Molecular hydrogen (H₂) as a potential treatment for acute and chronic fatigue

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Abstract
Many diseases as well as acute conditions can lead to fatigue, which can be either temporary or chronic in nature. Acute fatigue develops frequently after physical exercise or after alcohol hangover, whereas microbial infections such as influenza or COVID-19 and chronic diseases like Parkinson’s disease or multiple sclerosis are often associated with chronic fatigue. Oxidative stress and a resulting disturbance of mitochondrial function are likely to be common denominators for many forms of fatigue, and antioxidant treatments have been shown to be effective in alleviating the symptoms of fatigue. In this study, we review the role of reactive oxygen and nitrogen species in fatigue and the antioxidant effects of the intake of molecular hydrogen. We propose that molecular hydrogen is well suited for the treatment of temporary and chronic forms of oxidative stress-associated fatigue.

KEYWORDS
acute fatigue, chronic fatigue, COVID-19, hydrogen, inflammation, oxidative stress

1 INTRODUCTION

Fatigue, an overall lack of energy, can develop temporally, for example, after physical exercise¹,² and as a part of the detrimental consequences of alcohol intake.³ Fatigue can also be long-lasting in nature; chronic forms can result from viral and bacterial infections⁴,⁵ and they are frequent in severe diseases like Parkinson’s and Alzheimer’s diseases and multiple sclerosis.⁶ The diverse manifestations, causes, and possible treatments for chronic fatigue syndrome (also termed myalgic encephalomyelitis [ME/CFS]) have been extensively reviewed by Morris et al.⁶

Fatigue has emerged as a major adverse effect of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During acute infection, fatigue is observed in more than 70% of critical and noncritical cases of COVID-19.⁷ Worryingly, more than 50% of patients reported long-lasting fatigue even after passing through the acute phase of infection.⁸

In this short communication, we discuss reactive oxygen and nitrogen species (ROS/RNS) as potential triggers of acute and chronic fatigue. We briefly review the antioxidant effects of the intake of molecular hydrogen and suggest the use of molecular hydrogen for the treatment of acute and chronic fatigue. The inhalation of molecular hydrogen as a treatment for COVID-19 has also been recently discussed by Ostojic.⁹

1.1 Fatigue and ROS/RNS after exercise and alcohol intake

During physical exercise, muscle fibers experience significantly elevated levels of oxidative stress, for example, due to the increased formation of hydrogen peroxide.¹⁰ The relationship between muscle contraction, oxidative stress, and fatigue was discovered at the beginning of the 1990s.¹¹-¹³ and it was shown that the antioxidant...
N-acetylcysteine could prevent skeletal muscle fatigue.\(^\text{[13]}\) Another relevant radical is nitric oxide (NO), which is produced in muscles mainly by the enzyme neuronal NO synthase.\(^\text{[14]}\) NO can react with superoxide to form the highly oxidative peroxynitrite.\(^\text{[14]}\)

ROS/RNS also play an important role after alcohol intake. In mice, a massive disturbance of the redox homeostasis of mitochondria in synaptic terminals was found after ethanol treatment. Specifically, a three-fold increase in hydrogen peroxide production, increased monoamine oxidase activity, a decreased catalase activity (40%), and a massive depletion of oxidation-sensitive cardiolipin (55%) were observed.\(^\text{[15]}\) Analogously, a significant reduction of mitochondrial complexes I–IV and a massively enhanced concentration of hydrogen peroxide were found in another study after ethanol treatment of mice.\(^\text{[14]}\) Fatigue is a hallmark of a hangover. About 95% of participants in a survey of 1000 students reported fatigue as a symptom of hangover.\(^\text{[21]}\) In an animal model of hangover, the consumption of electrolyzed reduced water, which contains molecular hydrogen, was able to reduce ROS levels and improve enzymatic function.\(^\text{[17]}\)

### 1.2 Fatigue and ROS/RNS in association with inflammation

Inflammation is a highly complex process, which accompanies many diseases and is characterized by the release of cytokines such as interleukin 1 beta, interleukin-8, and tumor necrosis factor.\(^\text{[18]}\) Damage-associated molecular patterns (DAMPS), such as heat shock protein 60 and high-mobility group protein B1, can also be released during inflammation.\(^\text{[18,19]}\) During inflammation, nitric oxide is mainly produced by the inducible NO synthase enzyme.\(^\text{[20]}\) Peroxynitrite, meanwhile, can enhance the potential of already proinflammatory proteins\(^\text{[21]}\) leading to an amplification of inflammation via proteins such as toll-like receptor (TLR) 2 and TLR 4.\(^\text{[18,21]}\) An overshooting “cytokine storm” can be critical in individuals infected with COVID-19.\(^\text{[22]}\)

NADPH oxidases are membrane-bound enzyme complexes, which catalyze the reaction of NADPH and oxygen, resulting in superoxide, and are well-known sources of ROS.\(^\text{[23]}\) Nevertheless, for the development of acute fatigue and ME/CFS caused by inflammation, the production of mitochondrial ROS might be more relevant.\(^\text{[24]}\) In mitochondria, the electron transport chain consisting of complexes I–V is the site of energy production in the form of adenosine triphosphate. Under regular physiological conditions, electron leakage occurs mainly from complex I, at a rate of about 0.1–0.5%.\(^\text{[25]}\) These electrons can react with oxygen, resulting in the formation of superoxide.\(^\text{[25,26]}\)

TLRs are important regulators of inflammation, which detect microbial pathogen-associated molecular patterns (PAMPs) and DAMPs. When triggered, they activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor that regulates the expression of many cytokines and other inflammation-associated genes.\(^\text{[27,28]}\) Additionally, TLR signaling can enhance the production of mitochondrial ROS via TNF receptor-associated factor 6 (TRAF6). TRAF6 is best characterized as an important signaling molecule in the activation cascade of NF-κB. However, activated TRAF6 can also translocate into mitochondria, where it ubiquitinates the ECSIT signaling integrator.\(^\text{[29]}\) This leads to oxidative stress within mitochondria, which could potentially contribute to the lack of energy and fatigue in inflammation-related ME/CFS.\(^\text{[24]}\) The interaction of cytokines, DAMPs, TLRs, and ROS as factors causing mitochondrial dysfunction in COVID-19 sepsis has been discussed by Shenoy.\(^\text{[30]}\)

The negative effects of ROS/RNS can be mitigated by different antioxidants such as curcumin, N-acetylcysteine, or molecular hydrogen.\(^\text{[6]}\) In the next section, we will focus on the effects of molecular hydrogen.

## 2 Hydrogen in the Human Body and Its Antioxidant Effects

Hydrogen is no stranger to the human body and is commonly found in the gut. The human gut microbiome produces carbon dioxide, methane, hydrogen sulfide, and hydrogen.\(^\text{[31]}\) Clinical tests for diagnosis of carbohydrate maldigestion syndromes include breath tests for the detection of enhanced levels of methane and hydrogen.\(^\text{[32]}\)

In a groundbreaking publication from 2007, Ohsawa et al.\(^\text{[33]}\) described molecular hydrogen to be a therapeutic antioxidant gas, which selectively reduces cytotoxic oxygen radicals. However, the pronounced beneficial effects of hydrogen described for many diseases cannot be fully explained by ROS scavenging activity.\(^\text{[34]}\) Hydrogen may activate the nuclear factor erythroid 2-related factor 2 (NFE2L2, former Nrf-2),\(^\text{[34,35]}\) a transcription factor that is the key regulator of the cellular antioxidant system.\(^\text{[36]}\) Under physiological conditions, the hydrogen molecule is highly inert and is generally not expected to react with organic molecules or ions, except for highly reactive species. Recent studies have discovered another mechanism by which hydrogen exerts beneficial effects in the human body. Mitochondria contain enzymes that are evolutionarily closely related to hydrogenases, enzymes that can metabolize hydrogen.\(^\text{[37]}\) Surprisingly, molecular hydrogen can reverse the direction of transport of electrons in the inner membrane of mitochondria and can further suppress the generation of superoxide in mitochondrial complex I.\(^\text{[37]}\) Despite several hundred studies on the beneficial effects of hydrogen,\(^\text{[38]}\) the molecular mechanisms of its action remain enigmatic.

Hydrogen is generally administered by one of three delivery routes; via inhalation, injection of a hydrogen-saturated salt solution, or ingestion of hydrogen-enriched water.\(^\text{[39]}\) Usually, for safety reasons, a concentration of 1–4% is used for inhalation. The injection of hydrogen-saturated saline solutions is mostly limited to animal studies, where it allows well-controlled doses.\(^\text{[38]}\) The most widely used form of human hydrogen intake is the ingestion of hydrogen-enriched water. In the simplest form, hydrogen can be dissolved in water and packed in an appropriate material. Such products, packed in aluminum foil or cans, are available, for example, in Japan and China. Moreover, several electrical devices in the market allow the generation of hydrogen-enriched water by electrolysis. When using this method, the material used to produce the electrodes and the purity of the water are critical factors to avoid
unwanted, potentially toxic chemical byproducts. Additionally, tablets are available, which mostly combine a small amount of metallic magnesium and a water-soluble acid, such as malic acid, tartaric acid, and adipic acid.\[40]\] The reaction of the metal with the acids generates hydrogen when disintegrated in water. We have developed an effervescent hydrogen-releasing tablet, using magnesium, citric acid, and ascorbic acid, which is in accordance with the European regulations for nutritional supplements.

3 | EFFECTIVENESS OF MOLECULAR HYDROGEN AGAINST FATIGUE

In a double-blind, placebo-controlled clinical study, participants underwent exercises after drinking hydrogen-enriched water. Effects were determined in an untrained group, in which mild exercises began 30 min after consumption of 500 ml of hydrogen-enriched water (0.8 mg/l). Additionally, a well-trained group was investigated in which the participants drank 500 ml hydrogen-enriched water (1.0 mg/l) 10 min before starting moderate exercise.\[41]\] For the first group, a significant reduction of psychometric fatigue was determined, for the second group, an improvement of maximal oxygen consumption (VO2 max) was observed.\[41]\] Another study on 10 male soccer players with hydrogen-enriched water showed reduced blood lactate levels and alleviation of muscle fatigue.\[42]\] An animal study reported not only antifatigue effects of drinking hydrogen-enriched water but also lower NO concentrations in serum, reduction of blood glucose and lactate levels, as well as decreased levels of proinflammatory cytokines in serum.\[43\] Already in the year 2018, Morris et al.\[44]\] suggested treating chronic fatigue syndrome with molecular hydrogen and found no specific study that had explored this treatment. To the best of the authors’ knowledge, the situation has not changed since then.

3.1 | Safety

Molecular hydrogen is safe and is an authorized food additive (E 949) according to the regulations of the European Commission. Hydrox and Hydreliox are gas mixtures for deep-sea divers. The hydrogen concentration can be about 50% in deep-sea diving settings.\[45]\] The proposed therapeutic dose of about 80 ml hydrogen gas (equals 6.6 mg or 3.3 mmol) per day is vanishingly small as compared with the hydrogen doses taken by deep-sea divers, often over days and under enormous pressure. Toxic effects of molecular hydrogen intake have not been described.\[46]\]

4 | CONCLUSIONS

Fatigue in both its temporary and chronic forms often results from excessive oxidative and nitrosative stress.\[6,11-13\] A disturbance of mitochondrial function by ROS/RNS may explain the loss of energy.\[24\] The intake of molecular hydrogen has been shown to activate the endogenous antioxidant system via the transcription factor NFE2L2 in murine cells.\[38,46\] In several publications, the beneficial effects of hydrogen in cases of fatigue have been shown,\[41,43-47\] and we suggest that the potential role of molecular hydrogen in preventing and treating fatigue, alone or in combination with other treatments, is worthy of further attention. This is supported by the reasoning that many cases of fatigue result from ROS/RNS disturbance of mitochondria and based on the observation that molecular hydrogen can reduce oxidative stress.

CONFLICT OF INTEREST

Kurt Lucas is an inventor and assignee and the Max Planck Gesellschaft zur Förderung der Wissenschaften e.V. is an assignee of the international patent application WO2014048953A1, titled "Therapeutic use of hydrogen molecules."

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