Research Highlight

Hydrogen Therapy Reduces Oxidative Stress-associated Risks Following Acute and Chronic Exposure to High-altitude Environment*

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Low pressure, low oxygen concentration, and intense ultraviolet (UV) radiation in high-altitude environments, can cause oxidative stress which can trigger mountain sickness. A recent study demonstrated that hydrogen gas with a good permeability in biological membranes can treat various disorders by exerting its selective anti-oxidation and anti-inflammatory effects, indicating that hydrogen therapy plays a role in scavenging free radicals and in balancing oxidation and anti-oxidation systems of cells. Therefore, we hypothesize that inhaling low-dose hydrogen or drinking hydrogen-saturated water is a novel and simple method to prevent and treat oxidative stress injury caused by low pressure, low oxygen concentration and intense UV radiation in plateaus, thus reducing the risk of mountain sickness.

Oxidative Stress after Acute and Chronic Exposure to High Altitudes

In natural environments, plateau is characterized by low pressure, low oxygen concentration, low temperature, dust, wind, and strong solar radiation[1]. A significant impact is felt on the human body at an altitude >3000 m above the sea level. People having lived in plains for several generations present with altitude stress after reaching such an altitude, which is manifested as dizziness, headache, nausea, vomiting, disorientation, dyspnea, irritability, loss of appetite, and fatigue. Hence, this altitude can result in acute or chronic mountain sickness due to its great impact on the normal physiological functions of human body[2].

Low pressure, low oxygen concentration, and strong solar radiation at plateaus are closely associated with oxidative stress reactions in organisms. At an altitude >5000 m above the sea level, the oxygen content in air is approximately 50% that observed in plains. Low pressure and low oxygen concentration can significantly decrease the partial pressure of oxygen in alveolar air and arterial oxygen saturation, thus leading to insufficient supply of oxygen and producing a series of hypoxic oxidative stress reactions in cells and tissues. If an individual enters into such a high-altitude environment rapidly, his or her partial pressure of oxygen in alveolar air drops suddenly. The compensatory process for quick adaptation to hypoxia greatly aggravates hypoxic oxidative stress reactions in cells and tissues[3].

Ultraviolet (UV) radiation at 5000 m above the sea level is approximately 3-4-times that observed in plains. Strong UV radiation is another environmental factor inducing oxidative stress reactions in plateaus[1]. Low pressure, low oxygen concentration, and intense UV radiation cause disorders in the balance between oxidation and anti-oxidation systems of cells. Accumulation of an excessive amount of free radicals in human body cannot be cleared in a timely fashion, thus leading to the production of poisonous lipid peroxides that undermine the structure and function of cells and tissues at all levels and an increase in membrane permeability, protein crosslinking, enzyme inactivation, and DNA damage to cells. These phenomena result in apoptosis and tissue necrosis, thus leading to organ dysfunction. This chain of events will lead to mountain sickness and endpoints, such as pulmonary edema, cerebral edema, and polycythemia[4].

In general, oxidative stress is closely associated with mountain sickness. How oxidative stress is involved specifically in the occurrence and

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development of mountain sickness in plateaus (and its mechanism of action) still remains unknown. However, the levels of oxidative stress indicators are increased while those of antioxidants are decreased in humans who enter plateaus (or who participate in activities in plateaus)[5]. It was reported that some agents with an antioxidant activity, such as antioxidant vitamin supplements[6], rhodiola extract[7], and ginkgo biloba extract[8], can prevent altitude stress, promote acclimatization to high altitudes, and reduce the risk of mountain sickness.

Biological Eefficacy of Hydrogen Therapy

Hydrogen is a physiologically inert gas, just like helium. It has been shown that hydrogen has selective anti-oxidation and anti-inflammatory effects, and can thus be used in treatment of various illnesses.

Ohsawa et al. found that inhalation of low-dose hydrogen is effective against ischemia /reperfusion(I/R) injury in the cerebrum[9]. It was reported that hydrogen therapy is effective against I/R injury in the liver[10], heart[11], retina[12], Alzheimer's disease[13], Parkinson's disease[14], sepsis[15], spinal-cord injury[16-17], kidney injury after renal transplantation[18], hemorrhagic shock[19], acute peritonitis[20], acute pancreatitis[21], type-2 diabetes mellitus[22], metabolic syndrome[23], adverse reactions after radiotherapy for liver cancer[24], inflammatory, and mitochondrial myopathies[25], acute infarction in brainstem[26], Parkinson's disease[27], and chronic infection with hepatitis-B virus[28].

The mechanisms involved in hydrogen therapy are believed to be selective scavenging of hydroxyl free radicals and peroxynitrite, as well as alterations in expression of specific genes. Selective scavenging of hydroxyl free radicals can significantly down-regulate the expression of oxidative stress markers, such as 8-Oxo-2'-deoxyguanosine, 4-hydroxynonenal, malondialdehyde, and thiobarbituric acid reactive substances[9]. Scavenging of peroxynitrite can effectively reduce the level of nitric oxide-induced nitrotyrosine[9]. Changes in expression of specific genes can down-regulate the expression of inflammatory cytokines [e.g., tumor necrosis factor-alpha and -beta, interleukin (IL)-1, IL-6, and IL-12[29]], apoptosis-associated genes (e.g. caspases)[30], transcription factors (e.g., nuclear factor kappa B[31]). Hence, the possible mechanisms of hydrogen therapy for various diseases can be attributed to its selective antioxidant and anti-inflammatory effects.

If tissues suffer from ischemic hypoxia, an excessive amount of hydroxyl and peroxynitrite free radicals is produced in cells, which are not able to scavenge them sufficiently. These free radicals can cause considerable oxidative damage to the proteins, lipids and nucleic acids in cells, and destroy the structure and function of cells and tissues. Hydrogen therapy can selectively scavenge these free radicals, effectively maintain the balance between oxidation and antioxidant systems in cells, and slow down or eliminate oxidative stress-induced dysfunction and damage of multiple systems.

Hypothesis

It was reported that inhalating hydrogen or drinking hydrogen containing water can effectively relieve or eliminate oxidative stress-induced dysfunction and damage of multiple systems, suggesting that hydrogen therapy can also relieve oxidative stress injury and mountain sickness caused by low pressure, low oxygen concentration, intense UV radiation in plateaus.

Low pressure, low oxygen concentration and intense UV radiation in plateaus can lead to dysfunction and damage of different systems by producing excessive hydroxyl and peroxynitrite free radicals in cells and tissues. It was reported that drugs with antioxidant activity taken in advance can prevent altitude stress, promote acclimatization to high altitudes, and reduce the risk of mountain sickness[6-8].

The main mechanism of hydrogen is a selective antioxidant effect[9], indicating that hydrogen can also relieve oxidative stress injury due to the extreme environment at plateaus. In addition, the molecule of hydrogen is smaller than that of oxygen and electrically neutral with a better membrane permeability to penetrate the cell membrane into organelles (especially the main organelle producing reactive oxygen species: mitochondria). Hydrogen therapy is thus more likely to play a role in scavenging free radicals and in maintaining the balance between oxidative and antioxidant systems in cells.

If individuals enter plateaus (or participate in activities in plateaus), they would inhale low-dose hydrogen by mixing hydrogen into pure oxygen with its safe concentration <4% and can thus drink hydrogen-saturated water[22], receive hydrogen-saturated saline injection[11], and endogenous hydrogen gas generated by intestinal bacteria[32].

In conclusion, hydrogen therapy can effectively prevent altitude stress, promote acclima-tization to high altitudes, and reduce the risk of mountain sickness.

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