively, be incorporated into healthcare.

H_2 forms through the amalgamation of two hydrogen atoms, resulting in an H-H bonding energy of 107 kcal/mol (4.64 eV)[8] and a redox potential ($2H + 2e^- \rightarrow H_2$) of -0.421 eV at pH 7 relative to the standard hydrogen electrode[9]. While the primary mechanism of H_2 activity remains unclear, a prevalent hypothesis posits that H_2 can mitigate excessive reactive oxygen and nitrogen species (ROS/RNS) through direct interaction with radical and ionic species such as hydroxyl radicals ($^{\bullet}OH$) and peroxynitrite ($ONOO^-$). However, the favourability of these reaction kinetics *in vivo* is still a matter of debate[10-12].

Despite the documented clinical benefits of H_2 therapies[13-16], significant questions remain about the distribution and molecular mechanisms of H_2 within biological systems. Key questions include how H_2 reaches target tissues, what the primary physiological targets of H_2 interactions are, and how H_2 maintains its influence over time. In response, international research institutions are dedicating resources to understanding the effects of H_2 on cellular and systemic physiology. This editorial assesses emerging research on H_2 distribution and molecular activity of H_2 in biological systems.

The physical and chemical characteristics of H_2 (e.g., electrochemically neutral, lightweight, non-polarity, etc.), should permit the molecule to diffuse through biological fluids, the extra-cellular matrix, cellular membranes and cytosolic compartments[17,18]. However, it is undetermined whether this mechanism of

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dispersal would be able to explain the effects seen in distal organs. For example, when hydrogen-rich saline (HRS) is administered via intraperitoneal delivery, substantial amounts of H_2 are recorded in proximal sites such as the pancreas and spleen, whilst stepwise reductions, progressing radially, are shown for the distal organs[19]. Interestingly, when H_2 is delivered via inhalation, although the primary beneficiary organs are typically in close proximity (e.g., the brain, respiratory system and heart), significant increases in H_2 concentration are also seen in the spleen and skeletal muscle 30 minutes after application. Although this research[20] identified that intraperitoneal injection with HRS resulted in H_2 elevation in the majority of tissues analysed, this method was not effective in delivering capacious amounts of H_2 into the bloodstream or the wider cardiovascular system but was highly effective in delivering H_2 to proximal organs including the intestines, liver, pancreas and spleen. Such results suggest a preference for distribution by simple diffusion, however, this still does not explain the elevated levels of H_2 in distal organs such as the brain and kidneys, when elevated H_2 levels in the blood are not detected. However, this factor could be explained if H_2 were to transitorily reside within micropores, or pockets, formed within haemoglobin of red blood cells[21-23]; or if H_2 could be temporarily retained by molecules suspended in the serum such as carbohydrates (e.g., glycogen), or inorganic ions, calcium, potassium, or phosphates, as examples. This potential for temporary retention and residence within biological structures might contribute to observed biological effects of H_2 administration.

While evidence supporting the mitigation of cellular component oxidation and peroxidation by H_2 is clear[24-28], evidence that this diatom acts as a direct antioxidant remains sparse. Although seminal calculations conducted by Kim et al. (2022)[29] suggest antioxidant activity through interactions between H_2 and protohaem, kinetic modelling indicates that H_2 is unlikely to react with other reactive gases *in vivo*, **Table 1**. To elucidate, the superoxide ($O_2^{\bullet-}$) anion, the principal molecule for reactive oxygen and reactive nitrogen species formation, has a spontaneous dismutation rate constant of 8×10^4 M^{-1} sec^{-1} (pH 7.8), albeit, this is a second-order rate reaction[30]. The first-order rate reaction is calculated to be 10^6 -fold more expedient[31]. Additionally, both the hydroxyl radical and the peroxynitrite ion, which are significant contributors to oxidative stress[32,33], have reaction kinetics that far surpass the reactions that may occur with H_2. The reaction kinetics of $^{\bullet}OH$ with H_2 are calculated to be 4.2×10^7 M^{-1} s^{-1}[34], whilst $ONOO^-$ is reported not to have a spontaneous dismutation rate of 1.1 - 1.3 M^{-1} s^{-1}, with or without the addition of H_2[35].

Table 1. Data extracted and adapted from Zhang et al. (2019)[36]. Lifetime: natural log2 divided by the sum of the products of rate constant and concentrations for all molecules that ROS react with. Diffusion distance: calculated with the formula x = (6Dt)1/2 (x, D, t stand for diffusion distance, diffusion coefficients and lifetime, respectively).

Substance	Chemical Nomenclature	Theoretical Distance Travelled (meters)	Theoretical Longevity (seconds)	Primary Targets
Hydrogen Peroxide	H_2O_2	10^{-3} m	10^{-3} s	Metal groups and thiols
Hydroxyl Radical	$^{\bullet}OH$	10^{-9} m	10^{-9} s	Indiscriminate – all organic macromolecules
Nitric Oxide Radical	$NO^{\bullet}$	10^{1} m	10^{-1} s	Metal groups and thiols
Peroxynitrite	$ONOO^-$	10^{-6} m	10^{-6} s	CO_2, Cys, Trp, Met and metal groups
Superoxide	$O_2^{\bullet-}$	10^{-9} m	10^{-3} s	Fe–S clusters and $NO^{\bullet}$

Given the favourable reaction rates of >1 x $10^{\wedge 9}$ M^{-1} s^{-1} for most radical interactions, the neutralisation of ROS/RNS in the milieu of amino acids, lipids and other reactive gases, by H_2, appears biologically insignificant. Therefore, while H_2 shows promise as an antioxidant, it is unlikely to be due to direct interactions with highly reactive biological compounds.

Offering another explanation into the antioxidant activity of H_2, *in silico* research infers that H_2 can bind to the iron (Fe^{2+}) in haem via asymmetric dihydrogen bonds and symmetric bilateral electron transfer, known as Kubas bonding[37]. The authors report that symmetric binding is more favourable under physiological conditions due to a moderately lower activation energy (2.04 eV vs. 2.14 eV). Wherein, Fe^{2+} is hypothesized to reduce the dissociation energy of the H-H bond in H_2, forming an $Fe^{2+}/H^{\bullet}$ complex that can reduce highly reactive ions and radicals. The dissociation energy of $Fe^{2+}/H^{\bullet}$ was calculated to be 2.78 eV, allowing the bound $H^{\bullet}$ radical to neutralise other reactive species[38]. However, the kinetics of this proposed mode of action remain unclear.

Given these complexities, it is conceivable that the therapeutic potential of H_2 extends beyond simple antioxidant activity. The effects of H_2 on signaling pathways and gene expression modulation might offer alternative explanations for its observed benefits. For example, the downregulation of the NADPH oxidase (NOX-1) enzyme noted in H_2-treated models suggests a regulatory role that could mitigate oxidative stress indirectly, by reducing the production of superoxide anions[39]. Additionally, H_2 has been observed to influence cell signalling pathways involved in inflammation and oxidative stress, hinting at a broader regulatory function within cellular systems. Empirical studies demonstrate that H_2 can modulate signal transduction pathways such as the Nrf2 pathway, which is crucial for cellular defence against oxidative stress[40-42]. This may be important as activation of Nrf2 leads to the expression of antioxidant enzymes including haem oxygenase-1 (HO-1) and superoxide dismutase (SOD), which can enhance the cell's intrinsic ability to manage oxidative damage[43]. This indirect mechanism of reducing oxidative stress through upregulation of endogenous antioxidant systems could be a significant aspect when considering the therapeutic efficacy of H_2.

As we delve deeper into the mechanisms and biomedical applications of H_2, we stand at the cusp of unlocking new therapeutic strategies that could significantly impact the treatment of oxidative stress-related diseases. While the antioxidant properties of H_2 are well-documented, its therapeutic potential likely extends

beyond direct radical scavenging[44]. The modulation of signaling pathways, gene expression, and inflammatory responses represents promising avenues through which H_2 may exert its beneficial effects. As the scientific community continues to explore the potential of H_2, several key areas warrant further investigation. Firstly, the development of advanced analytical techniques to accurately measure H_2 concentration and distribution in biological tissues will be pivotal. Secondly, understanding the interaction of H_2 with cellular components at the molecular level will provide insights into its precise mechanisms of action. And lastly, clinical trials assessing the efficacy and safety of H_2 in various disease models will help establish its therapeutic potential and inform clinical guidelines. By creating a robust, interdisciplinary, evidence-based library of research, it is possible that H_2 therapeutics may herald new, innovative treatments for chronic inflammatory and oxidative stress-related diseases.

Conflict of interest

The authors declare that they have a financial and professional affiliation with Water Fuel Engineering, a company that designs and manufactures oxyhydrogen-producing electrolysers.

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