MEDICAL SCIENCE MONITOR

HYPOTHESIS

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 3191-3195
DOI: 10.12659/MSM.899807

Received: 2016.05.30
Accepted: 2016.07.14
Published: 2016.09.08

Hydrogen-Rich Saline as an Innovative Therapy for Cataract: A Hypothesis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: This work was supported by the National Key Basic Research Program of China (No. 2013CB967001)

Cataract is the leading cause of irreversible blindness worldwide. Increasing evidence indicates that oxidative stress is an important risk factor contributing to the development of cataract. Moreover, the enhancement of the antioxidant defense system may be beneficial to prevent or delay the cataractogenesis. The term oxidative stress has been defined as a disturbance in the equilibrium status of oxidant/antioxidant systems with progressive accumulation of reactive oxygen species (ROS) in intact cells. Superfluous ROS can damage proteins, lipids, polysaccharides, and nucleic acids within ocular tissues that are closely correlated with cataract formation. Therefore, prevention of oxidative stress damage by antioxidants might be considered as a viable means of medically offsetting the progression of this vision-impairing disease. Molecular hydrogen has recently been verified to have protective and therapeutic value as an antioxidant through its ability to selectively reduce cytotoxic ROS such as hydroxyl radical (OH). Hitherto, hydrogen has been used as a therapeutic element against multiple pathologies in both animal models and human patients. Unlike most well-known antioxidants, which are unable to successfully target organelles, hydrogen has advantageous distribution characteristics enabling it to penetrate biomembranes and diffuse into the cytosol, mitochondria, and nucleus. Consequently, we speculate that hydrogen might be an effective antioxidant to protect against lens damage, and it is important to further explore the biological mechanism underlying its potential therapeutic effects.

MeSH Keywords: Antioxidants • Cataract • Hydrogen Peroxide • Oxidative Stress

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/899807

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Background

Cataract is the leading cause of irreversible blindness worldwide [1]. Over 50 million people suffer from cataracts and the number will increase as populations of the current generation grow older [2]. Currently, the only treatment for cataracts is the surgical removal of the opaque lenses and substitution with clear ones. Intraocular lens implantation is verified to be the most effective method to treat cataract, but it involves risks such as irreversible impairments of vision, retinal detachment, and endophthalmitis [3]. Surgery is not equally available to all patients and an artificial lens does not always attain the overall optical qualities of a normal lens [4]. In addition, the cost of surgery imposes economic burdens on patients. Therefore, preventing or delaying the onset of cataract by pharmacological approaches may lessen this burden, reduce the occurrence of blindness, and enhance the quality of life for older populations [5].

Overwhelming evidence indicates that oxidative stress is involved in the pathophysiology of a wide variety of human diseases, including cancer [6], cardiovascular disease [7], acquired immune deficiency syndrome (AIDS) [8], diabetes mellitus [9], and neurodegenerative disorders such as aging, Parkinson's disease, and Alzheimer's disease [10]. Recently, both epidemiological and experimental studies have provided evidence that the oxidative stress is a critical mechanism responsible for the initiation and progression of cataracts [11,12]. The term oxidative stress has been defined as a disturbance in the equilibrium status of oxidant/antioxidant systems with progressive accumulating of reactive oxygen species (ROS) in intact cells. Lens epithelium cells (LEC) are the center of metabolic activities in lenses, and the oxidative stress on LEC significantly contributes to the pathogenesis of cataracts [13].

ROS are short-lived and highly chemically reactive. At low concentrations, ROS serve as cellular signaling molecules [14]. However, at high concentrations, ROS may give rise to both beneficial and unbeneficial effects. In the latter case, ROS may not only kill invading pathogens and microbes, but also damage the components of the cell, including proteins, lipids, carbohydrates, and DNA [15]. In the eye, ROS subtypes such as the hydroxyl radicals (OH–) and the peroxynitrite (ONOO–) can attack the aforementioned biological molecules, leading to lipid peroxidation and depletion of the antioxidant enzymes superoxide dismutase (SOD) and glutathione (GSH), which further exacerbate oxidative stress [16]. ROS is mostly generated within the mitochondria in lens epithelium cells and the superficial fiber cells, which are highly reactive and can damage macromolecules in living cells, such as lipids, proteins, and nucleic acids, causing mutagenesis and cell death [17]. These ROS significantly contribute to the pathogenesis of many ophthalmological disorders including cataract, and are neutralized by presence of endogenous antioxidants in the eye. However, if the endogenous antioxidant system is not potent enough to counter excessive oxidative stress, the surplus ROS inevitably gives rise to impairment of the lens. It has been confirmed that ROS which mediate the formation of cataract are mostly brought about by age [18]. Accordingly, lenses have evolved antioxidant systems to defend against the toxic ROS via endogenous or exogenous antioxidants, such as GSH, and SOD, catalase (CAT), glutathione S-transferase (GST), and glutathione reductase/peroxidase (GR/Gpx) [19].

Hydrogen is the lightest and most abundant chemical element. Molecular hydrogen is a colorless, odorless, nonmetallic, tasteless, highly flammable diatomic gas which was first documented by Philippus Aureolus Paracelsus in 1520 as a kind of flammable gas [20]. In 2007, Ohsawa et al. found that molecular hydrogen could selectively reduce cytotoxic reactive oxygen species *in vitro* and thereby exert therapeutic antioxidant activity [21]. From then on, research on hydrogen set off a worldwide upsurge in research interest [22–26].

Hydrogen has been shown to exert protective effects on transplantation-induced intestinal graft injury [27], chronic liver inflammation [28], and vestibular hair cells [29], as well as regional myocardial ischemia and reperfusion [30].

Intriguingly, hydrogen does not disturb the metabolic oxidation-reduction reactions, innate immune system, or physiologic parameters [31]. It has been found that hydrogen selectively quenches detrimental ROS such as OH and ONOO, while maintaining metabolic oxidation-reduction reaction and other less potent ROS, such as superoxide anion radical (O_2), hydrogen peroxide (H_2O_2), and nitric oxide (NO) [32,33].

Hydrogen gas can penetrate biomembranes, diffuse into the cytosol, mitochondria, and nucleus, and protect cells and tissues against oxidative stress by scavenging ROS [34]. Especially in humans, the fact that the amount of hydrogen dissolved in venous blood is less than that in artery blood suggests that hydrogen can penetrate most membranes and diffuse into organelles [35]. It was supposed that the elevated hydrogen level in serum might lead to the incorporation of hydrogen into organs, and thus control the oxidative stress-induced tissue damage. On the other hand, hydrogen as a natural molecule could be a safe and effective antioxidant without known toxic effects [36]. However, hydrogen inhalation is not convenient and may be dangerous because it is inflammable and explosive if the concentration of hydrogen in the air is greater than 4%. Hydrogen can be dissolved in water up to 0.8 mM under atmospheric pressure at room temperature and its solubilized form, the hydrogen-rich saline (HRS), is advantageous since it is a safe, portable, and easily handled approach for delivery. More importantly, a higher concentration of hydrogen can be dissolved into HRS

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[28]. The HRS can be administered by drinking, or by peritoneal or intravenous injections, and has shown effective therapeutic effects on oxidative stress in several models: both *in vitro* and *in vivo* studies have verified that the antioxidant properties of HRS can decrease the incidence of ROS-related diseases [37,38]. Studies from other laboratories have proven that HRS provides protection against oxidative damage induced by ischemia/reperfusion in lung, intestinal, liver, and brain [39–41]. Researchers first demonstrated that HRS might have great radioprotective effects in 2010 [42,43]. Since then, application of HRS in radioprotection was further investigated [44–47]. It was also then used to improve the quality of life of patients clinically treated with radiotherapy for liver tumors [48].

Our Hypothesis

Previous studies indicated that disruption of the balance between ROS production and scavenging leads to human lens epithelial (HLE) cell apoptosis, which is closely associated with cataract formation. Therefore, the cellular antioxidant defense system has been proposed as an important factor in protecting HLE cells against oxidative stress and postponing cataract formation. The system includes oxygen eliminators such as GSH, SOD, CAT, Gpx, GR, and GST, which protect the crystallins from oxidative damage. However, their active oxygen-scavenging activities are not potent enough to counteract cataract formation in the lens [49]. Therefore, it may be necessary and reasonable to supply exogenous antioxidants to suppress oxidative damage to the lens proteins. Administration of HRS might provide a higher concentration of hydrogen and a better spread of hydrogen into the HLE cell, scavenging the toxic ROS in the aged lens, and thereby acting as an innovative therapy against cataracts. It is a logical step to verify the therapeutic effects of HRS on various models of cataract, and eventually apply them in the treatment of cataract patients.

The Feasibility of the Hypothesis

Under physiological conditions, ROS are products of normal oxygen metabolism and have beneficial biological effects at low concentrations, but higher levels of ROS can harm the body. External environmental factors (e.g., heat, UV light, X and gamma radiation, and therapeutic drugs), behavioral activities (e.g., smoking, long-duration exercise) and inflammatory cells (e.g., activated macrophages and neutrophils) can trigger the release various ROS (e.g., H_2O_2, NO, O_2^-, HO, and HOCl) [50,51]. Although ROS have extremely short half-lives, they can cause substantial damage to tissues and cellular components.

Some ROS, such as superoxide anion and H_2O_2, can be detoxified by antioxidant defense enzymes, but there has been no information about enzymes that can detoxify OH and ONOO–, which are extremely reactive free radicals in cells since they can easily react with cellular macromolecules to exert a strong cytotoxic effect, until a recent study reported that hydrogen gas can selectively reduce these 2 harmful free radicals [52]. Hydrogen reacts only with the strongest oxidants (OH and ONOO), which is advantageous for medical procedures, since it is mild enough not to disturb metabolic oxidation-reduction reactions or disrupt ROS involved in cell signaling [32]. Moreover, the hydrogen molecule is electronically neutral and has the ability to penetrate the membranes of cell, nucleus, and mitochondria. Recently, the application of hydrogen-rich saline (HRS) represents an alternative model of delivering molecular hydrogen, and it may be of potential therapeutic value in the treatment of oxidative stress-associated pathologies.

In the cells of the eye, ROS can initiate a surge of toxic biochemical reactions, such as peroxidation of the membrane lipids and extensive damage of the proteins, which cause intracellular protein aggregation and precipitation [11]. Accordingly, oxidative stress is believed to play a pivotal role in cataract formation [53]. It is well known that damage to HLE cells is an early event in cataract development, and HLE cell apoptosis is suggested as a crucial cause of cataract formation [54]. The administration of HRS has been shown to be beneficial for several ophthalmological pathologies, such as reducing retinal ischemia, protecting against glutamate-induced retinal injury and the hyperoxia-induced retinal neovascularization, inhibiting corneal neovascularization caused by alkali burn, and preventing diabetic retinopathy [55]. HRS can be administered by drinking, or by peritoneal, intravenous, or subcutaneous injection [56].

Therefore, it is reasonable and interesting to investigate whether molecular hydrogen has a potential therapeutic value for cataractogenesis. Recent pioneering studies represent an early attempt to evaluate the potential therapeutic effects of antioxidants against cataract formation [57,58]. The results suggest that HRS could reduce cataract formation and restore antioxidant capacity in the selenite-induced cataract model.

Conclusions

The potential clinical use in cataract patients relies on providing a safe source of hydrogen and exact curative effect analysis. However, in clinical practice, use of hydrogen in ophthalmology is rare. We cannot determine the optimal hydrogen treatment dose without confirming the treatment to be safe and effective. Therefore, our hypothesis needs to be translated into effective treatment strategies for patients. Considering the characteristics of the slow development of cataract, assessing the long-term safety and effectiveness of hydrogen treatment is of great importance.

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Large-scale, randomized, controlled, double-blind clinical trials are needed to determine the clinical feasibility of hydrogen treatment.

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Conflicts of interest statement

All the authors declare that they have no conflicts of interest.

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