



Molecular Hydrogen: A New Treatment Strategy of Mitochondrial Disorders

Chapter

First Online: 17 February 2024

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Molecular Hydrogen in Health and Disease

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Part of the book series: [Advances in Biochemistry in Health and Disease](#) ((ABHD, volume 27))

394 Accesses **1** Citations **1** Altmetric

Abstract

Disturbances of mitochondrial function and oxidative stress are considered to be the molecular basis of the origin and development of various diseases, including mitochondrial diseases. The beneficial effect of molecular hydrogen (H_2) has been proven in the prevention and supportive therapy of patients with cardiovascular disease, Parkinson's disease, in patients with metabolic syndrome, in respiratory system disease, in oncology patients treated with radiation, in cerebral infarction, in diabetes mellitus, in

rheumatoid arthritis. Exact molecular mechanisms of H₂ on mitochondrial level are not fully understood. We proposed new mechanism of the H₂ effect in mitochondrial respiratory chain function. H₂ may be a donor of both electron and proton to the Q-cycle of the mitochondrial respiratory chain and thus can preserve coenzyme Q level with the subsequent ATP production via oxidative phosphorylation. H₂ was shown to alter the direction of the electron flow of mitochondrial respiratory chain system, which depends on NAD⁺/NADH ratio. We also found beneficial effect of H₂ on platelet mitochondrial bioenergy function in patients with NAFLD. The application of H₂ appears to be a new treatment strategy for targeted therapy of mitochondrial disorders.

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References

Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yagamata K, Katsura K, Katayama Y, Asoh S, Ohta S (2007) Hydrogen as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med* 13(6):688–694

[Article](#) [CAS](#) [PubMed](#) [Google Scholar](#)

Slezák J, Kura B, Frimmel K, Zálešák M, Ravingerová T, Vinczenczová C, Okruhlicová L, Tribulová N (2016) Preventive and therapeutic application of molecular hydrogen in situations with excessive production of free radicals. *Physiol Res* 65(Suppl. 1):S11–S28

[Article](#) [PubMed](#) [Google Scholar](#)

Ohta S (2014) Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine. *Pharmacol Ther* 144:1–11

[Article](#) [CAS](#) [PubMed](#) [Google Scholar](#)

Slezak J, Kura B, LeBaron TW, Singal PK, Buday J, Barancik M (2020) Oxidative stress and pathways of molecular hydrogen effects in medicine. *Curr Pharm Des* 26:1–16. <https://doi.org/10.2174/1381612826666200821114016>

[Article](#) [CAS](#) [Google Scholar](#)

Yoritaka A, Takanashi M, Hirayama M, Nakahara T, Ohta S, Hattori N (2013) Pilot study of H₂ therapy in Parkinson's disease: a randomized double-blind placebo-controlled trial. *Mov Disord* 28:836–839

[Article](#) [CAS](#) [PubMed](#) [Google Scholar](#)

LeBaron TW, Singh RB, Fatima G, Kartikey K, Sharma JP, Ostojic SM, Gvozdjakova A, Kura B, Noda M, Mojto V et al (2020) The effects of 24-week, high-concentration hydrogen-rich water on body composition, blood lipid profiles and inflammation biomarkers in men and women with metabolic syndrome: a randomized controlled trial. *Diabetes Metab Syndr Obes* 13:889–896

[Article](#) [CAS](#) [PubMed](#) [PubMed Central](#) [Google Scholar](#)

Ono H, Nishijima Y, Ohta S, Sakamoto M, Kinone K, Horikosi T, Tamaki M, Takeshita H, Futatuki T, Ohishi W et al (2017) Hydrogen gas inhalation treatment in acute cerebral infarction: a randomized controlled clinical study on safety and neuroprotection. *J Stroke Cerebrovasc Dis* 26:2587–2594

[Article](#) [PubMed](#) [Google Scholar](#)

Kajiyama S, Hasegawa G, Asano M, Hosoda H, Fukui M, Nakamura N, Kitawaki J, Imai S, Nakano K, Ohta M et al (2008) Supplementation of hydrogen-rich water improves lipid and

glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance. Nutr Res 28:137–143

[Article](#) [CAS](#) [PubMed](#) [Google Scholar](#)

Ishibashi T, Sato B, Rikitake M, Seo T, Kurokawa R, Hara Y, Naritomi Y, Hara H, Nagao T (2012) Consumption of water containing a high concentration of molecular hydrogen reduces oxidative stress and disease activity in patients with rheumatoid arthritis: an open-label pilot study. Med Gas Res 2:27

[Article](#) [CAS](#) [PubMed](#) [PubMed Central](#) [Google Scholar](#)

Gvozdjáková A, Sumbalová Z, Kucharská J, Szamosová M, Čárová L, Rausová Z, Vančová O, Mojto V, Langsjoen P, Palacka P (2021) Platelet mitochondrial respiration and coenzyme Q10 could be used as new diagnostic strategy in rheumatoid diseases. PLOS ONE 16/9:e0256135. <https://doi.org/10.1371/journal.pone.0256135>

Gvozdjáková A, Sumbalová Z, Kucharská J, Komlósi M, Rausová Z, Vančová O, Számošová M, Mojto V (2020) Platelet mitochondrial respiration, endogenous coenzyme Q10 and oxidative stress in patients with chronic kidney disease. Diagnostics 10:176. <https://doi.org/10.3390/diagnostics10030176>

[Article](#) [CAS](#) [PubMed](#) [PubMed Central](#) [Google Scholar](#)

Sumbalova Z, Kucharska J, Palacka P, Rausova Z, Langsjoen PH, Langsjoen AM, Gvozdjakova A (2022) Platelet mitochondrial function and endogenous coenzyme Q10 levels are reduced in patients after COVID-19. Bratisl Med J 123(1):9–15. https://doi.org/10.4149/BLL_2022_002

Guan WJ, Wei CH, Chen AL, Sun XC, Guo GY, Zou X, Shi JD, Lai JD, Lai PZ, Zheng ZG, Zhong NS (2020) Hydrogen/oxygen mixed gas inhalation improves disease severity and dyspnea in patients with Coronavirus diseases 2019 in a recently multicenter open-label clinical trial. *J Thorac Dis* 12:3448–3452

Hirano S, Ichikawa Y, Sato B, Yamamoto H, Takfuji Y, Satoh F (2021) Potential therapeutic application of hydrogen in chronic inflammatory disease: possible inhibiting role on mitochondrial stress. *Int J Mol Sci* 22:2549. <https://doi.org/10.3390/ijms22052549>

Tian Y, Zhang Y, Wang Y, Chen Y, Fan W, Zhou J, Qiao J, Wei Y (2021) Hydrogen, a novel therapeutic molecule, regulates oxidative stress, inflammation, and apoptosis. *Front Physiol* 12:789507. <https://doi.org/10.3389/fphys.2021.789507>

Alwazzer D, Fuh-Ching Liu F, Wu XY, LeBaron TW (2021) Combating oxidative stress and inflammation in COVID-19 by molecular hydrogen therapy: mechanisms and perspective. *Ox Med Cell Long*, Article ID 5513868, pp 17. <https://doi.org/10.1155/2021/5513868>

Ohta S (2011) Recent progress toward hydrogen medicine: potential of molecular hydrogen for preventive and therapeutic application. *Current Pharmaceut Design* 17:2241–2252

Zha QB, Wei HX, Li CG, Liang YD, Xu LH, Bai WJ, Pan H, He XH, Ouyang DY (2016) ATP-induced inflammasome activation and pyroptosis is regulated by AMP-activated protein kinase in macrophages. *Front Immunol* 7:597

[Article](#) [PubMed](#) [PubMed Central](#) [Google Scholar](#)

Hasegawa T, Ito M, Hasegawa S, Teranishi M, Takeda K, Negishi S, Nishiwaki H, Takeda J-I, LeBaron TW, Ohno K (2022) Molecular hydrogen enhances proliferation of cancer cells that exhibit potent mitochondrial unfolded protein response. *Int J Mol Sci* 23:2888

[Google Scholar](#)

Gvozdjáková A (2018) Mitochondrial physiology. In: Gvozdjáková A, Cornélissen G, RB Singh (eds) Recent advances in mitochondrial medicine and coenzyme Q10, NOVA Sciences, NY, USA, pp 13–36

[Google Scholar](#)

Otera H, Ishihara N, Mihara K (2013) New insight into the function and regulation of mitochondrial fission. *Biochim Biophys Acta* 1833:1256–1268

[Article](#) [CAS](#) [PubMed](#) [Google Scholar](#)

Schäfer E, Dencher NA, Vonck J, Parcej DN (2007) Three-dimensional structure of the respiratory chain supercomplexes II III₂ IV₁ from bovine heart mitochondria. *Biochemistry* 46(44):12579–12585

[Article](#) [PubMed](#) [Google Scholar](#)

Ďuračková Z (2010) Some current insight into oxidative stress. *Physiol Res* 59:459–469

Gvozdjáková A (2008) Mitochondrial free radicals and antioxidants. In: Gvozdjáková A (ed) Mitochondrial medicine, Springer, Netherlands, pp 50–54

[Google Scholar](#)

Kura B, Bagchi AK, Singal PK et al (2019) Molecular hydrogen: potential in mitigating oxidative stress-induced radiation injury. *Can J Physiol Pharmacol* 97(4):287–292

Slezák J, Kura B, LeBaron TW, Singal PK, Buday J, Barančík M (2021) Oxidative stress and pathways of molecular hydrogen effects in medicine. *Current Pharmaceutical Design* 27/5:610–625

[Google Scholar](#)

Farrokhfall K, Hashtrouudi A, Ghasemi A, Mehrani H (2015) Comparison of inducible nitric oxide synthase activity in pancreatic islets of young and aged rats. *Iran J Basic Med Sci* 18(2):115–121

Ni HM, Williams JA, Ding WX (2015) Mitochondrial dynamics and mitochondrial quality control. *Redox Biol* 4:6–13

Yapa NMB, Lisnyak V, Reljic B, Ryan MT (2021) Mitochondrial dynamics in health and disease. *FEBS Lett* 595:1184–1204

[Article](#) [CAS](#) [PubMed](#) [Google Scholar](#)

Tilokani L, Nagashima S, Paupe V, Prudent J (2018) Mitochondrial dynamics: overview of molecular mechanisms. *Essays in Biochem* 62:341–360. <https://doi.org/10.1042/EBC20170104>

[Article](#) [Google Scholar](#)

Goede P, Wefers J, Brombacher EC, Schrauwen P, Kalsbeek A (2018) Circadian rhythms in mitochondrial respiration. *J Mol Endocrinol* 60:R115–R130. <https://doi.org/10.1530/JME-17-0196>

[Article](#) [PubMed](#) [PubMed Central](#) [Google Scholar](#)

Osborne B, Bentely NL, Montgomery MK, Turner N (2016) The role of mitochondrial sirtuins in health and disease. *Free Rad Biol Med.* <https://doi.org/10.1016/j.freeradbiolmed.2016.04.197>

[Article](#) [PubMed](#) [Google Scholar](#)

Li X, Kagan N (2011) Mammalian sirtuins and energy metabolism. *In J Biol Sci* 7(5):575–587

[CAS](#) [Google Scholar](#)

Van de Ven RAH, Santos D, Haigis MC (2017) Mitochondrial sirtuins and molecular mechanisms of aging. *Trends Mol Med* 23/4:320–331. <https://doi.org/10.1016/molmed.2017.02.005>

Cornélissen G, Gvozdjaková A, Lee Gierke C, Gumarova L, Sackett Lundeen L (2018) Chronobiology of mitochondria. In: Gvozdjaková A, Cornélissen G, Singh RB (eds) Recent advances in mitochondrial medicine and coenzyme Q10, NOVA Science, NY, USA, pp 37–56

[Google Scholar](#)

Wilking M, Ndiaye M, Ahmad N (2013) Circadian rhythm connections to oxidative stress: implication for human health. *Antioxidants and Redox Signaling* 213(19/2). <https://doi.org/10.1089/ars.2012.4889>

Richardson RB, Maillous RJ (2023) Mitochondria need their sleep: redox, bioenergetics, and temperature regulation of circadian rhythms and the role of cystein-mediated redox signaling, uncoupling proteins and substrate cycles. *Antioxidants* 12:674. <https://doi.org/10.3390/antiox12030674>

[Article](#) [CAS](#) [PubMed](#) [PubMed Central](#) [Google Scholar](#)

Aguilar-López BA, Moreno-Altamirano MMB, Dockrell HM, Duchen MR, Sánchez-García FJ (2020) Mitochondria: an integrative hub coordinating circadian rhythms, metabolism, the microbiome, and immunity. *Front Cell Developm Biol* 8:51. <https://doi.org/10.3389/fcell.2020.00051>

[Article](#) [Google Scholar](#)

Kawasaki H, Guan J, Tamama K (2010) Hydrogen gas treatment prolongs replicative lifespan of bone marrow multipotential stromal cells in vitro while preserving differentiation and paracrine potentials. *Biochem Biophys Res Commun* 397:608–613

[Article](#) [CAS](#) [PubMed](#) [Google Scholar](#)

Yang M, Dong Y, He Q, Zhu P, Zhuang Q, Shen J, Zhang X, Zhao M (2020) Hydrogen: a novel option in human disease treatment. *Ox Med Cell Longevity Article ID 8384742.* <https://doi.org/10.1155/2020/8384742>

Mikulecký M (2008) Methods of chronobiometrics analysis of mitochondrial function. In: Gvozdjáková A (ed) Mitochondrial medicine, Springer, Netheralnds, pp 93–102

[Google Scholar](#)

Gvozdjáková A (2008) Mitochondrial physiology. In: Gvozdjáková A (ed) Mitochondrial medicine, Springer, Netherlands, pp 1–17

[Google Scholar](#)

Yang WC, Li T, Wan Q, Zhang X, Sun L, Zhang Y, Lai P, Li W (2022) Molecular hydrogen mediates neurorestorative effects after stroke in diabetic rats: the TLR4/NF- κ B inflammatory pathway. *J Neuroimmun Pharmacol.* <https://doi.org/10.1007/s11481-022-10051-w>

Reddy PH, Reddy TP (2011) Mitochondria as a therapeutic target for aging and neurodegenerative diseases. *Current Alzheimer Res* 8(4):393–409

[Article](#) [CAS](#) [Google Scholar](#)

Sebastián D, Palacin M, Zorzano A (2017) Mitochondrial dynamics: coupling mitochondrial fitness with healthy aging. *Trends in Molecular Med* 23(3):201–215

[Article](#) [Google Scholar](#)

Fu Z, Zhang J, Zhang Y (2022) Role of molecular hydrogen in ageing and ageing-related diseases. *Ox Med Cell Long Article ID 2249749*. <https://doi.org/10.1155/2022/2249749>

Murphy MP (2009) How mitochondria produce reactive oxygen species. *The Biochem J* 417/1:1–13

[Google Scholar](#)

Liguori I, Russo G, Curcio F et al (2018) Oxidative stress, aging and diseases. *Clinical Intervent Aging* 13:757–772

[Article](#) [CAS](#) [Google Scholar](#)

Ishihara G, Kawamoto K, Komori N, Ishibashi T (2020) Molecular hydrogen suppresses superoxide generation in the mitochondrial complex I and reduced mitochondrial membrane potential. *Biochem Biophys Res Comm* 522(4):965–970

[Article](#) [CAS](#) [Google Scholar](#)

Ohta S (2012) Molecular hydrogen is a novel antioxidant to efficiently reduce oxidative stress with potential for the improvement of mitochondrial diseases. *Biochimica Biophysica Acta* 1820:S86–S94

[Google Scholar](#)

Wang B, Zhuoshu L, Mao L et al (2022) Hydrogen: a novel treatment strategy in kidney disease. *Kidney Dis* 8:126–136. <https://doi.org/10.1159/000520981>

[Article](#) [Google Scholar](#)

Dohi K, Kraemer BC, Erickson MA et al. (2014) Molecular hydrogen in drinking water protects against neurodegenerative changes induced by traumatic brain injury. *PLoS ONE* 9/9:e108034. <https://doi.org/10.1371/journal.pone.0108034>

Gvozdjáková A, Kucharská J, Kura B, Vančová O, Rausová Z, Sumbalová Z, Uličná O, Slezák J (2019) A new insight into the molecular hydrogen effect on coenzyme Q and mitochondrial function of rats. *Can J Physiol Pharmacol.* <https://doi.org/10.1139/cjpp-2019-0281>

Kucharská J, Gvozdjáková A, Kura B, Rausová Z, Slezák J (2018) Effect of molecular hydrogen on coenzyme Q in plasma, myocardial tissue and mitochondria of rats. *J Nutritional Health and Food Eng* 8(5):362–364

[Google Scholar](#)

Hirst J, Roessler MM (2016) Energy conversion, redox catalysis and generation of reactive oxygen species by respiratory complex I. *Biochim Biophys Acta* 1857: 872–883. <https://doi.org/10.1016/J.bbabi.2015.12.009>

Trefs E, Gannon M, Wasserman DH (2017) The liver. *Curr Biol* 27:R1147–R1151

[Article](#) [Google Scholar](#)

Mateoni CA, Younossi M, Gramlich T, Boparai N, Liu YC, McCullough AJ (1999) Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity.

Moore MP, Cunningham RP, Meers GM, Johnson SA, Wheeler AA, Ganga RR, Spencer NM, Pitt JB, Diaz-Arias A, Swi AIA et al (2022) Compromised hepatic mitochondrial fatty acid oxidation and reduced markers of mitochondrial turnover in human NAFLD. *Hepatology* 76(5):1452–1465. <https://doi.org/10.1002/hep.32324>

[Article](#) [CAS](#) [PubMed](#) [Google Scholar](#)

Mihajlovic M, Vinken M (2022) Mitochondria as the target of hepatotoxicity and drug-induced liver injury: molecular mechanisms and detection methods. *Int J Mol Sci* 23:3315. <https://doi.org/10.3390/ijms23033315>

[Article](#) [CAS](#) [PubMed](#) [PubMed Central](#) [Google Scholar](#)

Dabrevolski SA, Bezsonov EE, Orekhov AN (2021) The role of mitochondria dysfunction and hepatic senescence in NAFLD development and progression. *Biomed Pharmacol* 142:112041

[Article](#) [CAS](#) [Google Scholar](#)

Prasun P, Ginevic I, Oishi K (2021) Mitochondrial dysfunction in nonalcoholic fatty liver disease and alcohol related liver disease. *Transl Gastroenterol Hepatol* 6:4. <https://doi.org/10.21037/rgh-20-125>

Ramanathan R, Ali AH, Ibdah JA (2022) Mitochondrial dysfunction plays central role in nonalcoholic fatty liver disease. *Int J Mol Sci* 23:7280. <https://doi.org/10.3390/ijms23137280>

Nassir F, Ibdah JA (2014) Role of mitochondria in nonalcoholic fatty liver disease. *Int J Mol Sci* 15:8713–8874. <https://doi.org/10.3390/ijms15058713>

Sumbalova Z, Kucharska J, Rausova Z, Szantova M, Mojto V, Kura B, Gvozdjakova A, Slezak J (2022) Effect of molecular hydrogen on antioxidant content and mitochondria function in patients with non-alcoholic fatty liver disease. In: 1st Conference of European academy for molecular hydrogen research in biomedicine “Hydrogen for Biomedicine”. Smolenice, Slovakia, October 17th–20th, pp 74–75

Gvozdjáková A, Singh RB (2018) Mitochondrial diseases. In: Gvozdjáková A, Cornélissen G, Singh RB (eds), Recent advances in mitochondrial diseases and coenzyme Q₁₀, NOVA Sciences, USA, pp 71–79