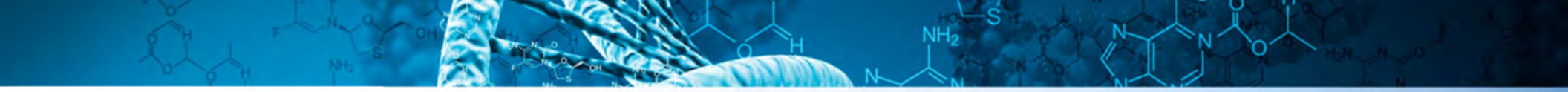

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# Molecular Hydrogen: The Health Molecule of the 21st Century

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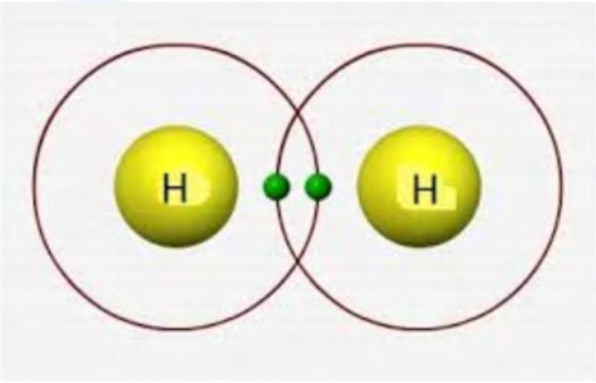
# What is molecular hydrogen?

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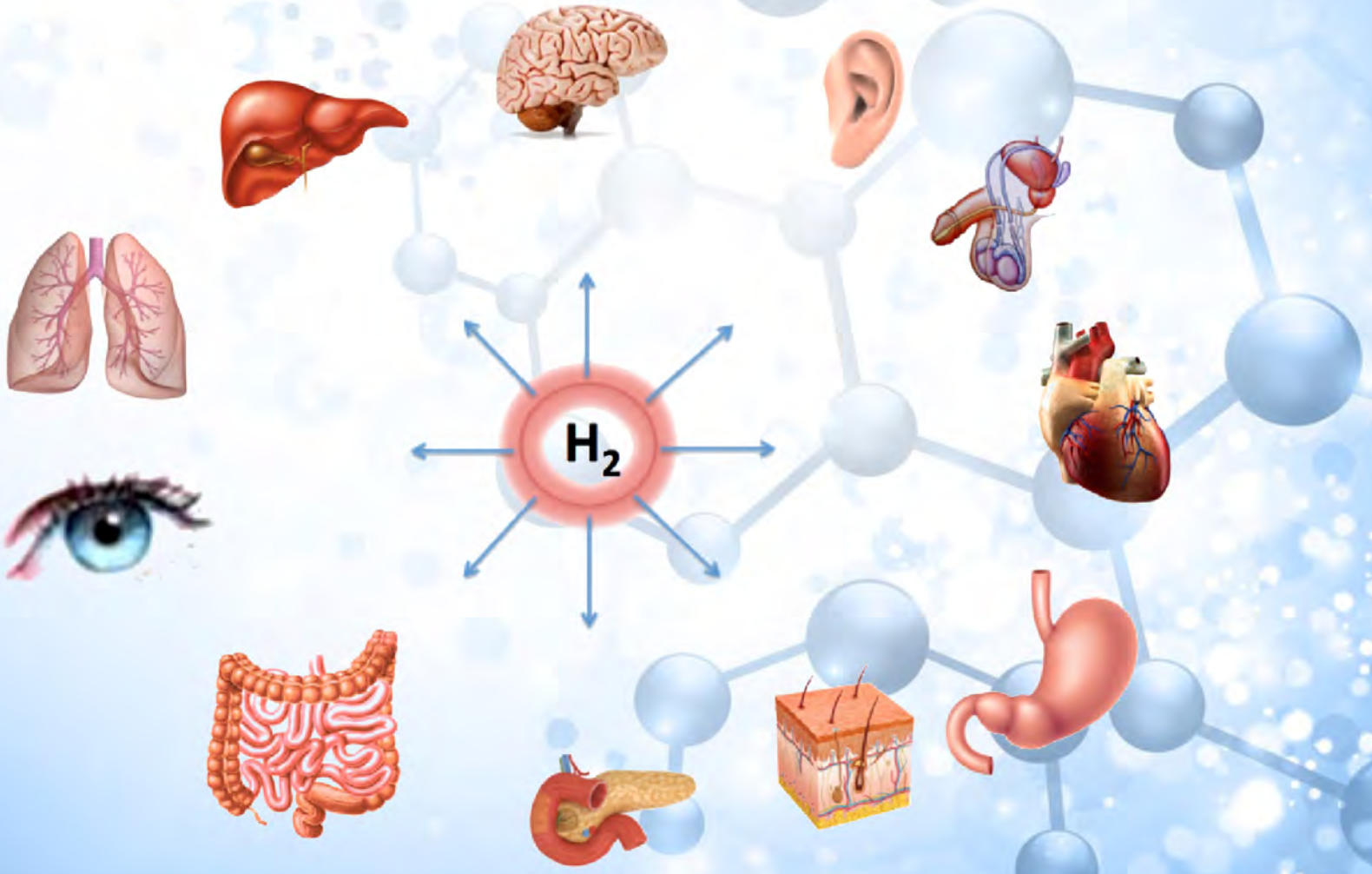
**Hydrogen has shown to have therapeutic potential in 150 different human and animal disease models and in essentially every organ of the human body.**



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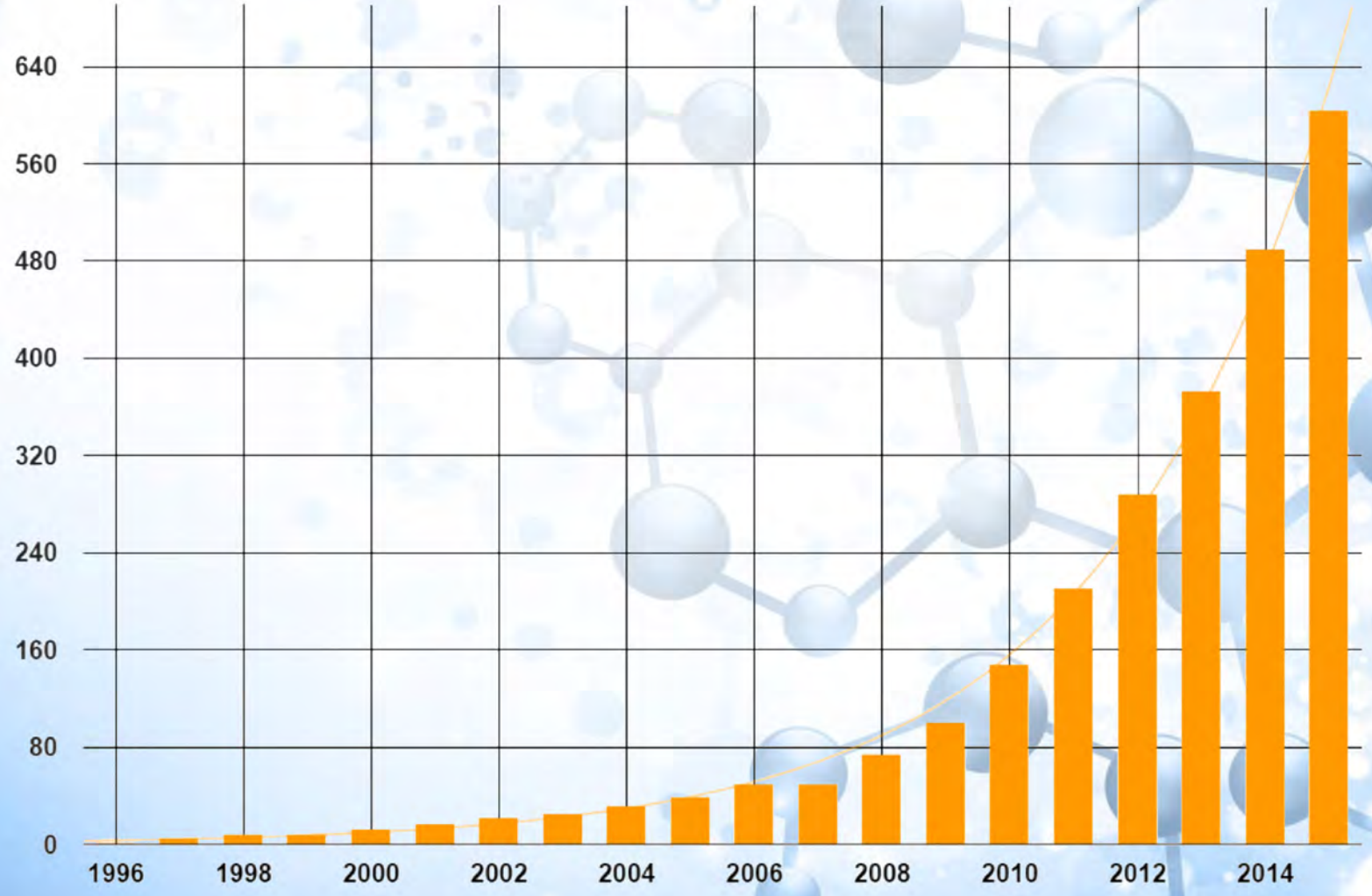
# The number of Molecular Hydrogen Research Publications is growing exponentially



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# $H_2$ research is growing in USA

UAMS
UNIVERSITY OF ARKANSAS
FOR MEDICAL SCIENCES

OHIO STATE

UF | UNIVERSITY of FLORIDA

UNIVERSITY OF WASHINGTON · 1861 · LVX · SIT

Cleveland Clinic

Forsyth

NASA

UPMC
University of Pittsburgh
Medical Center

Duke
UNIVERSITY

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LOMA LINDA UNIVERSITY
HEALTH SYSTEM

# Dixon and colleagues from Loma-Linda University, hydrogen has marked therapeutic potential to help with the top 8 fatality causing diseases listed by the CDC

Dixon, B.J., J. Tang, and J.H. Zhang, The evolution of molecular hydrogen: a noteworthy potential therapy with clinical significance. Med Gas Res, 2013. 3(1): p. 10.

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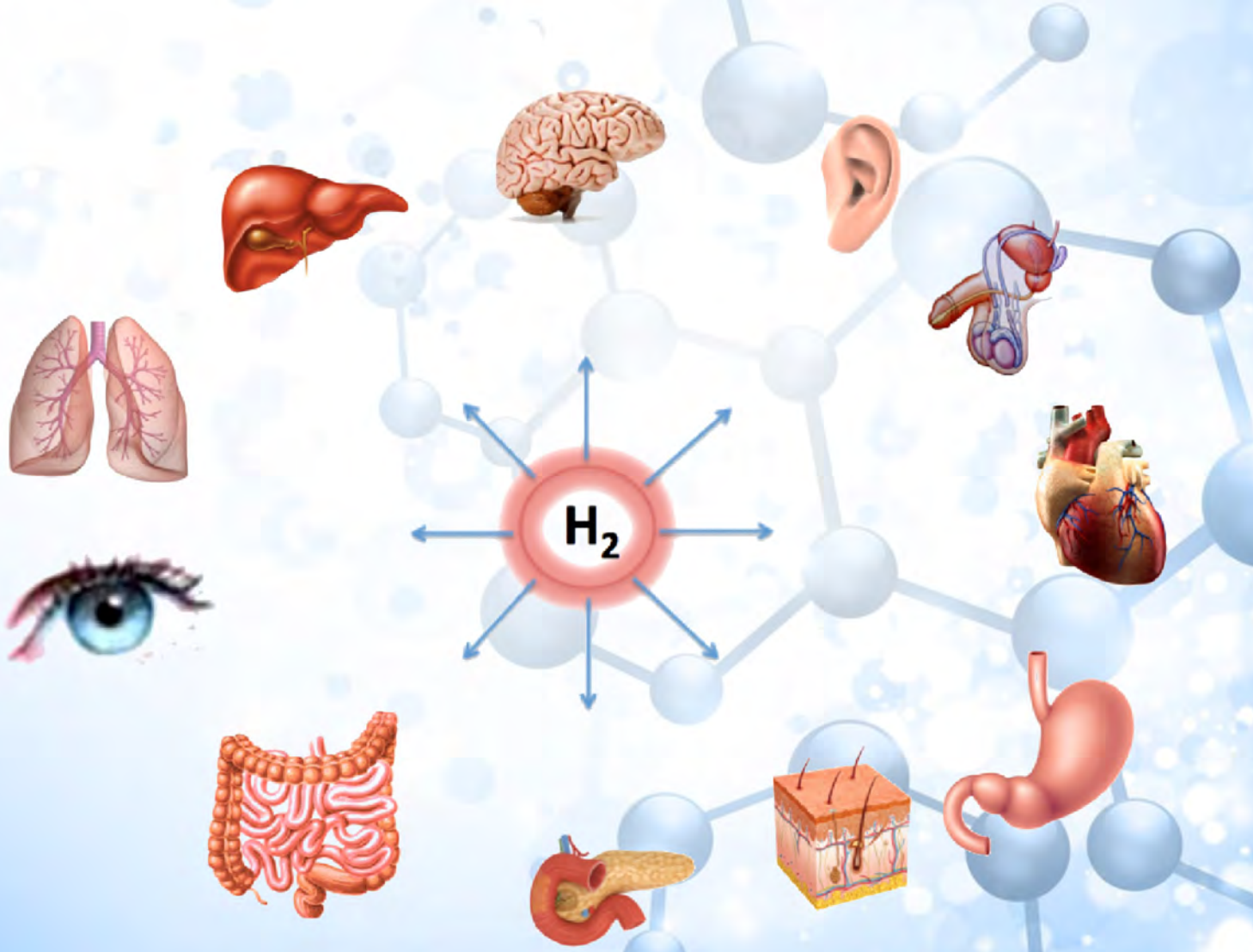
# HOW does Hydrogen exert these biological effects?



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# Hydrogen neutralizes toxic radicals. It is a Therapeutic Antioxidant

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Advanced

Abstract Send to:

Nat Med. 2007 Jun;13(6):688-94. Epub 2007 May 7.

## Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals.

Ohsawa I[1], Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, Katsura K, Katayama Y, Asoh S, Ohta S.

Author information

**Abstract**

Acute oxidative stress induced by ischemia-reperfusion or inflammation causes serious damage to tissues, and persistent oxidative stress is accepted as one of the causes of many common diseases including cancer. We show here that hydrogen (H(2)) has potential as an antioxidant in preventive and therapeutic applications. We induced acute oxidative stress in cultured cells by three independent methods. H(2) selectively reduced the hydroxyl radical, the most cytotoxic of reactive oxygen species (ROS), and effectively protected cells; however, H(2) did not react with other ROS, which possess physiological roles. We used an acute rat model in which oxidative stress damage was induced in the brain by focal ischemia and reperfusion. The inhalation of H(2) gas markedly suppressed brain injury by buffering the effects of oxidative stress. Thus H(2) can be used as an effective antioxidant therapy; owing to its ability to rapidly diffuse across membranes, it can reach and react with cytotoxic ROS and thus protect against oxidative damage.

**Comment in**

The hydrogen highway to reperfusion therapy. [Nat Med. 2007]

PMID: 17486089 [PubMed - indexed for MEDLINE]

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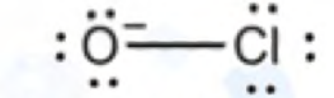
# What are free radicals Reactive oxygen species?



Hypochlorite

$OCl^-$

Superoxide anion

$\cdot O_2^-$

Peroxide

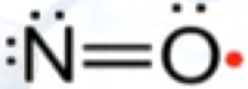
$\cdot O_2^{-2}$

Hydrogen Peroxide

$H_2O_2$

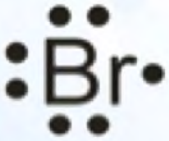
Hydroxyl radical

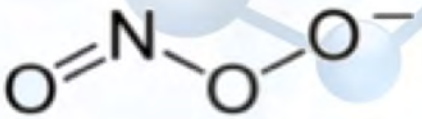
$\cdot OH$



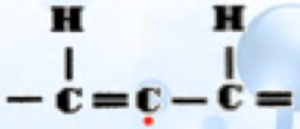
Nitric Oxide

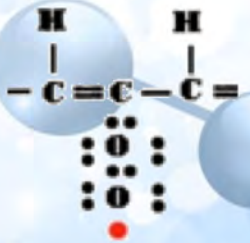
NO·











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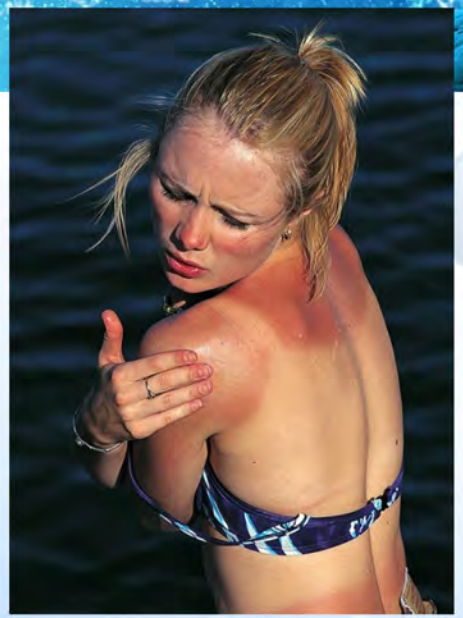
# Free radicals

- Linked to every disease
- Damaged DNA,RNA, cell membranes, protein
- Cell death and aging
- Cancer, diabeties, etc.
- Damaged cells
- Inflamation



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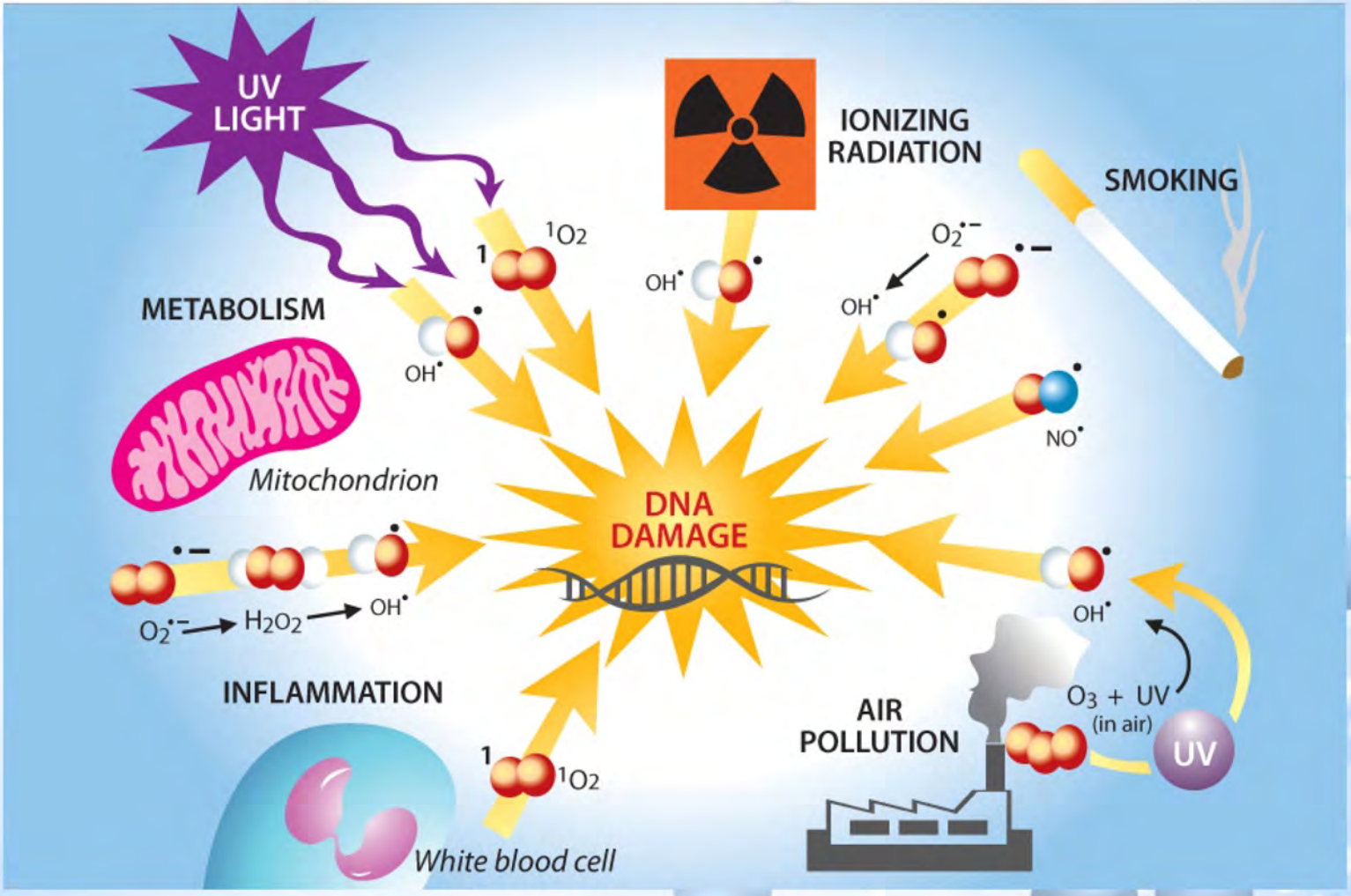
# How are they generated?




H.Barry." *Nutr. rev.* 70.5 (2012): 257

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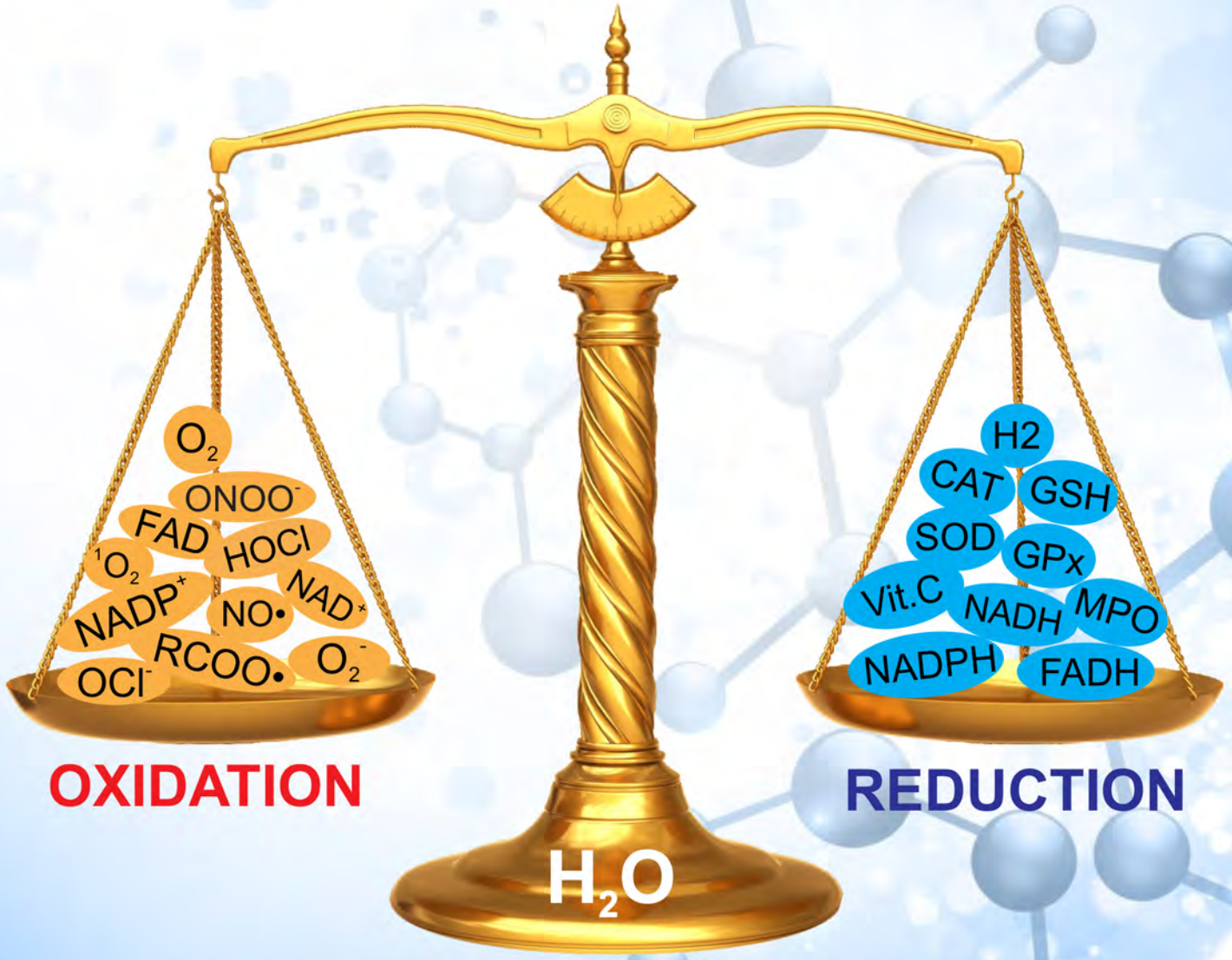
# Life is balanced between Oxidation and Reduction




**OXIDATION**

**REDUCTION**

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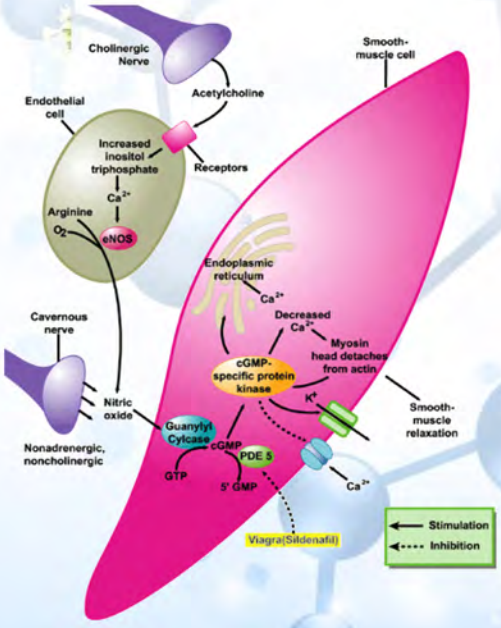
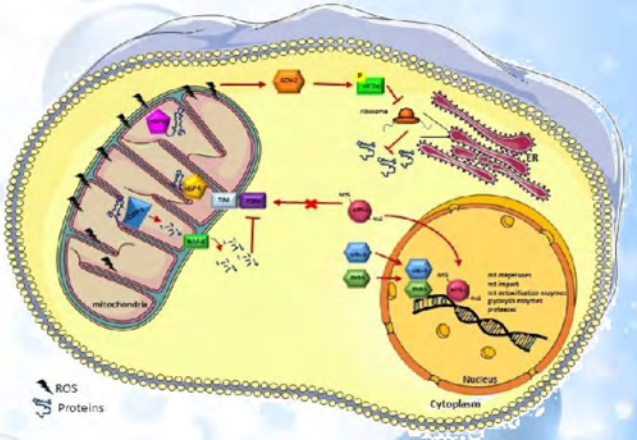
# Benefits of ROS

- Signal transduction
- Immunity
- Vasodilation
- Activation of protective transcription factors



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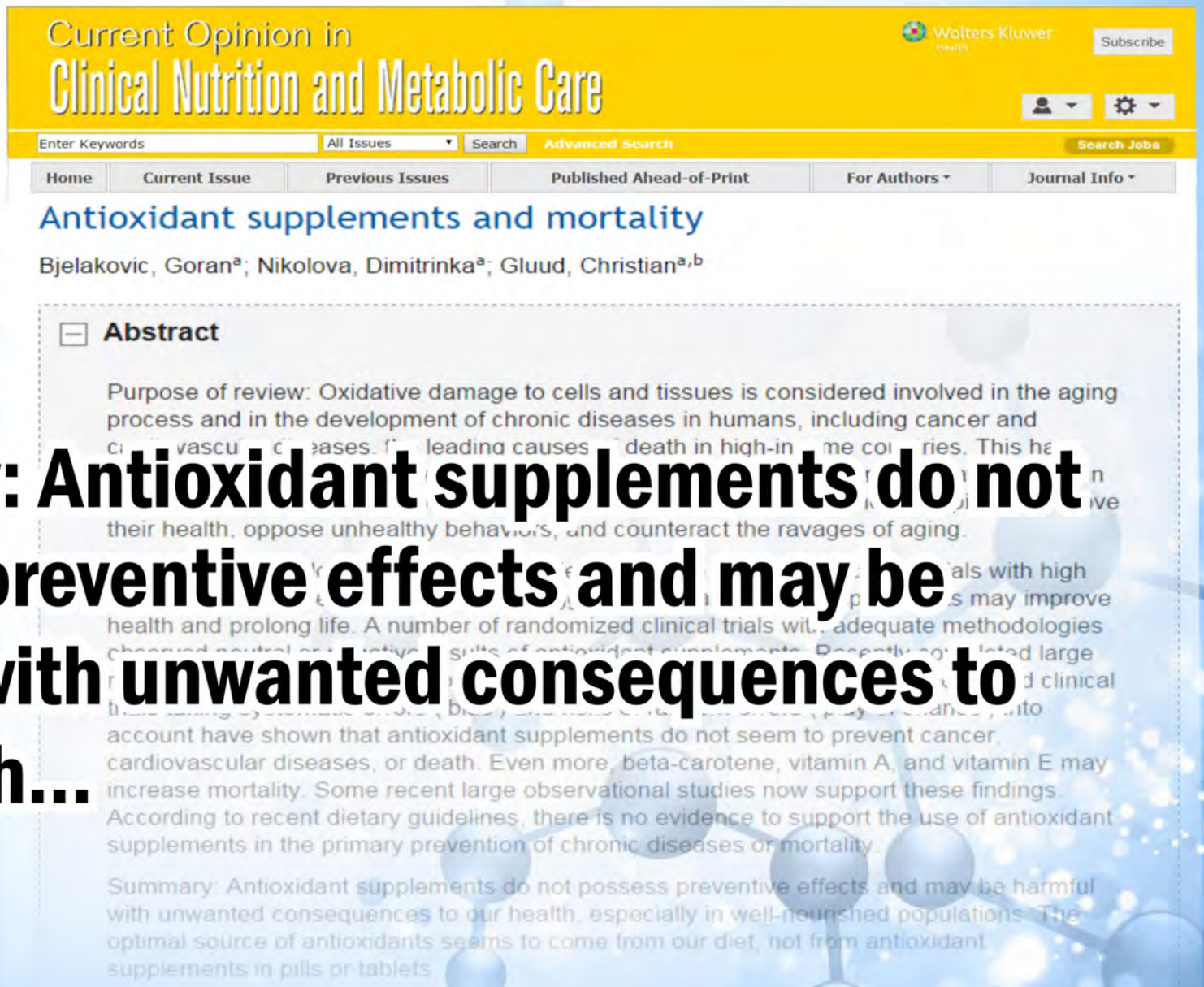
# Perhaps this is way clinical trials with supplemental antioxidants often have deleterious effects



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## Antioxidant supplements and mortality

Bjelakovic, Goran[a]; Nikolova, Dimitrinka[a]; Gluud, Christian[a,b]

**Abstract**

Purpose of review: Oxidative damage to cells and tissues is considered involved in the aging process and in the development of chronic diseases in humans, including cancer and cardiovascular diseases, the leading causes of death in high-income countries. This ha

their health, oppose unhealthy behaviors, and counteract the ravages of aging.

als with high
s may improve
health and prolong life. A number of randomized clinical trials wit adequate methodologies
d large
d clinical
into
account have shown that antioxidant supplements do not seem to prevent cancer, cardiovascular diseases, or death. Even more, beta-carotene, vitamin A, and vitamin E may increase mortality. Some recent large observational studies now support these findings. According to recent dietary guidelines, there is no evidence to support the use of antioxidant supplements in the primary prevention of chronic diseases or mortality.

Summary: Antioxidant supplements do not possess preventive effects and may be harmful with unwanted consequences to our health, especially in well-nourished populations. The optimal source of antioxidants seems to come from our diet, not from antioxidant supplements in pills or tablets.

**Summary: Antioxidant supplements do not possess preventive effects and may be harmful with unwanted consequences to our health…**

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## What makes $H_2$ any different?

**It is a selective antioxidant, only scavenges OH radicals**

$$H_2 + 2\,^{\bullet}OH \rightarrow 2H_2O$$

$$H_2 + ONOO \rightarrow NO_2 + H_2O$$

nature medicine

ARTICLES

# Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals

Ikuroh Ohsawa[1], Masahiro Ishikawa[1], Kumiko Takahashi[1], Megumi Watanabe[1,2], Kiyomi Nishimaki[1], Kumi Yamagata[1], Ken-ichiro Katsura[2], Yasuo Katayama[2], Sadamitsu Asoh[1] & Shigeo Ohta[1]

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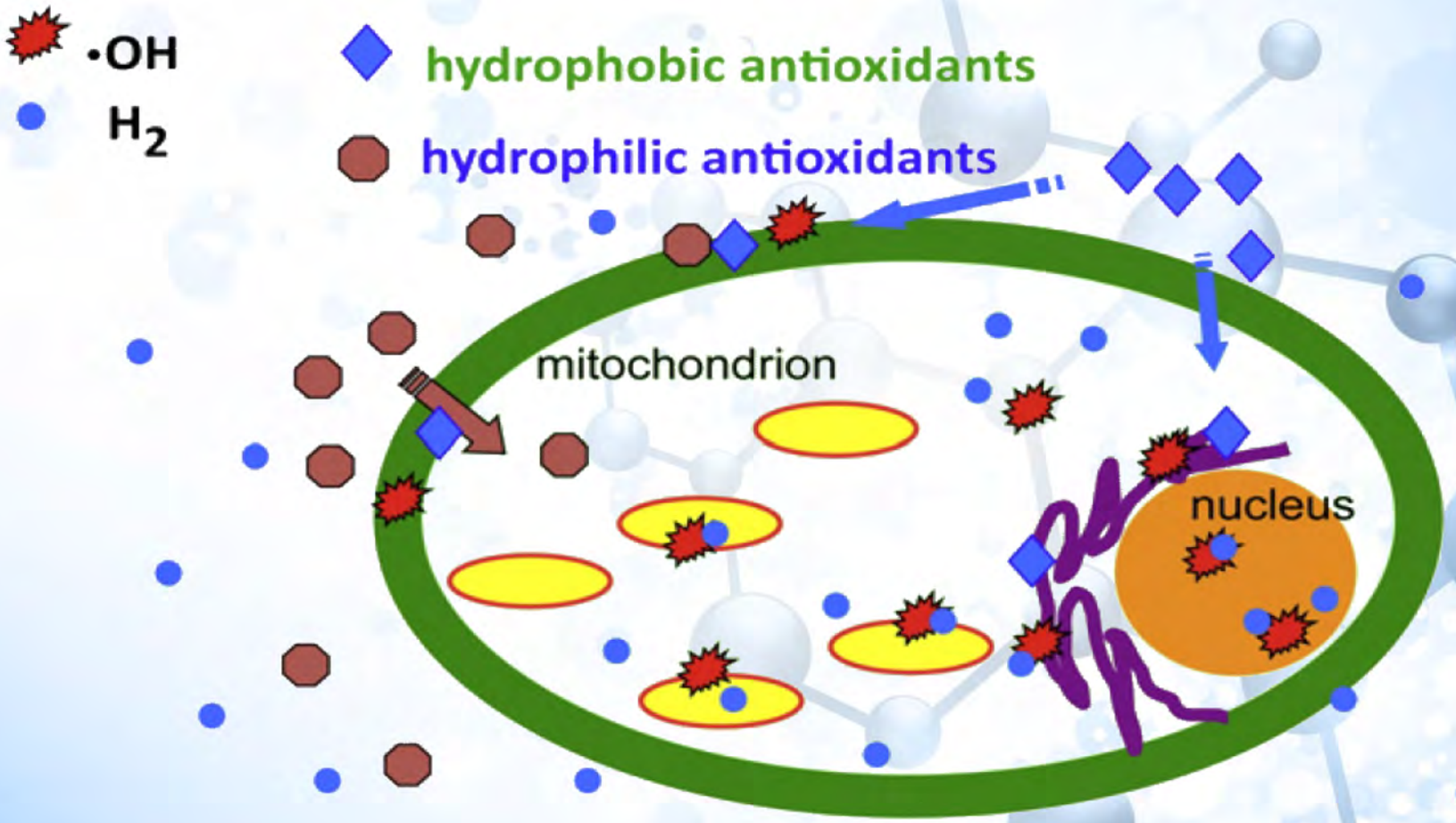
- **Rapid diffusion**
- **Small**
- **Hydrophobic**
- **No byproduct (water)**




O. Shigeo. Biochimica et Biophysica Acta (BBA)-General Subjects 1820.5 (2012): 586

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# Rate constants are slow and the concentration of $H_2$ is comparatively low

| Reaction | Rate constant *k* ($M^{-1} * S^{-1}$) |
|---|---|
| $^{\bullet}OH + {}^{\bullet}OH \rightarrow H_2O_2$ | $1.1 \times 10^{10}$ |
| $^{\bullet}OH + H_2O^{+}_{2} \rightarrow H_3O^{+} + O_2$ | $1.2 \times 10^{10}$ |
| $^{\bullet}OH + Cl^{-} \rightarrow HOCl^{\bullet}$ | $4.3 \times 10^{9}$ |
| $^{\bullet}OH + {}^{\bullet}H \rightarrow H_2O$ | $7.0 \times 10^{9}$ |
| $^{\bullet}OH + H_2 \rightarrow H_2O + {}^{\bullet}H$ | $4.2 \times 10^{7}$ |

Buxton, G.V., et al. J Phys. Chem. Ref Data, 1988. 17: p. 513-886.
Liao, C.H., et al. Chemosphere, 2001. 44(5): p. 1193-200.

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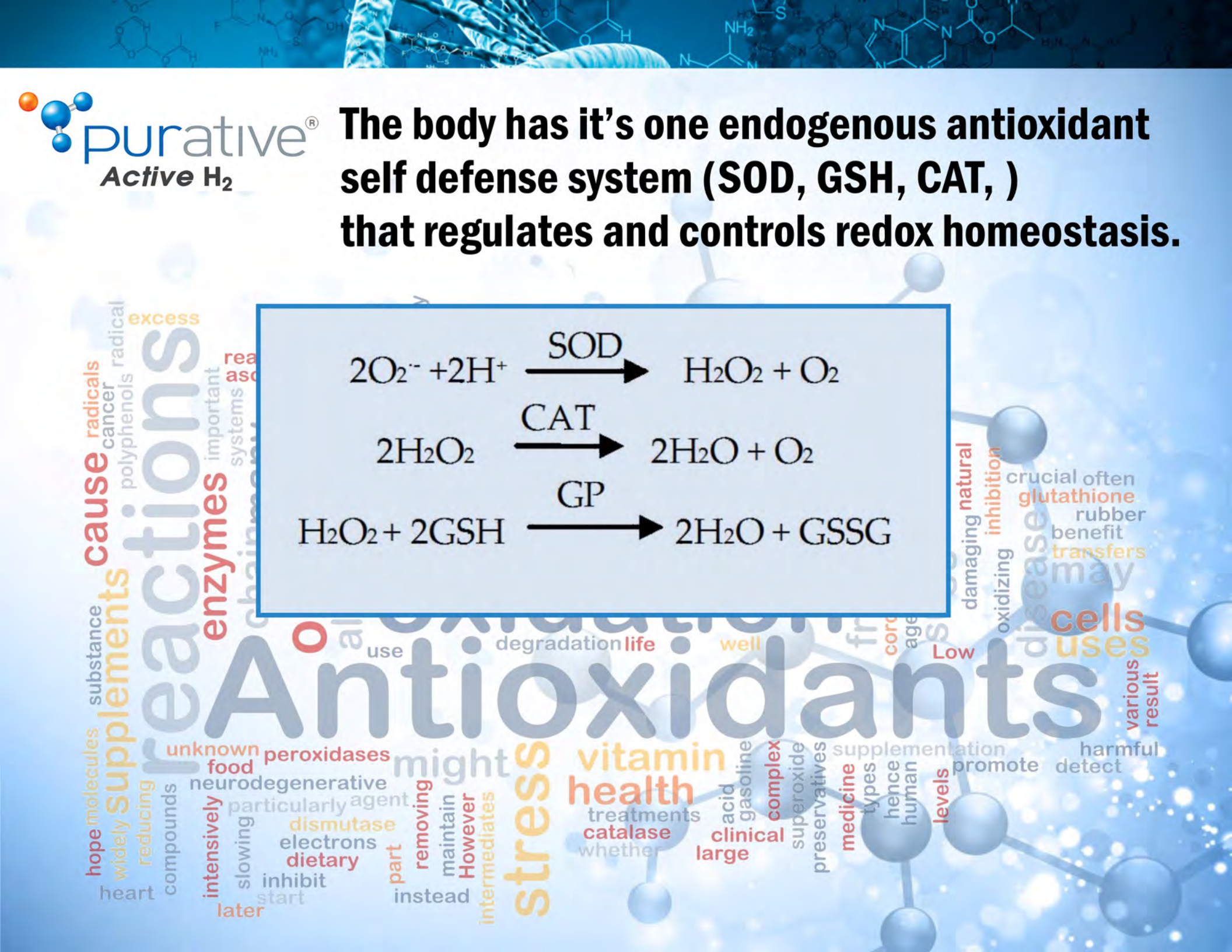
# The body has it's one endogenous antioxidant self defense system (SOD, GSH, CAT, ) that regulates and controls redox homeostasis.

$$2O_2^{\cdot-} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$$

$$2H_2O_2 \xrightarrow{CAT} 2H_2O + O_2$$

$$H_2O_2 + 2GSH \xrightarrow{GP} 2H_2O + GSSG$$



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# Aging, certain diseases, toxins, etc. can lower our body's antioxidant self-defense system.

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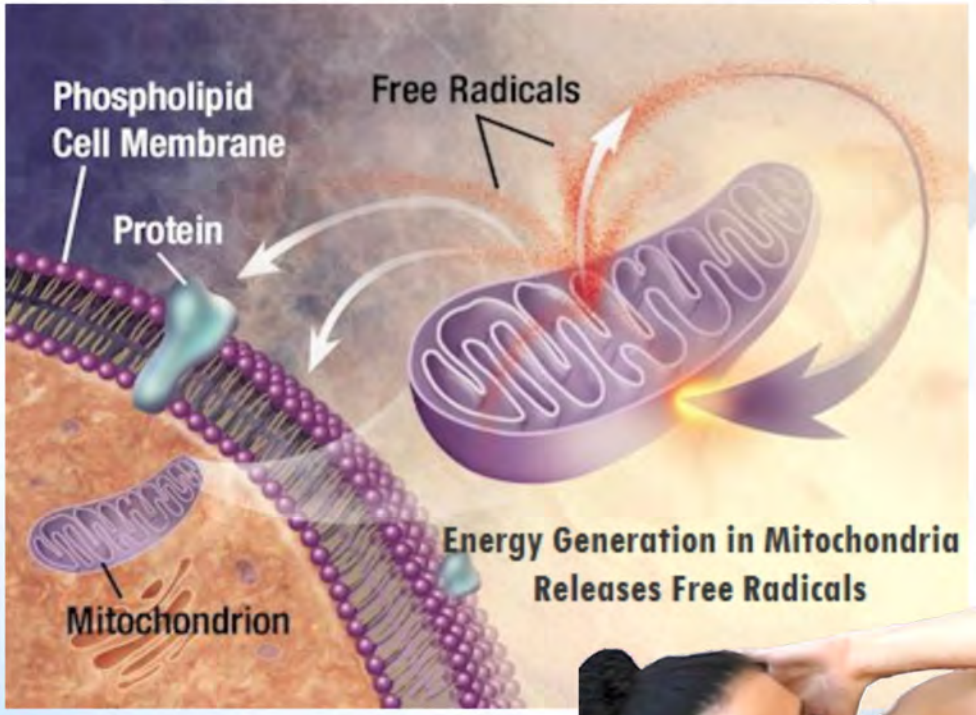
# Exercise creates many free radicals, but those ROS are important for training adaptations including increase antioxidant protection.




H.Barry." *Nutr. rev.* 70.5 (2012): 257

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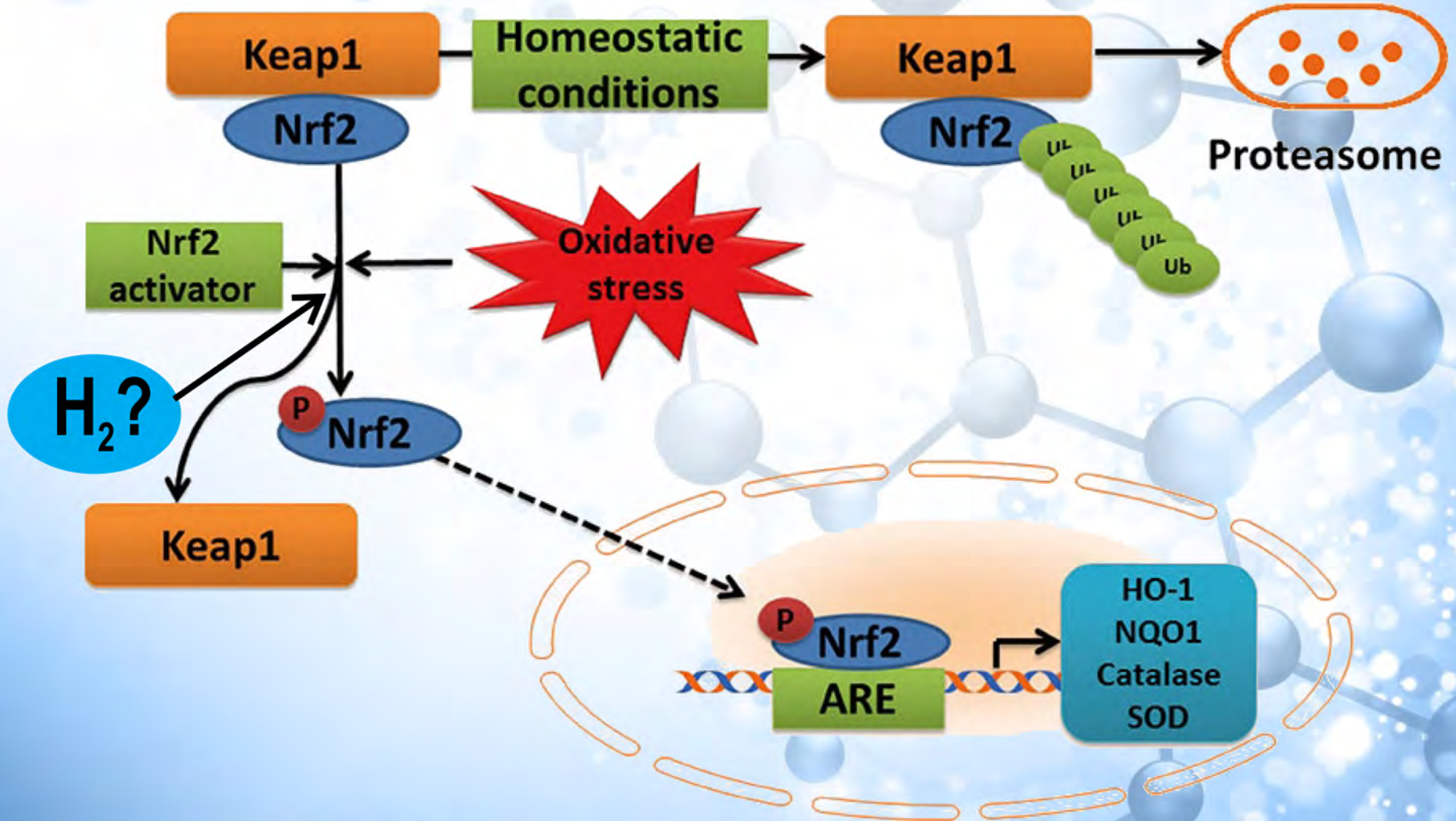
# Hydrogen gas can activate Nrf2 pathway leading to increased production of these antioxidants



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# Hydrogen reduces excessive ROS by Direct OH scavenging


Ohsawa, Ikuroh, et al. "Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals." Nature medicine 13.6 (2007): 688-694.

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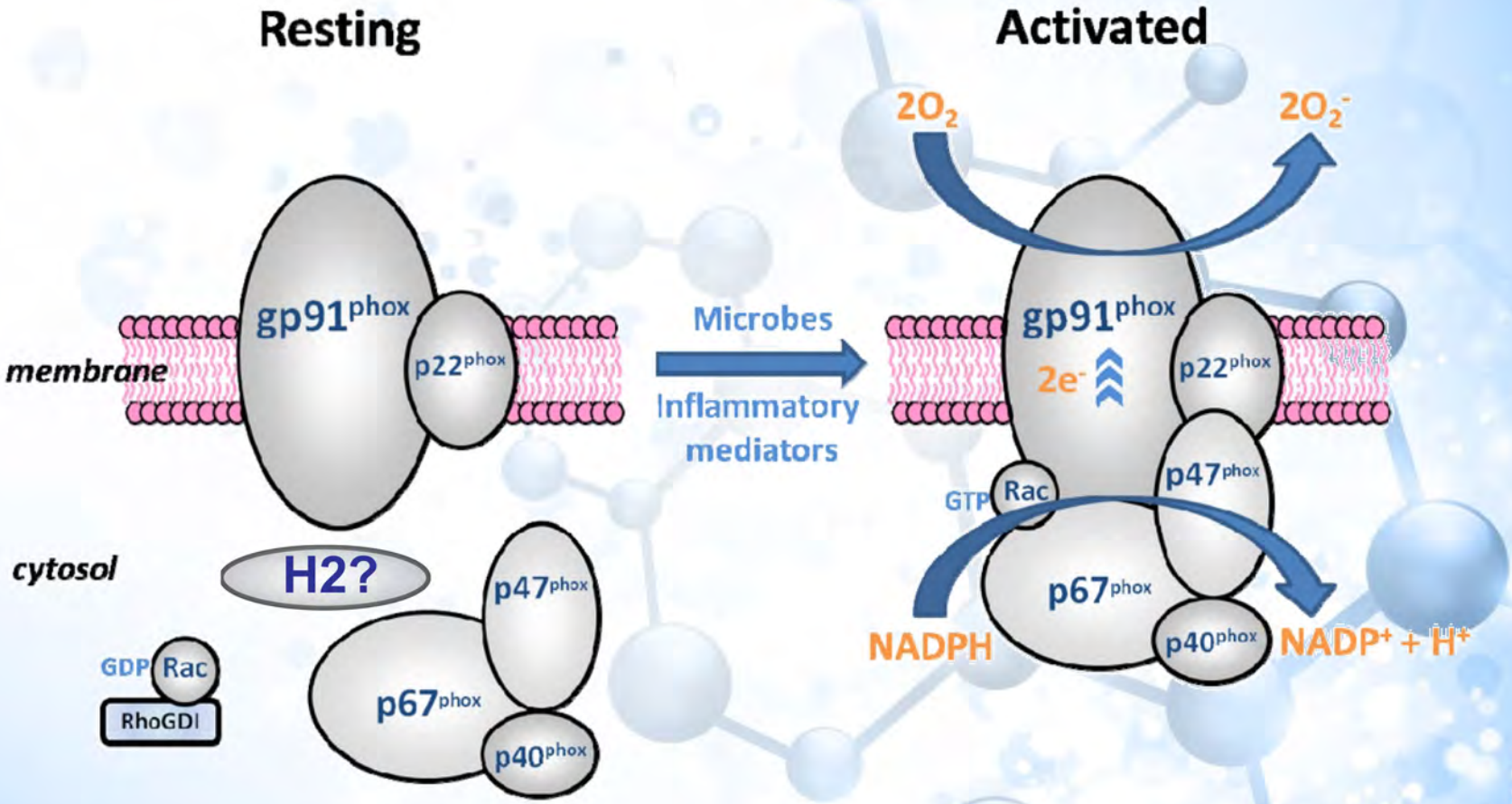
# Prevent ROS formation by cell modulation




Sato, Yasunori, et al. "Hydrogen-rich pure water prevents superoxide formation in brain slices of vitamin C-depleted SMP30/GNL knockout mice." Biochemical and biophysical research communications 375.3 (2008): 346-350.

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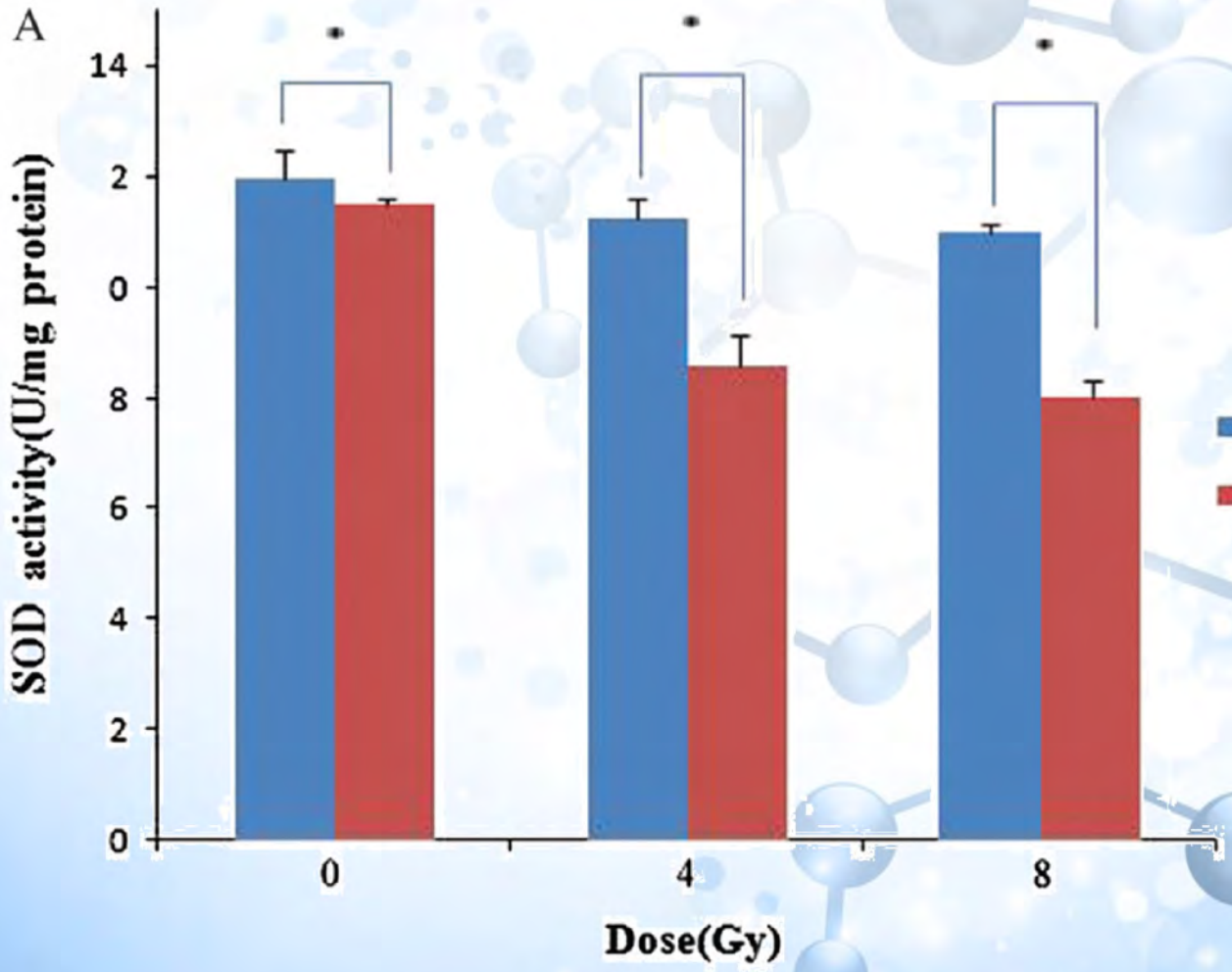
# Upregulates body's own antixidants





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# Hydrogen can clearly help reduce oxidative stress

| Markers of oxidative stress | | Markers of antioxidant status | |
|---|---|---|---|
| MDA | ↓ | Superoxide Dismutase (SOD) | ↑ |
| TBAR | ↓ | Glutathione (GSH) | ↑ |
| 8-OHdG | ↓ | Catalase (Cat) | ↑ |
| HNE | ↓ | Glutathione peroxidase(GPx) | ↑ |
| Protein carbonyl | ↓ | Glutathione S-transferase (GST) | ↑ |
| dROM | ↓ | Glutathione reductase | ↑ |
| 13-HODE | ↓ | Total Antioxidant Status (TAC) | ↑ |

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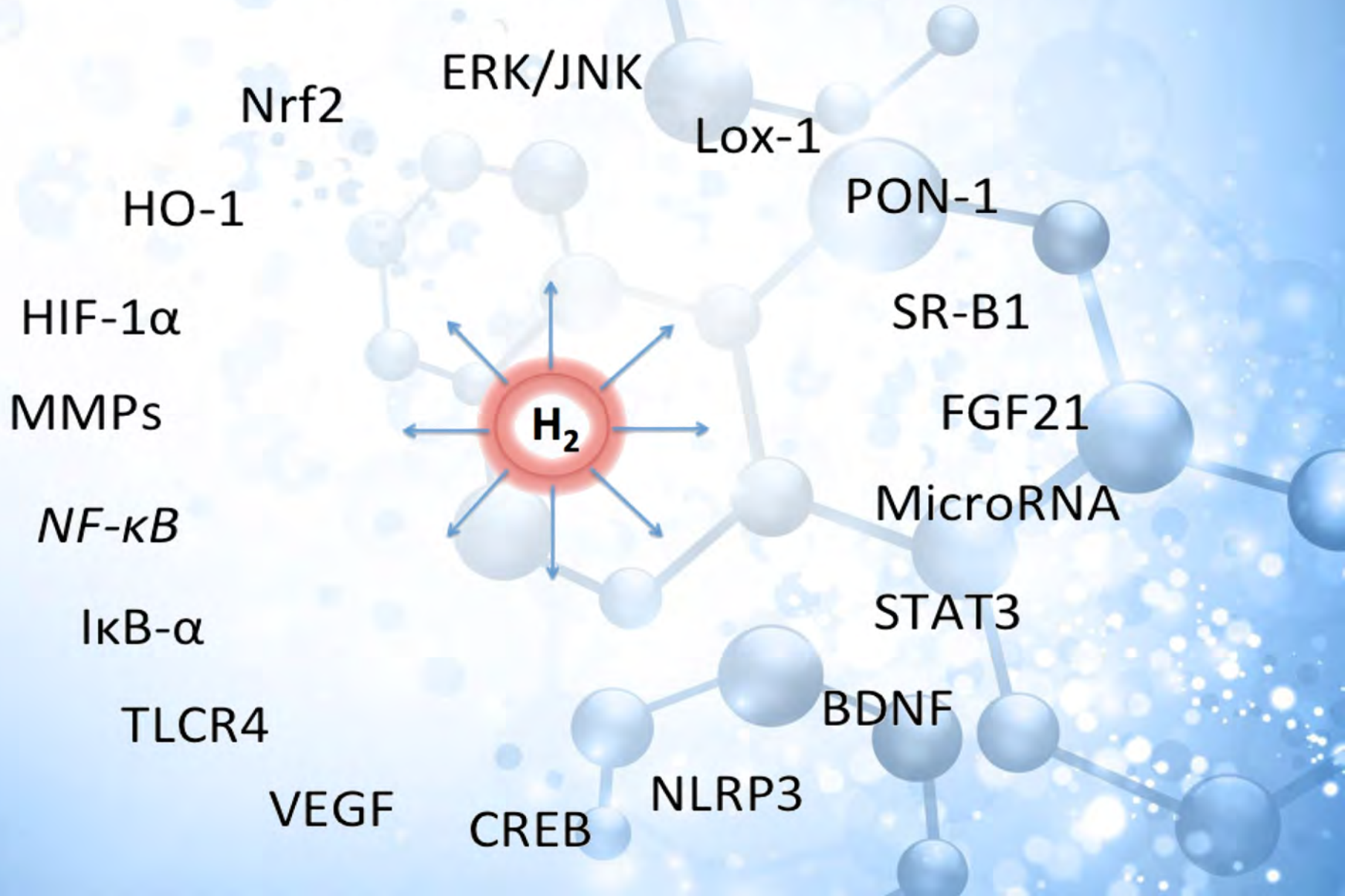
# Perhaps it acts as a signaling molecule?

## Under the right conditions hydrogen can alter the levels/activities of over 200 biomolecules



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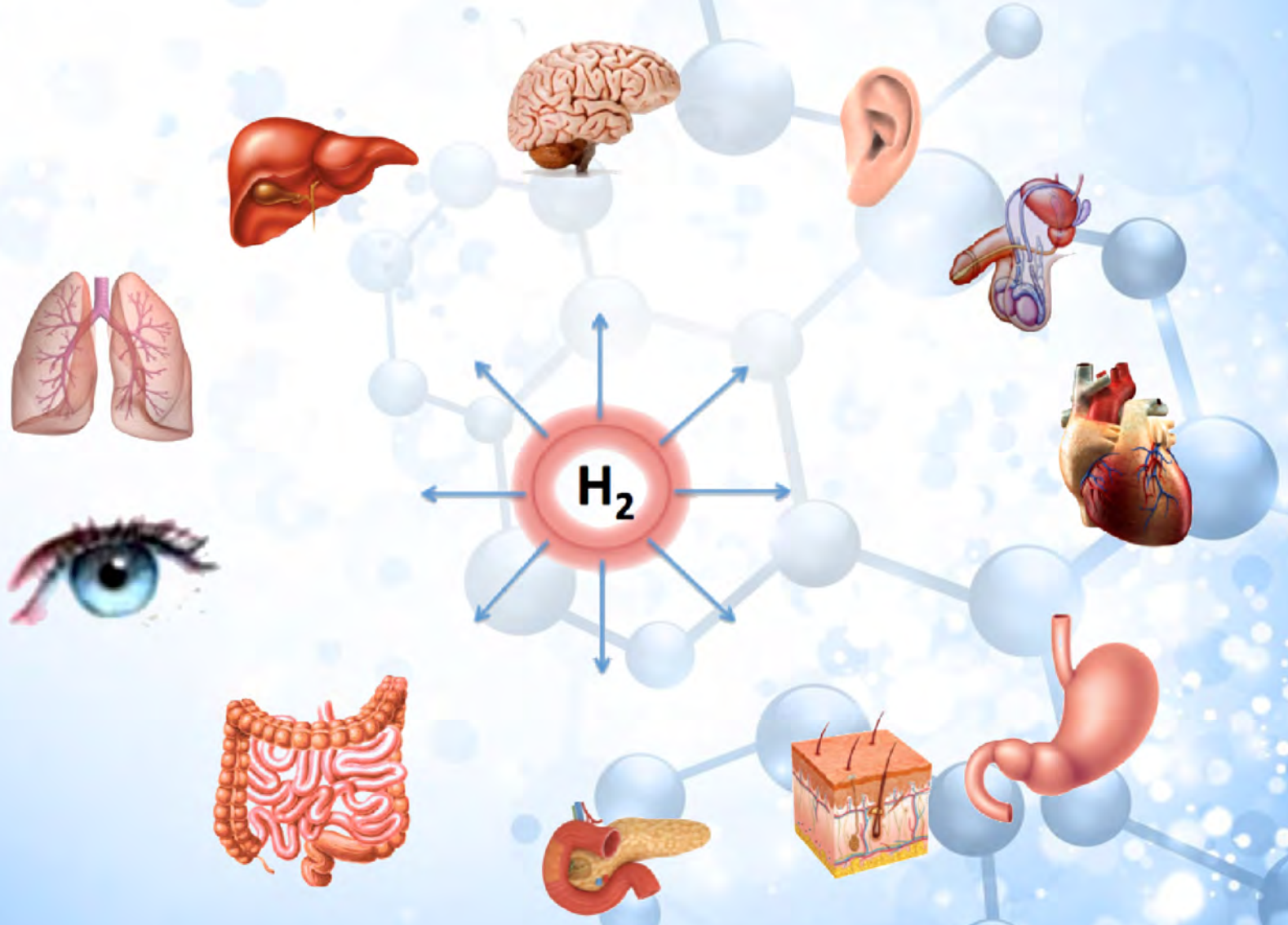
# Does the antioxidant explanation fully answer why it has so many benefits?



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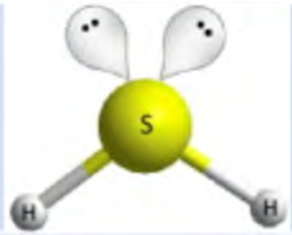
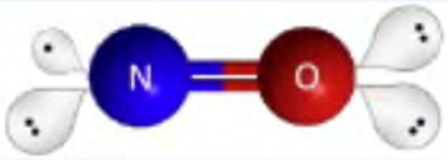
# Compared to other gaseous signaling molecules

| Molecule | Chemical structure | Mechanisms |
|---|---|---|
| Hydrogen Sulfide (polar) |   | • s-sulfhydration<br>• Proteins (cyst)<br>• etc. |
| Nitric oxide (polar, radical) |   | • Nitrosylation<br>• guanylyl cyclase (Fe)<br>• etc. |
| Carbon monoxide (polar) |   | • HIF-1α<br>• HO-1<br>• etc. |
| Molecular Hydrogen (nonpolar) |   | • ?<br>• ?<br>• etc. |

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# Here is what is known about "HOW" hydrogen works

| Mechanism | Data |
|---|---|
| Primary targets | Unknown |
| Binding sites | Unknown |
| Master regulators | Unknown |

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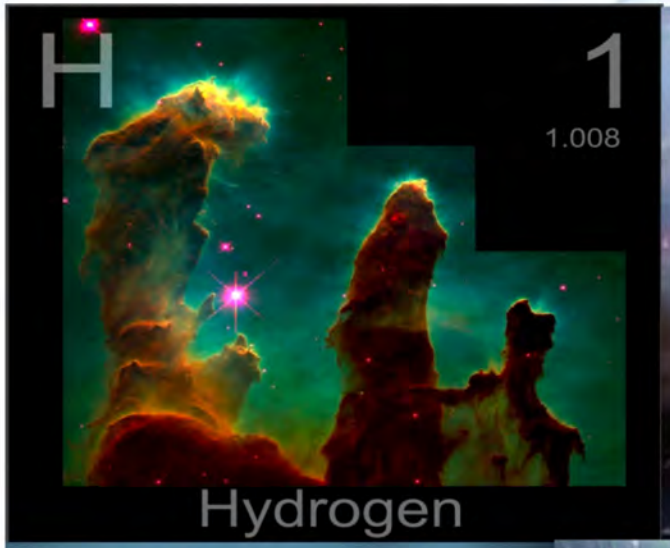
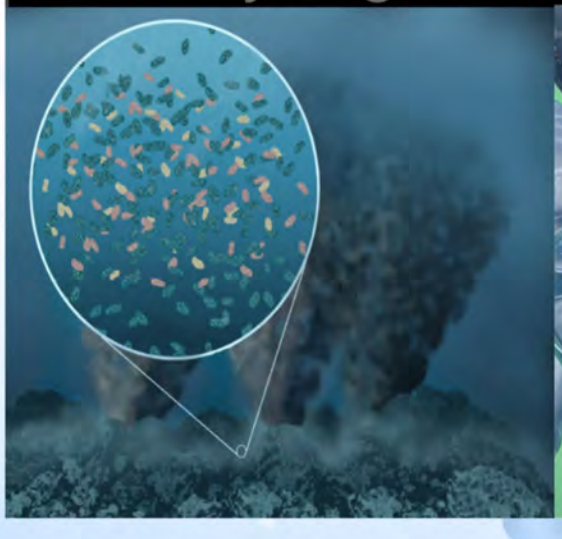
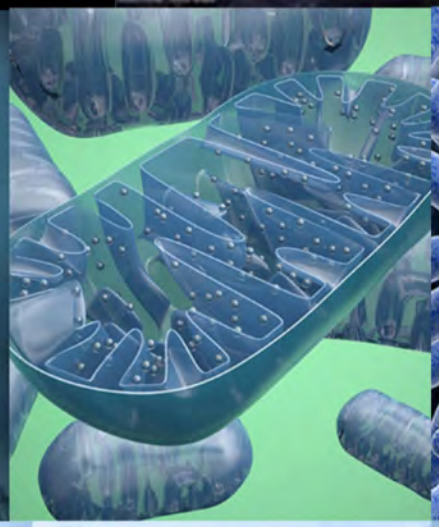
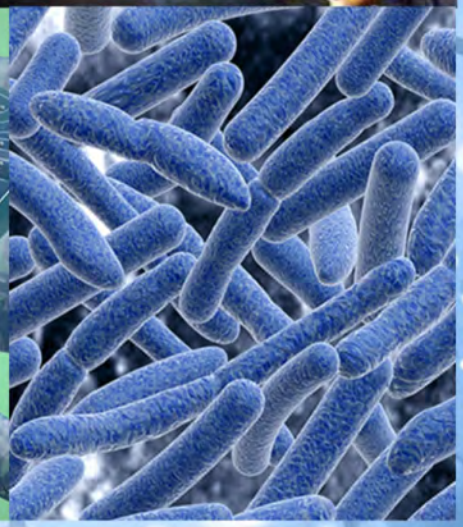
**Perhaps the reason that hydrogen exerts a biological effect is because hydrogen has been intimately involved in the origins of the Universe, the genesis of life, and the evolution of eukaryotes.**







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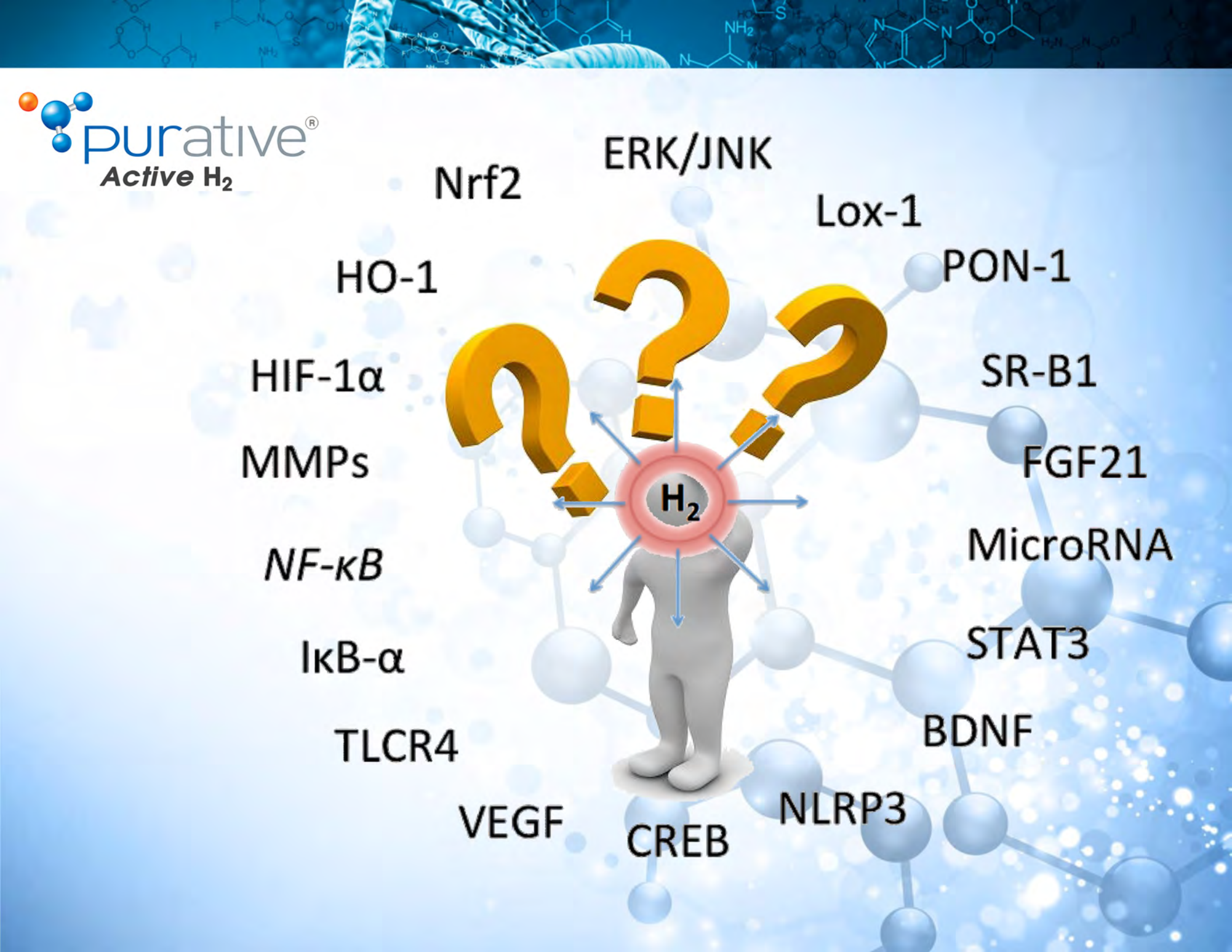

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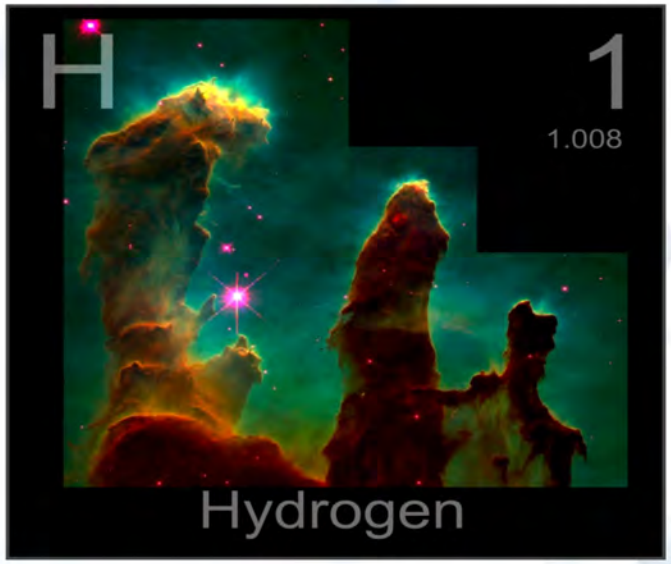
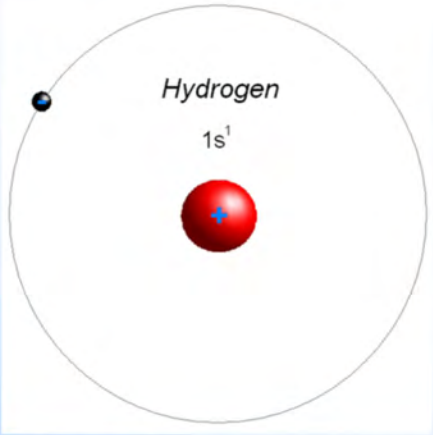
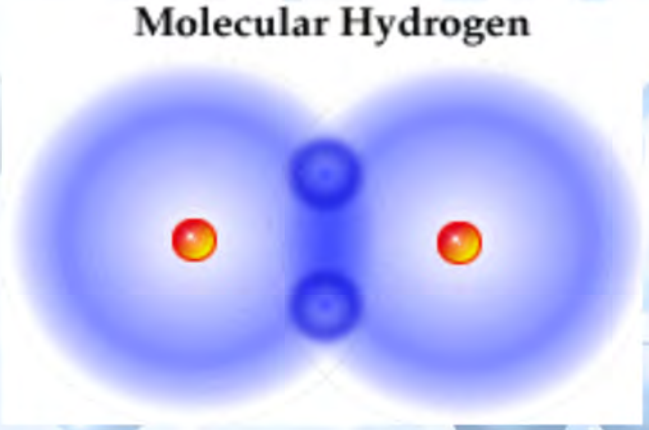
# Hydrogen was involved in the origins of the Universe




Black, J.H., Chemistry and cosmology.
Faraday Discussions, 2006. 133: p. 27-32; discussion 83-102, 449-52.

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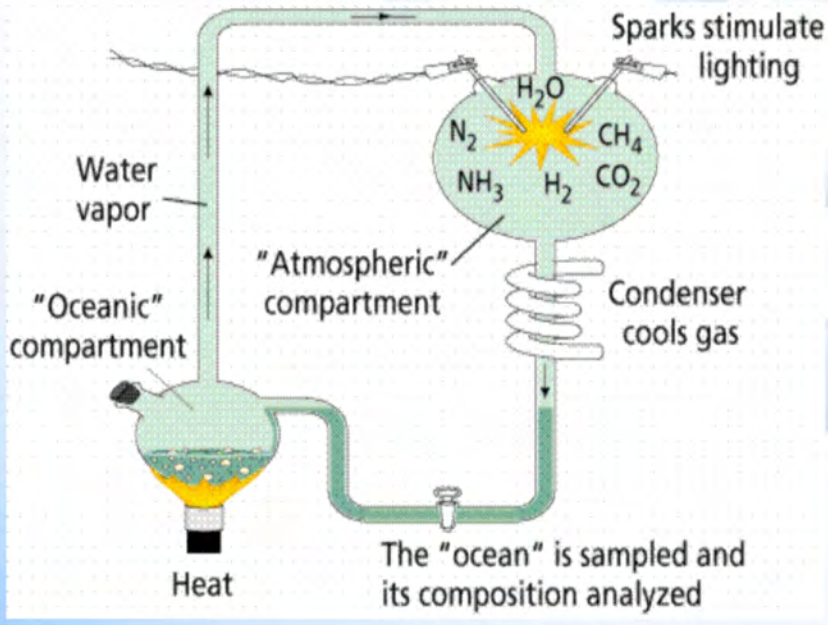
# Hydrogen was involved in the genesis of life

$$Fe^{o} + H_2S \longrightarrow FeS + H_2 + energy$$

$$FeS + H_2S \longrightarrow FeS_2 + H_2 + energy$$




Miller, Stanley L." Science 17.3046 (1953): 528-529.

Huber, C., et al. Science, 2006. 314(5799): p. 630-2.

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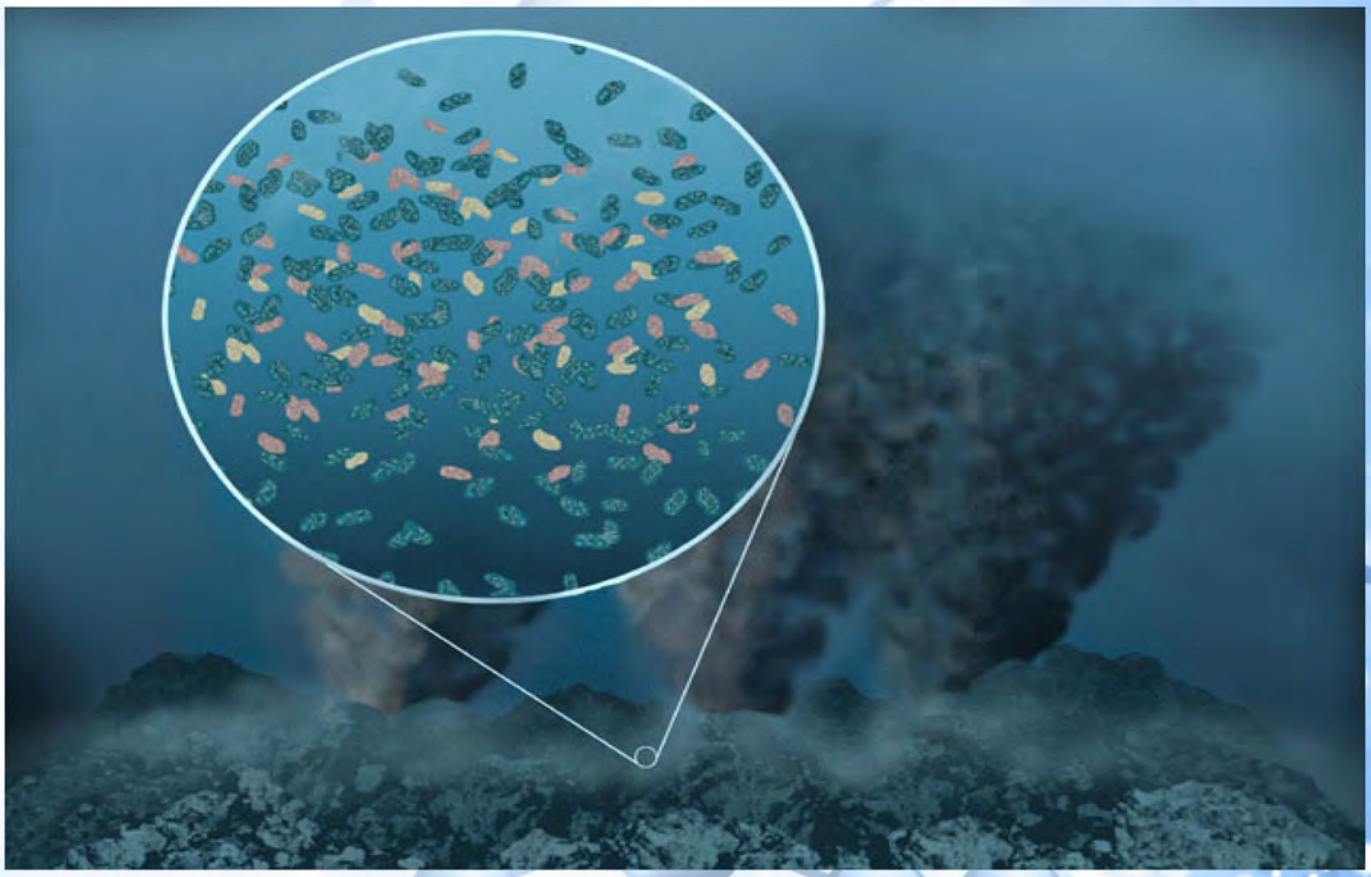
# $H_2$ from hydrothermal vents serve as an energy source to chemolithoautotrophs

**"...the last common ancestor of life also metabolized hydrogen for energy..."**



Pace, N. R. (1997). Science, 276(5313), 734-740

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# Hydrogen in natural “healing waters”

- Nordenau, Germany
- Tlacote, Mexico
- Hita Tenryosui, Japan
- Nadone, India

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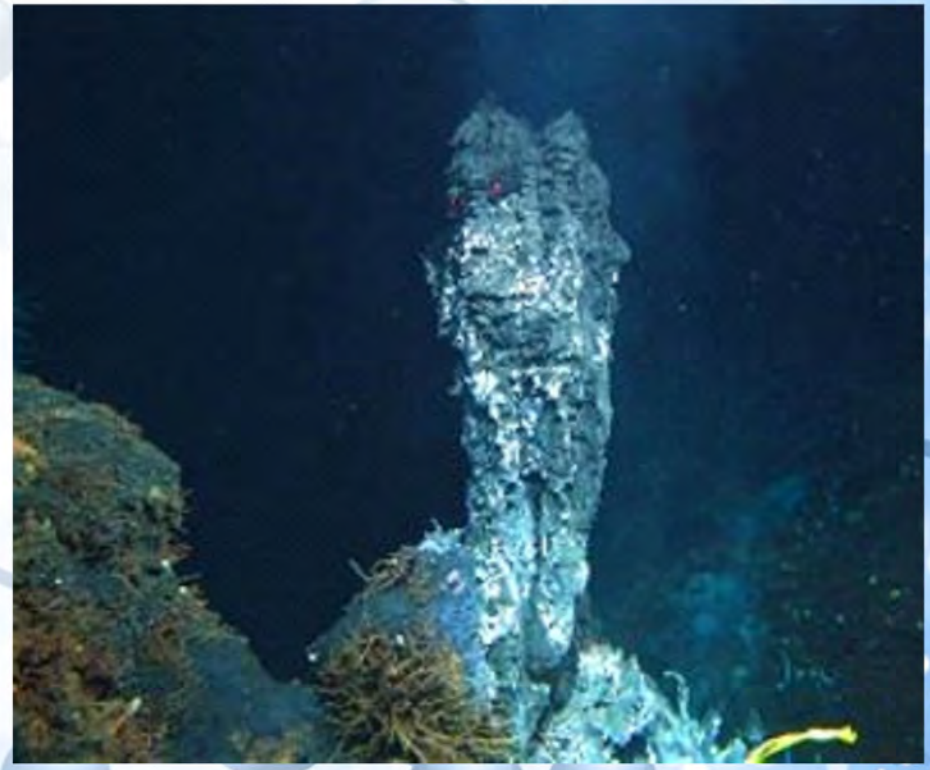
# Hydrogen gas present in certain waters

## Concentrations can range from micromolar amounts to 0.8 mM in certain locations



Barbara Sherwood Lollar, T. C. Onstott, G. Lacrampe-Couloume, C. J. Ballentine. The contribution of the Precambrian continental lithosphere to global H2 production. Nature, 2014; 516

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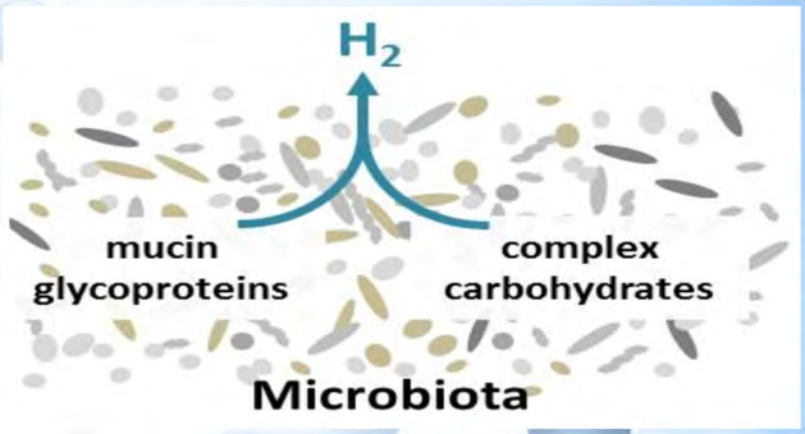
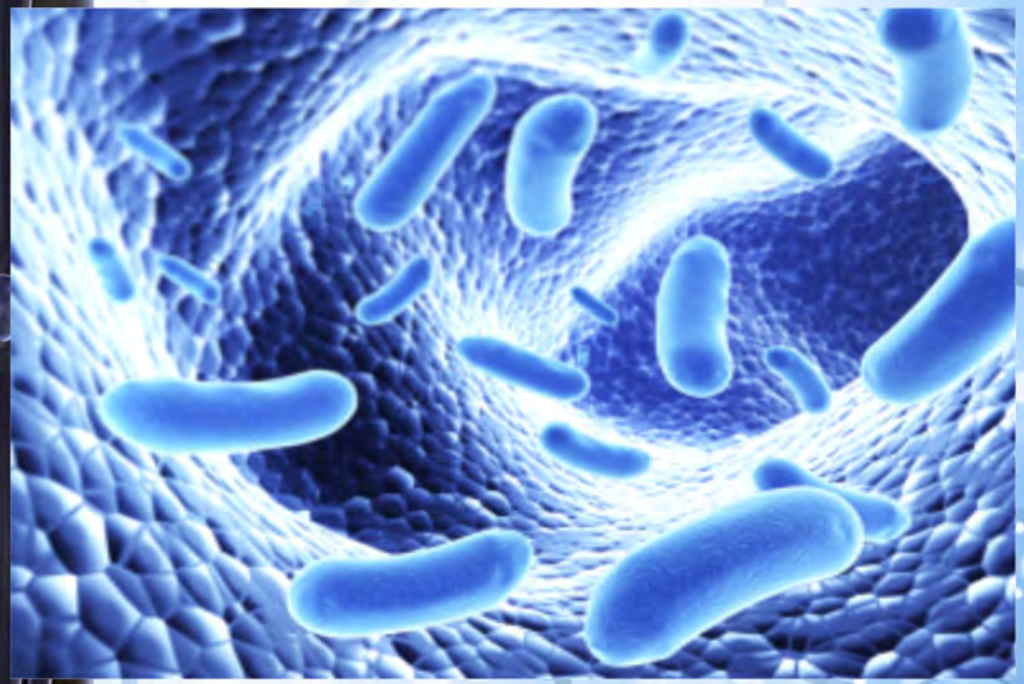
# Hydrogen from intestinal bacteria

- 10 liters of H2 per day
- 5-50 ppm breath hydrogen
- 1-5 micromolar levels in blood



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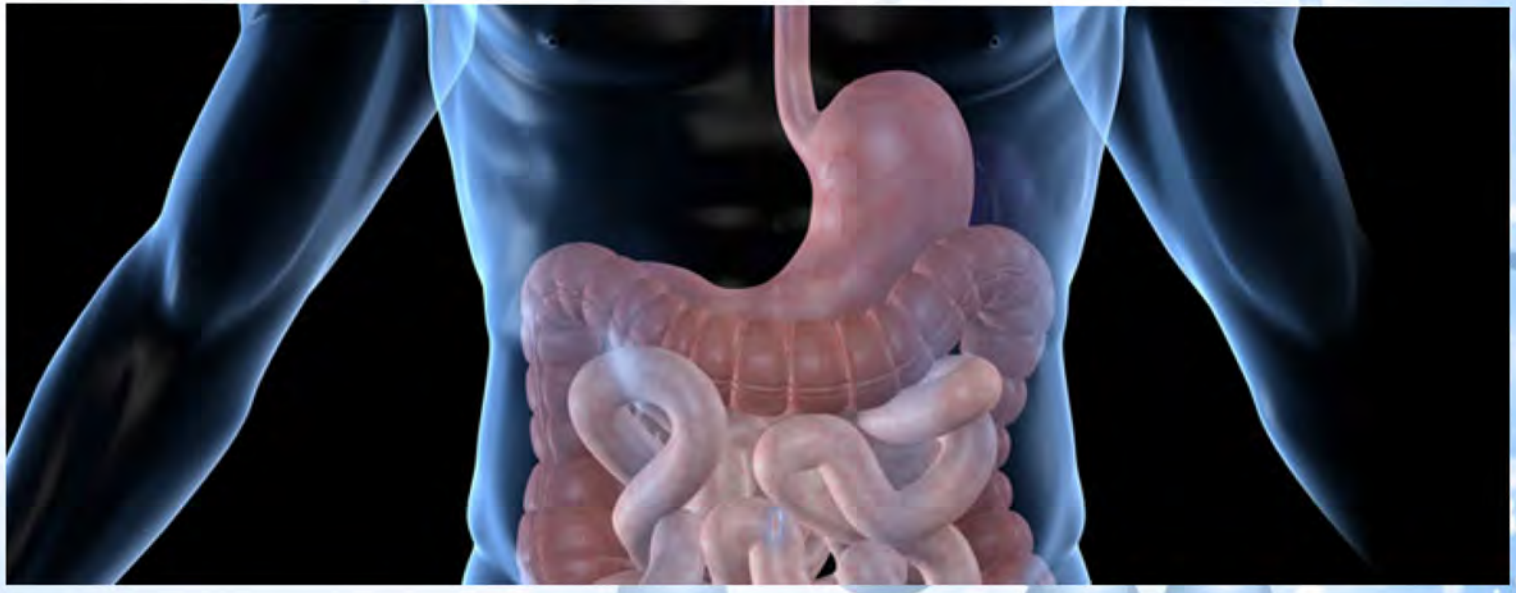
# Hydrogen gas from bacteria exerts therapeutic biological effects

**1988: hypothesized that hydrogen from bacteria could be therapeutic**

**2009: confirmed by a report from the Forsyth Institute in Boston MA and the University of Florida**



Neale, R.J. Medical Hypotheses, 1988. 27(1): p. 85-7.
Kajiya, M., et al. Biochem. Biophys. Res. Commun. 2009. 386(2): p. 316-21.

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# Resveratrol and hydrogen production?

THE JOURNAL OF PHYSICAL CHEMISTRY Letters
Letter
pubs.acs.org/JPCL


## Dissociative Electron Attachment to Resveratrol as a Likely Pathway for Generation of the $H_2$ Antioxidant Species Inside Mitochondria

Stanislav A. Pshenichnyuk*,†,‡ and Alexei S. Komolov‡

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# Methods of administration

- Hydrogen-rich saline injection
- Ingestion of hydrogen-rich water
- Taking a hydrogen water bath
- Inhalation of hydrogen gas.

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Int J Clin Exp Pathol. 2015 Mar 1;8(3):2680-9. eCollection 2015.

# Inhalation of hydrogen gas ameliorates glyoxylate-induced calcium oxalate deposition and renal oxidative stress in mice.

Peng Z[1], Chen W[1], Wang L[1], Ye Z[2], Gao S[3], Sun X[2], Guo Z[1].

Author information

## Abstract

The aim of this study is to evaluate the protective effect and underlying mechanism of hydrogen gas (H2) to glyoxylate induced renal calcium oxalate (CaOx) crystal deposition in mice. In present work, rodent renal CaOx crystal deposition model was introduced by intra-abdominal injection of glyoxylate (100 mg/kg/d) for 5 days. Two days before administration of glyoxylate, inhalation of H2 for 30 min per day was initiated and continued for 7 days. By the end of the study, the samples of 24 hours urine, serum and renal tissue were collected for biochemical and pathological assay. According to levels of urine calcium excretion, renal calcium deposition, a serum excretion of kidney injury molecule-1 (KIM-1) assay and a TUNEL assay, inhalation of H2 could successfully decrease the CaOx crystallizations and protect against renal injury. Crystal deposition in the kidneys is associated with oxidative stress, which was indicated by increased levels of renal malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG) and decreased activities of superoxide dismutase (SOD), glutathione (GSH) and catalase (CAT). These effects were reversed by a high-dose H2 pretreatment. The renal expressions of osteopontin (OPN), CD44, monocyte chemoattractant protein-1 (MCP-1) and interleukin-10 (IL-10) were markedly increased in glyoxylate-treated mice, and H2 significantly attenuated the increase of OPN, CD44 and MCP-1 but upregulated the expression of IL-10. Our findings demonstrate that inhalation of H2 reduces renal crystallization, renal oxidative injury and inflammation and it may be a candidate agent with few adverse effects for prevention of nephrolithiasis.

**KEYWORDS:** Hydrogen gas; calcium oxalate; glyoxylate; kidney injury molecule-1; oxidative stress

PMID: 26045773 [PubMed - in process] PMCID: PMC4440082 **Free PMC Article**

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Nutr Res. 2008 Mar;28(3):137-43. doi: 10.1016/j.nutres.2008.01.008.

# Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance.

Kajiyama S[1], Hasegawa G, Asano M, Hosoda H, Fukui M, Nakamura N, Kitawaki J, Imai S, Nakano K, Ohta M, Adachi T, Obayashi H, Yoshikawa T.

Author information

## Abstract

Oxidative stress is recognized widely as being associated with various disorders including diabetes, hypertension, and atherosclerosis. It is well established that hydrogen has a reducing action. We therefore investigated the effects of hydrogen-rich water intake on lipid and glucose metabolism in patients with either type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT). We performed a randomized, double-blind, placebo-controlled, crossover study in 30 patients with T2DM controlled by diet and exercise therapy and 6 patients with IGT. The patients consumed either 900 mL/d of hydrogen-rich pure water or 900 mL of placebo pure water for 8 weeks, with a 12-week washout period. Several biomarkers of oxidative stress, insulin resistance, and glucose metabolism, assessed by an oral glucose tolerance test, were evaluated at baseline and at 8 weeks. Intake of hydrogen-rich water was associated with significant decreases in the levels of modified low-density lipoprotein (LDL) cholesterol (ie, modifications that increase the net negative charge of LDL), small dense LDL, and urinary 8-isoprostanes by 15.5% ($P < .01$), 5.7% ($P < .05$), and 6.6% ($P < .05$), respectively. Hydrogen-rich water intake was also associated with a trend of decreased serum concentrations of oxidized LDL and free fatty acids, and increased plasma levels of adiponectin and extracellular-superoxide dismutase. In 4 of 6 patients with IGT, intake of hydrogen-rich water normalized the oral glucose tolerance test. In conclusion, these results suggest that supplementation with hydrogen-rich water may have a beneficial role in prevention of T2DM and insulin resistance.

PMID: 19083400 [PubMed - indexed for MEDLINE]

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J Assist Reprod Genet. 2014 Jan;31(1):109-14. doi: 10.1007/s10815-013-0102-2. Epub 2013 Nov 13.

# Long-term treatment of hydrogen-rich saline abates testicular oxidative stress induced by nicotine in mice.

Li S[1], Lu D, Zhang Y, Zhang Y.

Author information

## Abstract

**PURPOSE:** The present study was designed to test the hypothesis that long-term treatment with hydrogen-rich saline abated testicular oxidative stress induced by nicotine in mice.

**METHODS:** The effects of hydrogen-rich saline (6 ml/kg, i.p.), vitamin C (60 mg/kg, i.p.) and vitamin E (100 mg/kg, i.p.) on reproductive system and testicular oxidative levels in nicotine-treated (4.5 mg/kg, s.b.) mice were investigated.

**RESULTS:** It was found that vitamin C and vitamin E attenuated serum oxidative level, but did not lower testicular oxidative levels in mice subjected to chronic nicotine treatment, and did not improve the male reproductive damage and apoptosis induced by nicotine. Different from normal antioxidants, vitamin C and vitamin E, hydrogen-rich saline abated oxidative stress in testis, and protected against nicotine-induced male reproductive damages.

**CONCLUSION:** Our results first demonstrated that long-term treatment with hydrogen-rich saline attenuated testicular oxidative level and improved male reproductive function in nicotine-treated mice.

PMID: 24221909 [PubMed - indexed for MEDLINE] PMCID: PMC3909133 **Free PMC Article**

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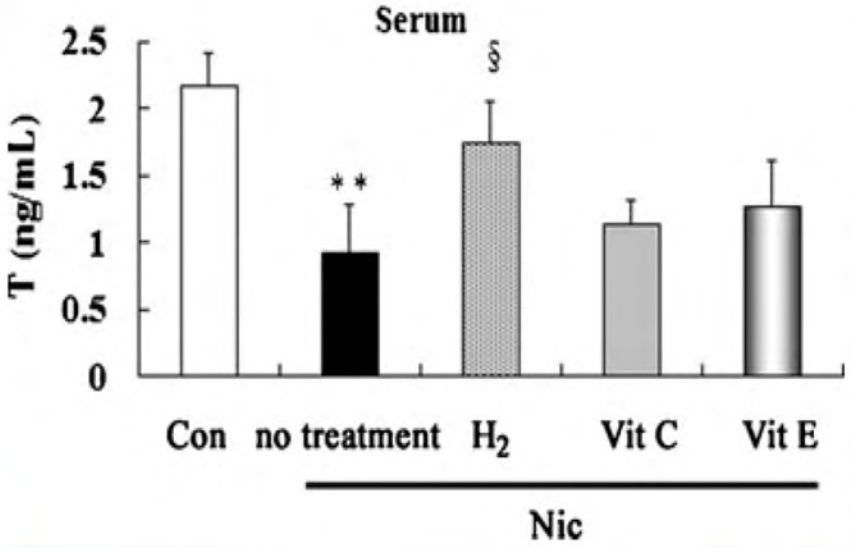


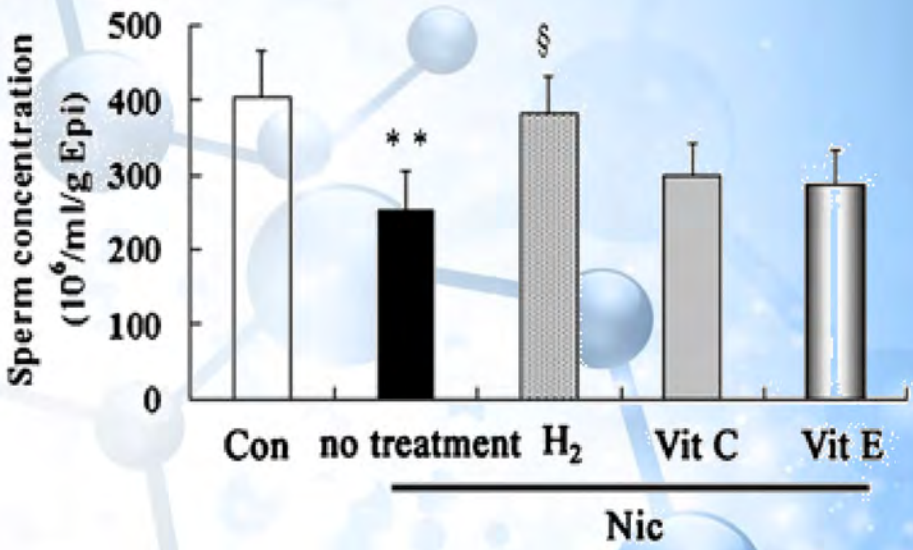


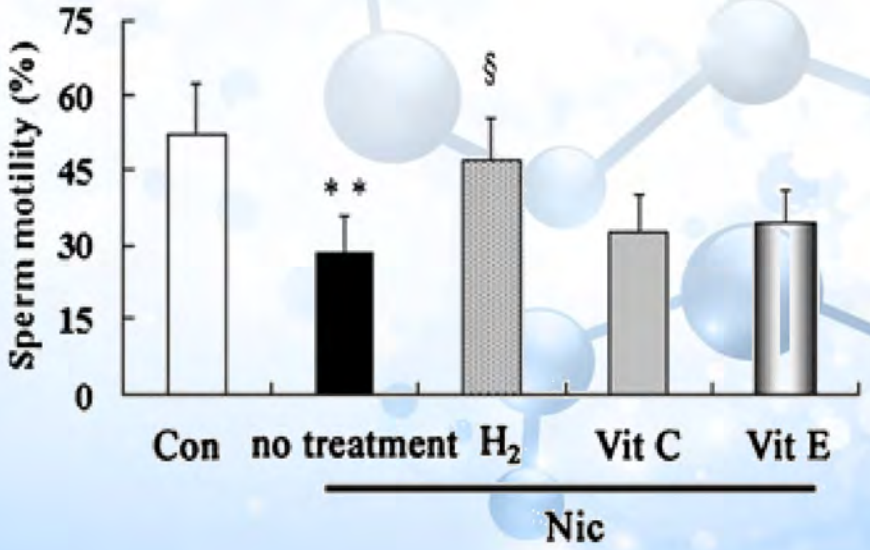

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Arch Gynecol Obstet. 2015 Aug;292(2):337-42. doi: 10.1007/s00404-015-3647-8. Epub 2015 Feb 14.

## Effects of vitamin C, vitamin E, and molecular hydrogen on the placental function in trophoblast cells.

Guan Z[1], Li HF, Guo LL, Yang X.

Author information

### Abstract

**AIM:** This study aimed to investigate the effects of three different antioxidants, namely vitamin C, vitamin E, and molecular hydrogen, on cytotrophoblasts in vitro.

**METHODS:** Two trophoblast cell lines, JAR and JEG-3, were exposed to different concentrations of vitamin C (0, 25, 50, 100, 500, 1,000, 5,000 μmol/L), vitamin E (0, 25, 50, 100, 500, 1,000, 5,000 μmol/L), and molecular hydrogen (0, 25, 50, 100, 500 μmol/L) for 48 h. The cell viability was detected using the MTS assay. The secretion of human chorionic gonadotropin (hCG) and the tumor necrosis factor-α (TNF-α) were assessed and the expression of TNF-α mRNA was observed by real-time RT-PCR.

**RESULTS:** Cell viability was significantly suppressed by 500 μmol/L vitamins C and E ($P < 0.05$), but not by 500 μmol/L molecular hydrogen ($P > 0.05$). The expression of TNF-α was increased by 100 μmol/L vitamin C and 50 μmol/L vitamins E, separately or combined ($P < 0.05$), but not by molecular hydrogen (0-500 μmol/L), as validated by real-time RT-PCR. But the secretion of hCG was both inhibited by 50-500 μmol/L molecular hydrogen and high levels of vitamin C and E, separately or combined.

**CONCLUSION:** High levels of antioxidant vitamins C and E may have significant detrimental effects on placental function, as reflected by decreased cell viability and secretion of hCG; and placental immunity, as reflected by increased production of TNF-a. Meanwhile hydrogen showed no such effects on cell proliferation and TNF-α expression, but it could affect the level of hCG, indicating hydrogen as a potential candidate of antioxidant in the management of preeclampsia (PE) should be further studied.

PMID: 25681223 [PubMed - in process]

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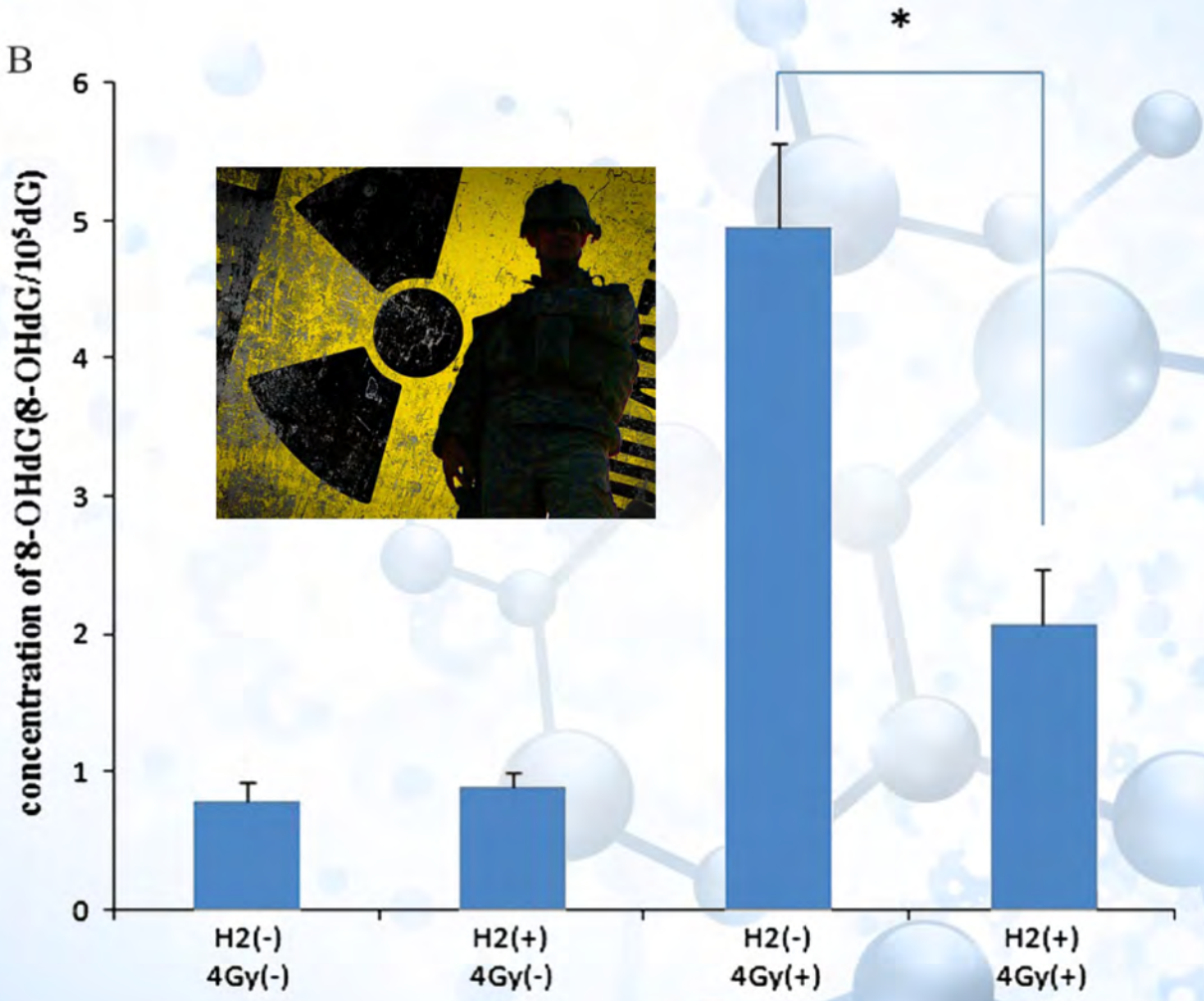
# Hydrogen protection from radiation




Qian, Liren, et al. Free radical research 44.3 (2010): 275-282.

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# Molecular hydrogen benefits mitochondria

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Med Gas Res. 2011 Oct 3;1(1):24. doi: 10.1186/2045-9912-1-24.

## Open-label trial and randomized, double-blind, placebo-controlled, crossover trial of hydrogen-enriched water for mitochondrial and inflammatory myopathies.

Ito M[1], Ibi T, Sahashi K, Ichihara M, Ito M, Ohno K.

Author information

### Abstract

**BACKGROUND:** Molecular hydrogen has prominent effects on more than 30 animal models especially of oxidative stress-mediated diseases and inflammatory diseases. In addition, hydrogen effects on humans have been reported in diabetes mellitus type 2, hemodialysis, metabolic syndrome, radiotherapy for liver cancer, and brain stem infarction. Hydrogen effects are ascribed to specific radical-scavenging activities that eliminate hydroxyl radical and peroxynitrite, and also to signal-modulating activities, but the detailed molecular mechanisms still remain elusive. Hydrogen is a safe molecule that is largely produced by intestinal bacteria in rodents and humans, and no adverse effects have been documented.

**METHODS:** We performed open-label trial of drinking 1.0 liter per day of hydrogen-enriched water for 12 weeks in five patients with progressive muscular dystrophy (PMD), four patients with polymyositis/dermatomyositis (PM/DM), and five patients with mitochondrial myopathies (MM), and measured 18 serum parameters as well as urinary 8-isoprostane every 4 weeks. We next conducted randomized, double-blind, placebo-controlled, crossover trial of 0.5 liter per day of hydrogen-enriched water or placebo water for 8 weeks in 10 patients with DM and 12 patients with MM, and measured 18 serum parameters every 4 weeks.

**RESULTS:** In the open-label trial, no objective improvement or worsening of clinical symptoms was observed. We, however, observed significant effects in lactate-to-pyruvate ratios in PMD and MM, fasting blood glucose in PMD, serum matrix metalloproteinase-3 (MMP3) in PM/DM, and serum triglycerides in PM/DM. In the double-blind trial, no objective clinical effects were observed, but a significant

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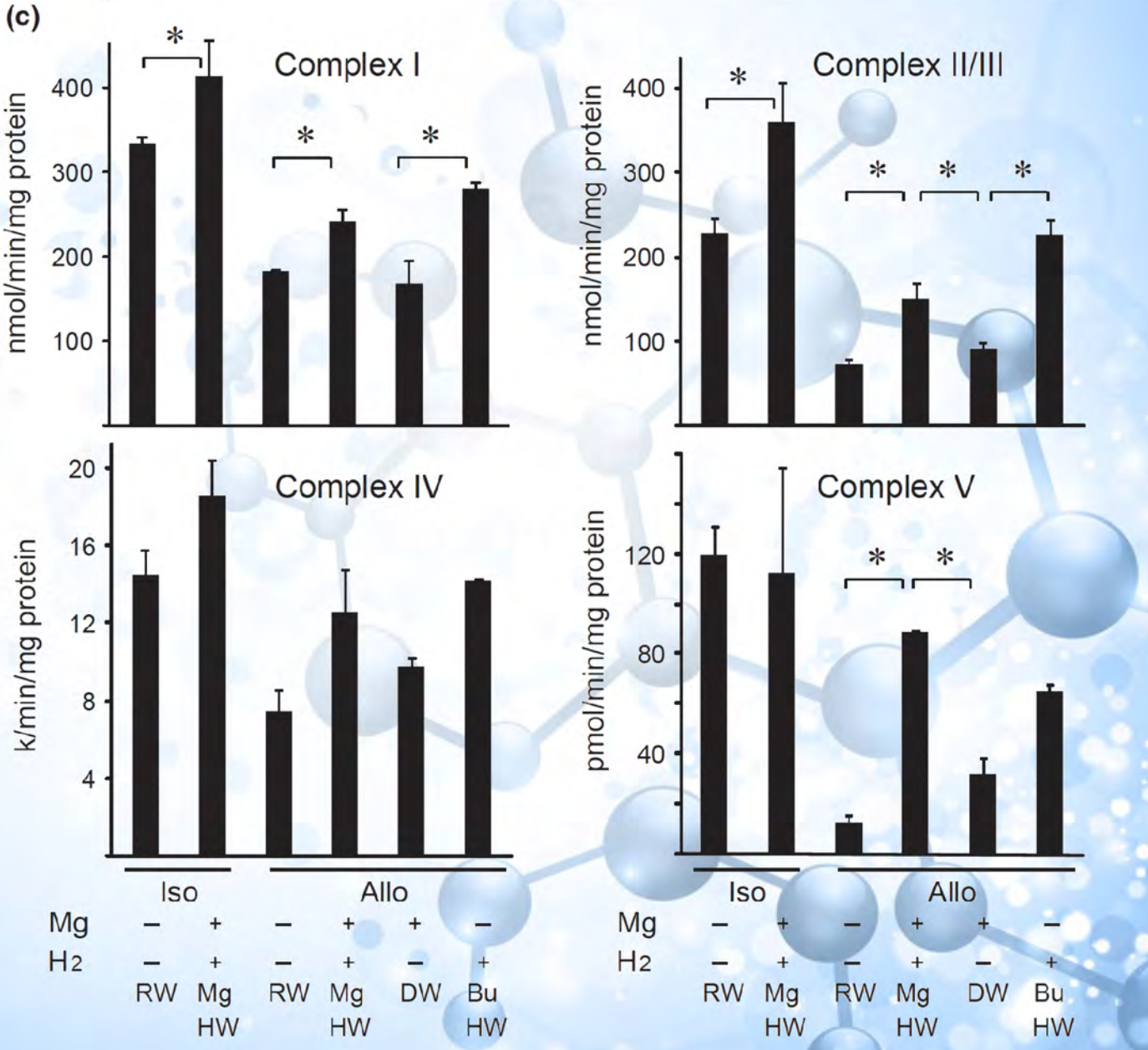
# Hydrogen stimulates mitochondrial function



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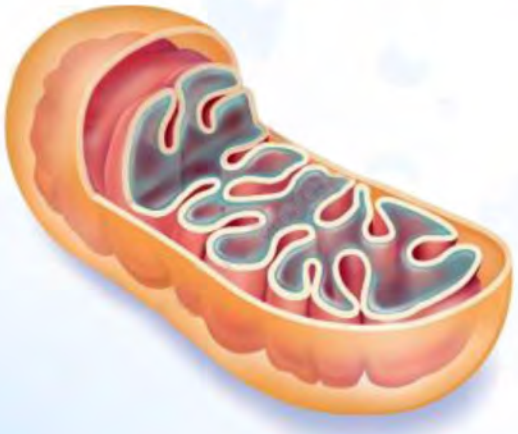
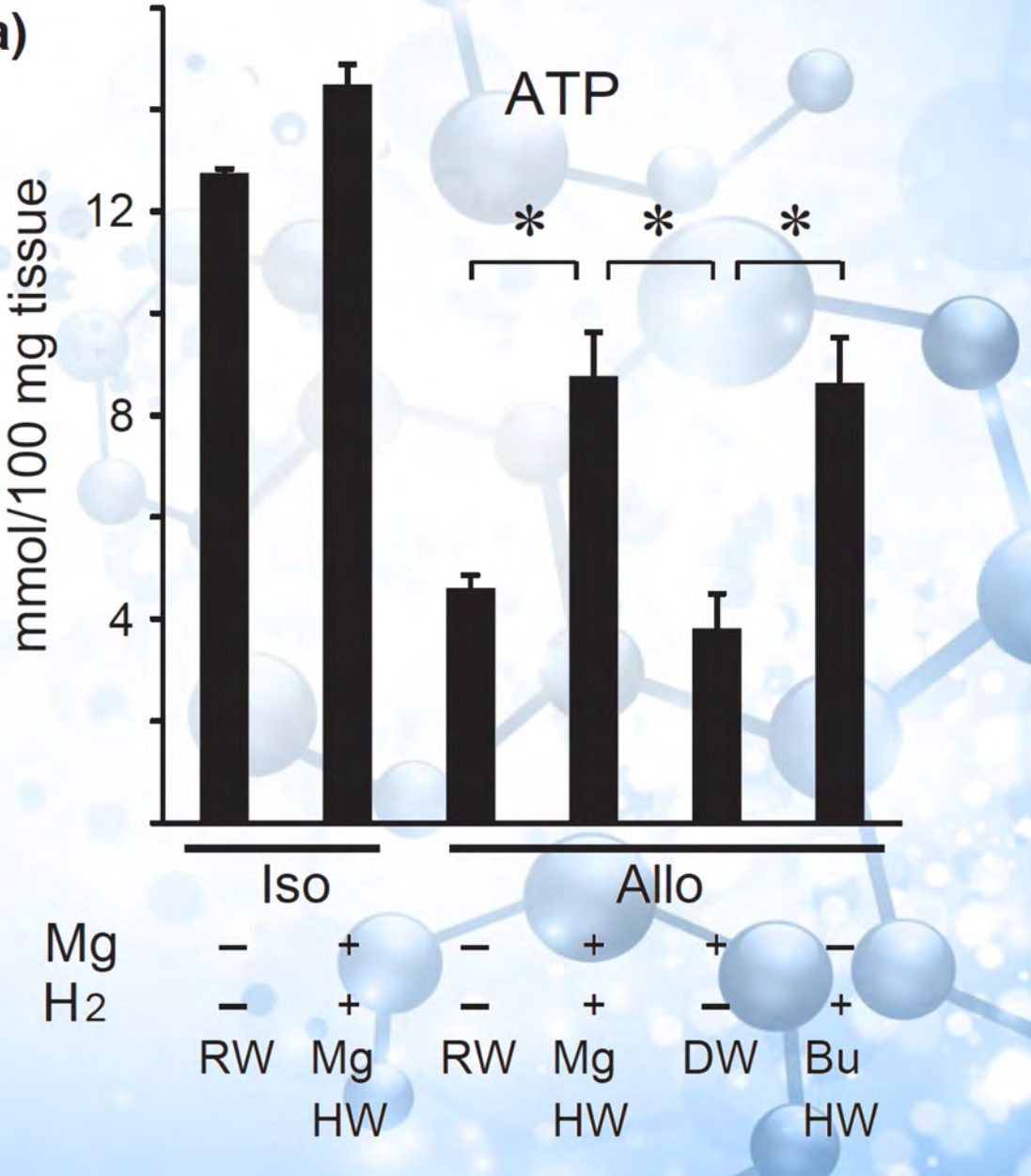
# Hydrogen promotes production of ATP





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Free Radic Biol Med. 2014 Apr;69:324-30. doi: 10.1016/j.freeradbiomed.2014.01.037. Epub 2014 Feb 6.

# Maternal molecular hydrogen administration ameliorates rat fetal hippocampal damage caused by in utero ischemia-reperfusion.

Mano Y[1], Kotani T[2], Ito M[3], Nagai T[4], Ichinohashi Y[5], Yamada K[4], Ohno K[3], Kikkawa F[2], Toyokuni S[6].

Author information

## Abstract

Molecular hydrogen (H2) scavenges hydroxyl radicals. Recently, H2 has been reported to prevent a variety of diseases associated with oxidative stress in model systems and in humans. Here, we studied the effects of H2 on rat fetal hippocampal damage caused by ischemia and reperfusion (IR) on day 16 of pregnancy with the transient occlusion of the bilateral utero-ovarian arteries. Starting 2 days before the operation, we provided the mothers with hydrogen-saturated water ad libitum until vaginal delivery. We observed a significant increase in the concentration of H2 in the placenta after the oral administration of hydrogen-saturated water to the mothers, with less placental oxidative damage after IR in the presence of H2. Neonatal growth retardation was observed in the IR group, which was alleviated by the H2 administration. We analyzed the neuronal cell damage in the CA1 and CA3 areas of the hippocampus at day 7 after birth by immunohistochemical analysis of the 8-oxo-7,8-dihydro-2′-deoxyguanosine- and 4-hydroxy-2-nonenal-modified proteins. Both oxidative stress markers were significantly increased in the IR group, which was again ameliorated by the H2 intake. Last, 8-week-old rats were subjected to a Morris water maze test. Maternal H2 administration improved the reference memory of the offspring to the sham level after IR injury during pregnancy. Overall, the present results support the idea that maternal H2 intake helps prevent the hippocampal impairment of offspring induced by IR during pregnancy.



**KEYWORDS:** Free radicals; In utero; Ischemia–reperfusion; Molecular hydrogen; Neuronal damage

PMID: 24509162 [PubMed - indexed for MEDLINE]

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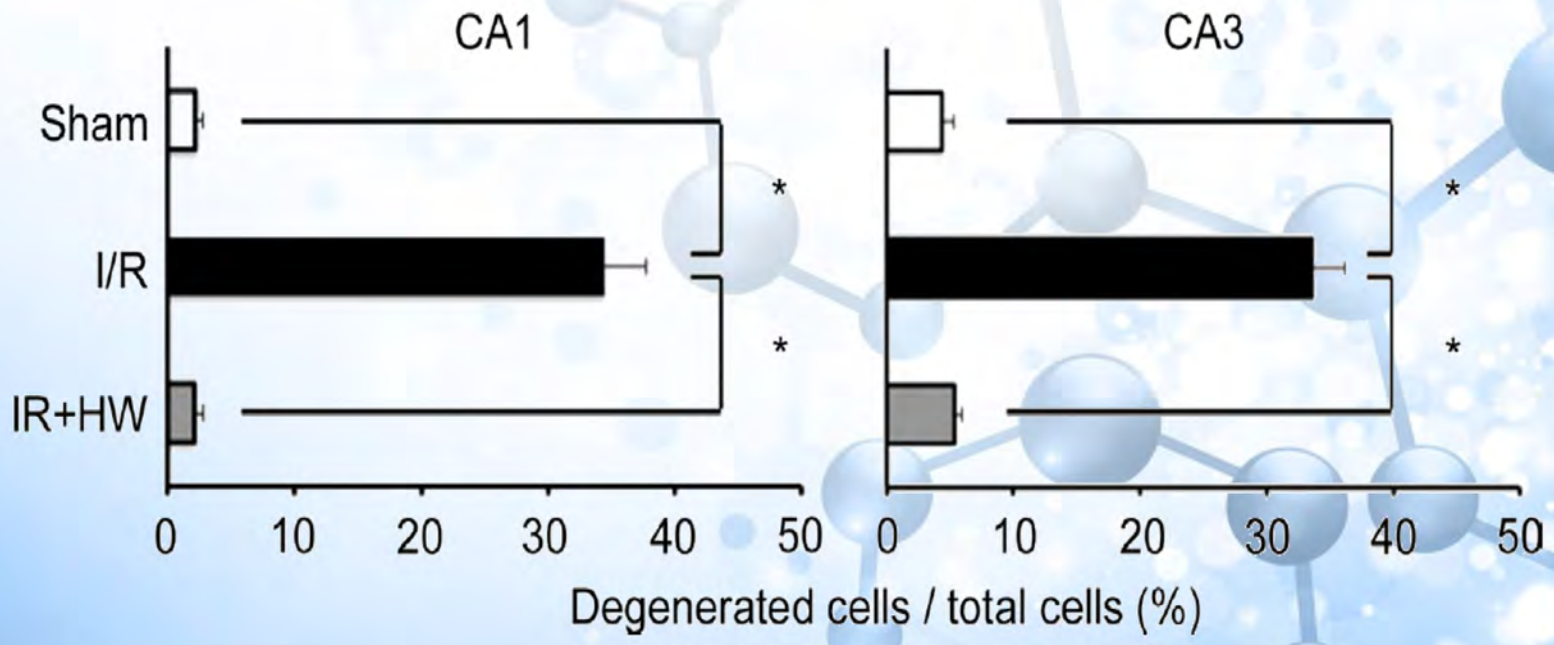
Free Radic Biol Med. 2014 Apr;69:324-30. doi: 10.1016/j.freeradbiomed.2014.01.037. Epub 2014 Feb 6.

## Maternal molecular hydrogen administration ameliorates rat fetal hippocampal damage caused by in utero ischemia-reperfusion.

Mano Y[1], Kotani T[2], Ito M[3], Nagai T[4], Ichinohashi Y[5], Yamada K[4], Ohno K[3], Kikkawa F[2], Toyokuni S[6].



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# Hydrogen and Cancer

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PeerJ. 2015 Apr 7;3:e859. doi: 10.7717/peerj.859. eCollection 2015.

## Hydrogen-water enhances 5-fluorouracil-induced inhibition of colon cancer.

Runtuwene J[1], Amitani H[2], Amitani M[2], Asakawa A[2], Cheng KC[2], Inui A[2].

Author information

**Abstract**

Oxidative stress is involved in cancer development. Hydrogen (H2) is a potent antioxidant and exhibits anti-inflammatory and potentially anticancer-like activities. This study aimed to investigate the role of H2 incombination with 5-fluorouracil (5-FU) in cancer treatment both in vitro and in vivo using the colon 26 cell line. The survival rate was determined using the Kaplan-Meier survival test, and cell viability was assessed using cell viability imaging kit and the MTT assay, and activation of the cell apoptosis pathway (Phosphorylated adenosine monophosphate activated protein kinase (p-AMPK), Apoptosis-inducing factor (AIF) and Caspase 3) were characterized by western blots. Hydrogen water administration improved the survival of mice with colon 26-induced cancer. Furthermore, hydrogen water enhanced cell apoptosis in cancer cells, resulting in a marked increase in the expression of p-AMPK, AIF and Caspase 3 in colon 26 cells. Hydrogen water also increased the inhibitory effect of 5-FU on colon 26 cells with spect to cell survival rate and anticancer functions. Additionally, high-content hydrogen water exhibited stronger antioxidative and anticancer activity than did the natural hydrogen water. In conclusion, high-content hydrogen water can inhibit colon cancer, particularly in combination with 5-fluorouracil.

**KEYWORDS:** 5-fluorouracil; Antioxidant; Apoptosis; Cancer; Hydrogen

PMID: 25870767 [PubMed] PMCID: PMC4393812 **Free PMC Article**

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Biochem Biophys Res Commun. 2008 Dec 26;377(4):1195-8. doi: 10.1016/j.bbrc.2008.10.156. Epub 2008 Nov 6.

**Consumption of hydrogen water prevents atherosclerosis in apolipoprotein E knockout mice.**

Ohsawa I[1], Nishimaki K, Yamagata K, Ishikawa M, Ohta S.

**When the preventive level of atherosclerotic lesions in this study is compared with the previous data that apoE-/- mice was used, the efficacy of hydrogen water seems to be greater than folic acid, vitamin E, iron, and alpha-lipoacid.**

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# High safety profile

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# PREDICTION


**Generally market is 10 years behind the science**

**2007 the beginning of active Hydrogen research**

# In 2017 Hydrogen will be ubiquitous!!