



The Actions of Molecular Hydrogen in the Body

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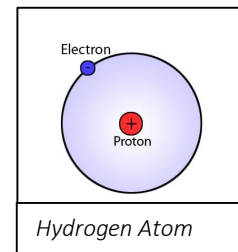
The Actions of Molecular Hydrogen in the Body

Molecular Hydrogen has recently emerged as a surprising molecule with broad therapeutic potential. Over 350 scientific studies indicate there may be a beneficial effect for over sixty conditions including: fatigue, cognitive impairment, pain, inflammation, metabolic syndrome, obesity and cardiovascular function.

Hydrogen is the simplest, smallest and most abundant element in the universe.. and is one of only four elements present in every living organism (*along with carbon, oxygen and nitrogen*). Its therapeutic uses stem from its actions as an anti-inflammatory, antioxidant mediator, and cell signalling molecule.

What does Hydrogen Look Like?

All hydrogen atoms have one proton, and one electron, but most have no neutrons. Naturally occurring atomic hydrogen is rare due to its propensity to bond with most elements. Elements bond together by sharing electrons. A hydrogen molecule consists of two bonded hydrogen atoms.



Hydrogen in the body is mostly bound to carbon and nitrogen. It is part of almost every molecule in your body: DNA, proteins, sugars, fats.

The hydrogen bond - which forms between atoms that "share" a hydrogen atom, is one of the most important interactions that make biological molecules behave as they do.

Free Radicals and Antioxidants

Quite simply, a free radical (*often referred to as a radical*) is an atom or molecule with an unpaired electron. Free radicals can be positively charged, negatively charged, or neutral. Two main types of radicals exist in the body: Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). An antioxidant is a molecule with the ability to donate an electron and thus neutralize free radicals.

Molecules with a spare electron are inherently unstable, and will take an electron from another molecule in order to increase their stability. This causes the molecule that has just lost an electron to become unstable and thus another free radical is created.

If this happens to enough molecules in the cell it results in damage to the cell.

If it happens to enough cells, the result is tissue damage.

The main oxygen based radicals are:

- Hydroxyl radical
- Superoxide
- Peroxide
- Hydrogen Peroxide

The main nitrogen containing radicals are:

- Nitric Oxide
- Peroxynitrite

Radicals are not always 'bad'.

Unlike what we hear in the advertising world, some of them are *essential* and play a vital role in the body's immune system by helping to eliminate viruses, bacteria, and abnormal cells. They are also important for gene expression (*whether a gene is switched off or on*) and cell signalling (*how cells talk to each other*). Caution is needed with many antioxidant supplements. They may inhibit the essential necessary actions of radicals.

A Matter of Balance

In a healthy body a balance exists between the generation of radicals and the antioxidant enzymes that neutralise them. Oxidative stress is the result of an imbalance between the production of ROS/RNS and the body's ability to detoxify the reactive intermediates or to repair the resulting damage. Cells are protected against oxidative stress by an interacting network of antioxidant enzymes. These are:

- Superoxide Dismutase (*SOD*) (*superoxide radical*)
- Catalase (*CAT*) (*hydrogen peroxide*) and
- Glutathione Peroxidase (*peroxide*).

Molecular Hydrogen is an excellent and a unique antioxidant. It is specific for the hydroxyl radical and increases the body's natural antioxidant molecules. Also, due to its small size, it easily crosses cell membranes and has access to parts of the cell that other antioxidants are too large to reach.

Molecular hydrogen has been shown to increase the levels of SOD, Catalase and Glutathione peroxidase. Thus it is increasing the body's innate antioxidant mechanisms.

Water, which we think of as H₂O, can be split into hydrogen (H) and hydroxide (OH⁻).

Hydroxide (OH⁻) consists of oxygen and hydrogen atoms and carries a negative electric charge. It is an important but usually minor constituent of water and functions as a base and a catalyst.

The hydroxyl radical, •HO, is the neutral form of the hydroxide ion (HO⁻). Hydroxyl radicals are highly reactive and are eliminated by hydrogen.

Hydrogen as an Anti-inflammatory

Believe it or not, inflammation is an essential part of the body's immune system and it is how our body naturally responds to any threatening stimuli. It comes about from an increased blood flow to an area of infection or injury, which in turn increases the supply of immune cells and healing nutrients to the area.

Acute inflammation is essential for immune function and healing.

Chronic inflammation has been linked to a variety of health conditions including obesity, the development of cardiovascular health problems, blood sugar abnormalities, abnormal cellular changes and arthritic complaints.

The inflammatory reaction results from the release of a number of *molecules (usually referred to as mediators)* that send a signal to the cells and molecules that are needed for healing. In chronic inflammation the body continually releases these mediators which results in a constant state of low level inflammation. This inflammation also causes an increase in oxidative species. The main molecules that have been shown to be effected by molecular hydrogen are Nuclear Factor kappa B (*NF-kB*), Tumour Necrosis Factor alpha (*TNFa*) and Interleukin 6 (*IL-6*). These molecules have been shown to increase the release of many other inflammatory molecules. The reduction of the release of these molecules is an important part of reducing chronic inflammation.

Genes, which are made up of DNA, act as instructions to make molecules called proteins. Genes can be turned off or on depending on the stimulus they receive. In chronic inflammatory states the genes that tell the body to release inflammatory mediators are **permanently switched** on so inflammatory molecules are constantly released. The molecules that can induce a change in gene status include NF-kB, TNFa, nitric oxide, peroxynitrite, SOD, glutathione, and catalase. Molecular hydrogen has been shown to directly or indirectly decrease excess circulation levels of all these molecules and thus is a potential agent for turning inflammatory genes off.

Hydrogen and Cell Signalling

Cells constantly send and receive signals to and from their surrounding environment. They use this information to maintain homeostasis and also to react to threats. This complex system of communication that governs basic cellular activities and coordinates cell actions is referred to as cell signalling.

It was long thought that only proteins such as hormones and neurotransmitters, and minerals such as sodium, potassium, calcium and magnesium were capable of being used as cell signalling molecules. It is now known that gases can also act in this role. Gases which act as cell signalling agents are: Nitric Oxide, Hydrogen Peroxide, Hydrogen sulphite, Carbon monoxide and - it has recently been established - hydrogen also plays this role.

The ability of cells to perceive and correctly respond to their microenvironment is incredibly important. It is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis.

Errors in cell signalling are responsible for diseases such as cancer, autoimmunity, and diabetes.

Homoeostasis: the ability of the body to maintain metabolic equilibrium of all relevant parameters within a narrow range that is essential to health, and in fact life.

Examples of these metabolic parameters are: temperature, pH and blood glucose levels.

Outside of major disease conditions the body maintains homoeostasis. The aspect of this that is relevant to maintaining health and the prevention of chronic disease is the question of how many of the body's resources and how much strain does it put on the body in order for this to happen.

For example, to maintain pH within range the body may take calcium from bones to use to help balance pH levels. This is an essential mechanism, but if left unchecked may result in osteoporosis.

Many of Molecular Hydrogen's abilities to reduce oxidative damage and inflammation stem from its role as a cell signalling agent.

Indications for Molecular Hydrogen

Research based on over 350 scientific studies into the potential health benefits of molecular hydrogen has shown a number of conditions, especially those with a strong oxidative and inflammatory element in their progression, may be improved by the therapeutic use of Molecular Hydrogen. These conditions include, but are not limited to:

- Metabolic Syndrome
- Cardiovascular health
- Obesity
- Fatigue
- Cognitive function
- Gastrointestinal Function including
 - Liver detoxification capacity
 - Pancreatitis
 - IBD
- Chronic pain and inflammation
- Abnormal cell division
- Immune function

Metabolic Syndrome

Metabolic syndrome is characterized by a group of risk factors that increase the likelihood of developing Type 2 Diabetes and cardiovascular health problems. These risk factors are:

- Insulin resistance & impaired glucose tolerance
- Obesity, especially central obesity
- Hypertension & dyslipidemia

Though obesity is considered a risk factor, it is not an essential component for someone to be considered to have Metabolic Syndrome. In fact, it has been shown that central obesity, or excess abdominal fat, is more often indicative of Metabolic Syndrome than simple obesity.

Insulin Resistance and Impaired Glucose Tolerance

Insulin is released by the pancreas; its role in the body is to take glucose (or sugar) out of the blood stream and transfer it into cells where it can be used as energy or stored as fat. The amount of insulin circulating in the blood is a result of how much glucose there is in the blood.

Insulin Resistance occurs when insulin can no longer easily enter the cell and thus glucose cannot be taken out of the blood stream. This results in higher levels of circulating glucose and insulin. Reduced ability of insulin means that the body can only deal with smaller quantities of glucose at any one time. This reduction is known as Impaired Glucose Tolerance.

If left unchecked impaired glucose tolerance and insulin resistance can result in Type 2 Diabetes Mellitus (T2DM). Insulin Resistance has also been linked to the development of cardiovascular disease.

There is a strong correlation between oxidative stress, inflammation, reduced cell signalling and the progression of insulin resistance to more serious conditions. All conditions which studies indicate may be beneficially affected by Molecular Hydrogen intake.

Obesity

Obesity, or more specifically central obesity, which is where the circumference of the waist is greater than the circumference of the hips, is one of the risk factors associated with the development of T2DM and cardiovascular disease.

Obesity is considered a chronic inflammatory state; it also increases oxidative stress on the body. Both of these are associated with the perpetuation of metabolic syndrome.

Hypertension and Dyslipidaemia

Hypertension is defined as having raised blood pressure, normally considered to be consistently above 140/90. Hypertension increases the risk of heart attack and stroke and is an inflammatory condition.

A contributor to hypertension is the deposition of atherosclerotic plaques (which are made from cholesterol) on the inside of artery walls. This results in narrowing of the artery and further increases blood pressure.

Systemic inflammation causes an increase in blood pressure, this increased blood pressure means more stress is put on valves and blood vessel walls which leads to damage. One of the functions of cholesterol in the blood stream is to protect lesions in blood vessel walls so they can heal (much like a scab on the skin). If the pressure is constant the size of the plaque will increase as the cause of the damage has not been removed. The plaque will remain and further occlude the blood vessel leading to increases in blood pressure.

Dyslipidemia is an abnormal amount of lipids (e.g. cholesterol and/or fat) in the blood.

Of particular note are Low Density Lipoproteins (LDL), with Small Dense LDL is seen as particularly bad. In addition, low levels of High Density Lipoproteins (HDL) are also indicative of the development of atherosclerosis. The latest research indicates that the development of dyslipidemia is due to high carbohydrate diet and not a high fat diet as is commonly thought.

An aspect of dyslipidemia of great significance in metabolic syndrome and its progression to cardiovascular disease and T2DM is free fatty acid metabolism. Fatty acids are the building blocks of the fat. During digestion, the body breaks down fats into fatty acids, which can then be absorbed into the blood. Fatty acid molecules are usually joined together in groups of three, forming a molecule called a triglyceride. Triglycerides are also made in our bodies from the carbohydrates

Research highlight: FGF21

Consumption of H₂-water increases the level of the hormone Fibroblast growth factor 21 (FGF21).

FGF21 is a metabolic hormone that improves insulin sensitivity and glucose clearance, reduces plasma triglyceride concentrations and suppresses weight gain.

FGF21 protects from diet-induced obesity when over expressed in transgenic mice and lowers blood glucose and triglyceride levels when administered to diabetic rodents.

Treatment of animals with FGF21 results in increased energy expenditure, fat utilization and lipid excretion.

Thus, drinking H₂-water, through its ability to increase FGF21, may suppress the gain of fat and body weight and improve metabolic parameters by stimulating energy metabolism.

Nuclear Factor Kappa B

Nuclear Factor Kappa B (NF-κB) is an inflammatory mediator and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. NF-κB plays a key role in regulating the immune response to infection.

Incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development.

Free fatty acids are fatty acids that are circulating in the blood. Most obese individuals have elevated plasma levels of FFA which are known to cause both peripheral (muscle) and hepatic (liver) insulin resistance. FFAs have recently been shown to activate inflammatory processes via NF- κ B.

There is a correlation between impaired free fatty acid (FFA) metabolism and

- obesity
- insulin resistance
- the development of coronary artery disease
- the development of non alcoholic fatty liver disease

Another aspect is lipid peroxidation, which refers to the oxidative degradation of lipids (fats). The cell membrane (wall) of every cell in the body is made of fats and ROS steal electrons from the lipids in cell membranes, resulting in cell damage and is a crucial step in the development of several disease states. Oxidized LDL is a major trigger of the Atherosclerotic process.

The consumption of hydrogen rich water for 8 weeks resulted in a 39% increase in the antioxidant enzyme superoxide dismutase (SOD) and a 43% decrease in thiobarbituric acid reactive substances (TBARS) in urine.

A double blind placebo controlled study into 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) found that consumption of 900ml per day of hydrogen-rich pure water was associated with significant decrease in the levels of:

- low-density lipoprotein (LDL) cholesterol, (15.5%),
- small dense LDL (5.7%)
- urinary 8-isoprostanes (measure of oxidative stress) (6.6%).
- oxidized LDL and free fatty acids,

There were also increased plasma levels of adiponectin (see *Research highlight*) and extracellular-superoxide dismutase (one of the body's antioxidant enzymes). In 4 of 6

TBARS are a measure of lipid peroxidation. End-products of lipid peroxidation may be mutagenic and carcinogenic. Animal studies show the removal of lipid peroxidases may be essential for life in mammals.

Superoxide Dismutase (SOD) neutralises the superoxide radical. It is important for the antioxidant defense in nearly all cells exposed to oxygen.

Research Highlight: Adiponectin

Adiponectin is a hormone that is released from adipose tissue (fat) into the blood stream and modulates a number of processes, including glucose regulation and fatty acid oxidation.

The higher the level of adiponectin, the lower the level of adipose tissue and vice versa.

Adiponectin has been shown to play a role in the suppression of

- Type 2 diabetes
- Obesity
- Atherosclerosis
- Non-alcoholic fatty liver disease

Molecular Hydrogen has been shown to raise the levels of adiponectin and thus may be indicated as part of the treatment plan for reducing Metabolic Syndrome.

The dose used was 900ml of Hydrogen Rich Water per day, and results were seen after 8 weeks.

patients with impaired glucose tolerance intake of hydrogen-rich water normalized the oral glucose tolerance test.

The results suggest that supplementation with hydrogen-rich water may have a beneficial role in prevention of T2DM and insulin resistance.

Obesity is inflammatory by nature and so it induces the release of NF-kB. In obesity, fat cells become less sensitive to adrenaline and this reduction in sensitivity is due to NF-kB. This reduced sensitivity in turn reduces energy expenditure, and the less energy you use, the more is stored as fat. In addition, the increased demand on adrenalin leads to a decrease in the availability of the dopamine. Dopamine is a chemical found mostly in the brain and is required for mood, memory, motivation and movement. If you have no motivation you don't exercise as much and thus energy expenditure is further reduced. Molecular hydrogen has been shown to decrease levels of NF-kB and thus reduce the obesity and inflammation cycle.

Long-term drinking H₂-water has been shown to significantly control fat and body weight, despite no change in the amount of water consumed. Moreover, drinking H₂-water decreased levels of plasma glucose, insulin, and triglyceride, the effect of which on hyperglycemia was similar to diet restriction.

Fatigue

Fatigue is characterised by a lack of energy and it can be either acute or chronic. Acute fatigue is generally the way the body signalling that it needs to rest, and is an important part of recovery from both exertion and illness. Chronic fatigue is seen as ongoing low levels of energy, both mental and physical, often with no discernable catalyst.

There are many causes of fatigue, from simple overexertion through to major disease conditions, and a state of ongoing or chronic fatigue should always be investigated by a health professional.

Though there are many causes of fatigue, the underlying physiological mechanism is often a decrease in mitochondrial function. Mitochondria are the part of almost every cell that creates energy, in the form of ATP, so the cell can function. Mitochondrial dysfunction is linked to:

- Fatigue
- Lifestyle diseases
- Cancers
- Neurodegenerative diseases

Mitochondrial function is important as if mitochondria aren't functioning optimally the body is less able to produce ATP. This decreases the ability of a cell to carry out its proper functions, leading to a decrease in overall

ATP, or Adenosine Triphosphate, is the molecule that is used by the body as energy. Like petrol in a car.

ATP generation in the presence of oxygen, or aerobic ATP production, can produce 30 molecules of ATP per glucose molecule. The waste products are CO₂ and H₂O.

ATP generation without oxygen is known as anaerobic and can produce 2 molecules of ATP per glucose molecule. The waste products are mostly CO₂ and lactic acid.

energy production and one of the results is fatigue. It can also lead to using anaerobic energy generation which leads to lactic acid build up and acidosis.

The production of ROS by the mitochondria occurs as a consequence of aerobic metabolism and plays an important role in cell signalling.¹ One consequence of mitochondrial dysfunction is increased production of free radicals which cause oxidative damage to the mitochondria and further limits its ability to generate energy and can ultimately lead to cell death.

Molecular Hydrogen is seen as an ideal antioxidant molecule for oxidative stress in the mitochondria due to its small size.

It is one of the very few, if not only antioxidant molecules that can reach the inside of the mitochondria. H₂ directly protects mitochondria that are exposed to reactive oxygen species. Preliminary clinical trials show that drinking hydrogen-dissolved water seems to improve the pathology of mitochondrial disorders. In the presence of increased H₂, mitochondrial energy metabolism functions against oxidative stress to efficiently expend glucose and fatty acid.

Drinking H₂-water stimulates energy metabolism as measured by O₂ consumption and CO₂ production. The enhancement of energy metabolism may explain why consumption of H₂-water suppresses the gain of fat and body weights and improves metabolic parameters.

Molecular Hydrogen and Energy for Organ Function

We often think of fatigue as the lack of energy to do things in terms of what the muscles can do. Our ability to get out of bed, go to work and exercise. However fatigue affects not only this obvious aspect but also the ability of every organ in the body to function optimally.

Glycogen is a form of glucose that serves as a form of energy storage for the body. It is stored mostly in the liver but also in small amounts in muscles and red blood cells. Only the glycogen stored in the liver can be made accessible to other organs; and then used by the organ for energy. Molecular Hydrogen increases glycogen stores in the liver and therefore may improve the functioning of all organs in the body by increasing the stores of available energy.

This means that there is more energy to do all the other things we want our bodies to do.

¹ Signal Transduction by Mitochondrial Oxidants Toren Finkel February 10, 2012 The Journal of Biological Chemistry, 287,

Gastrointestinal Function

The role of the gastrointestinal tract (GIT) is to digest foods, absorb nutrients and dispose of wastes. If the GIT is not functioning optimally a person can not be vitally alive. Gastrointestinal function generally decreases with age.

The majority of actions of Molecular Hydrogen on the GIT discussed and studies thus far have been a reduction of symptoms and indicators of damage in serious health conditions. Research thus far has indicated a potential role in reducing the symptoms of Inflammatory Bowel Disease, reduced liver function and pancreatitis.

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis. Symptoms include: abdominal pain, vomiting, diarrhoea, rectal bleeding and severe internal cramps/muscle spasms in the region of the pelvis and weight loss.

The development of IBD is thought to be associated with alterations to bacteria in the large intestine and these changes contribute to inflammatory damage to the lining of the intestine. By reducing the inflammation and addressing the bacteria in the intestine the symptoms of IBD have been shown to be reduced.

In an animal study of IBD, mice were given a chemical to mimic IBD. Some were also given H₂ water. The mice were then tested for:

- loss of body weight,
- increase of colitis score,
- shortening of colon length,
- elevated level of inflammatory mediators in colon lesion

All measures were significantly improved by the addition of H₂ and colonic tissue destruction accompanied by macrophage infiltration was remarkably suppressed.

The study indicated that H₂ can prevent the development of colitis in mice.

Pancreatitis

The pancreas is an organ of the digestive and endocrine systems and it releases several hormones, including insulin. It also secretes pancreatic juice containing digestive enzymes. Digestive enzymes travel from the pancreas to the small intestine where they act to help breakdown food.

Pancreatitis, which can be acute or chronic, is an inflammation of the pancreas and occurs when enzymes are activated in the pancreas before they reach the small intestine causing inflammatory and oxidative damage to the cells of the pancreas. Acute episodes are usually linked to gall stones; whereas chronic pancreatitis may lead to diabetes or pancreatic cancer.

In an animal study rats with acute pancreatitis were treated with Molecular Hydrogen. The results indicated that Molecular Hydrogen treatment has a protective effect against pancreatitis, and the effect is possibly due to its ability to inhibit oxidative stress, reduce cell death, decrease inflammation and to promote proliferation of healthy cells.

Liver Function

The functions of the liver include: detoxification, protein synthesis and the production of some of the chemicals necessary for digestion.

Ongoing reduction in liver function is seen as the precursor to damage to the liver.

Oxidative stress is accumulated in the liver in response to endogenous sources, such as infiltrating inflammatory cells, TNF α action, or storage of unsaturated fatty acids. Perhaps the most important consequence of oxidative stress in the development of liver disease is the promotion of inflammation.

The effect of H₂ on oxidative stress in the liver of diabetic mice was examined as judged by the level of an oxidative stress marker (MDA) derived from lipid peroxides. The MDA level in the liver of H₂-administered mice significantly fell to nearly the level in non-diabetes control mice, indicating that consumption of H₂-water markedly suppressed oxidative stress.

Non Alcoholic Liver Disease (NAFLD) is a condition where the fat accumulates in the cells of the liver. It is reversible, but if left untreated can lead to inflammation and liver damage. NAFLD predisposes to oxidative stress presumably by amplifying the capacity for free radical chain reactions. TNF α plays a critical role in early liver injury.

Treatment of NAFLD in animals has had significant protective effects towards liver injury, including increased antioxidant enzyme activity, decreased lipid peroxide levels and decreased circulating TNF- α levels. It is thought that Molecular Hydrogen inhibits signalling pathways in acute liver injury and inhibits fatty acid uptake and lipid accumulation in liver cells.

Chronic Pain & Inflammation

Pain is the body's way of saying "stop" and inflammation is one of the body's ways of stimulating pain receptors.

For both pain and inflammation, progression from being acute to chronic requires a change in gene expression (an epigenetic change).

Inflammation is an essential part of the immune response and without it the healing process would be greatly impaired. However, chronic inflammation can cause epigenetic changes. The cells that are repeatedly exposed to inflammatory mediators will have the genes that code for inflammatory response proteins switched on, and thus be in a constant state of inflammation. This leads to diseases and health conditions that are strongly linked to inflammation, including asthma and cardiovascular diseases.

Some of the molecules in the body that can instigate a change in gene expression are: Nf-kB, TNFa, and reactive nitrogen species such as nitric oxide and peroxynitrite.

Hydrogen indirectly affects gene expression through its actions to modulate molecules that have a direct epigenetic effect, Molecular Hydrogen can:

- Impede release of NF-kB
- Reduce TNFa
- Reduce excess nitric oxide
- Scavenge peroxynitrite

Molecular hydrogen has been shown to be an anti-inflammatory in acute conditions, but it is also a potential epigenetic modifying agent for genes that code for pain and inflammation. So therefore should be considered as part of a treatment plan for chronic pain.

Hydrogen & Immune Function

Research has not yet concluded if H₂ has a direct effect on the immune system in acute infectious conditions such as colds and flu's. However, its ability to reduce inflammation and oxidative damage may be beneficial in convalescence and recovery. There may be a role for H₂ in chronic immune conditions, including reduction in symptoms of autoimmune diseases.

Gene Expression is whether or not a gene is turned on or off.

We can not change our DNA, but we can influence whether or not a gene is active.

For example, a person can have the gene for diabetes, but if the gene is not turned on they will not develop diabetes.

The ability to affect gene expression is termed Epigenetics.

Allergy

An allergic reaction is an immune reaction. The immune system overreacts to a molecule thinking it is infectious and initiates an immune reaction. This involves ROS production, initiation of the inflammatory cascade and potentiation of the immune reaction. Hydrogen attenuates allergy via inhibiting intracellular signalling pathways and decreases the inflammatory and oxidant reactions.

Sepsis

Sepsis (previously known as septicemia) is a potentially fatal whole-body inflammation caused by the immune system's response to a serious infection. (It is most commonly caused by bacteria, but also fungi, viruses, and parasites.) Organ damage may result and occurs when blood clotting in response to the infection and inflammation reduces blood flow to limbs and internal organs, depriving them of nutrients and oxygen. Sepsis can be thought of as falling within a continuum from infection to multiple organ dysfunction syndrome.

Hydrogen treatment ameliorated polymicrobial sepsis and sepsis-associated organ damage in mice. This was thought to be primarily through the ability of hydrogen to decrease the levels of oxidative products and increase the activities of antioxidant enzymes; also to reduce levels of pro-inflammatory cytokines.

Autoimmune Conditions

An autoimmune condition is one in which the body's immune system reacts to its own healthy cells. There is no known cause but the development is thought to have a strong genetic element, with many autoimmune conditions having an hereditary aspect. It is thought that the epigenetic change which stimulates the development may be linked to viruses. An autoimmune disorder may result in:

- The destruction of one or more types of body tissue
- Abnormal growth of an organ
- Changes in organ function

Much of the treatment of autoimmune conditions revolves around reducing side effects and symptoms, many of which are due to inflammation and oxidative stress.

Though the research that has been done on autoimmune conditions thus far is limited, there is conjecture that Molecular Hydrogen may be beneficial.

For example, SLE, commonly referred to as Lupus, is an autoimmune condition where the body attacks its own DNA. One of the theories as to its development is that the destruction is thought to be caused by neutrophils, which are one of the types of white blood cell in the body. The change in the neutrophils action from targeting foreign invaders to attacking its own cells is thought to happen through an increase in nitric oxide, peroxynitrite and hydrogen peroxide levels in the nucleus of the cell; this causes a change in the DNA in the cell and thus a change in its activity.

As Molecular Hydrogen has been shown to either directly, or indirectly through its cell signalling action, decrease excessive nitric oxide, peroxynitrite and hydrogen peroxide levels it is conceivable that Molecular Hydrogen may be beneficial in reduction of symptoms of SLE.

Cognitive function and Neurodegeneration

Cognitive function refers to the ability to think, perceive, reason and remember. Ageing and disease can decrease cognitive function, resulting in memory loss.

Neuro degeneration is the term for loss of cognitive function due to loss of neurons. Neurodegenerative diseases include Alzheimer's disease and Parkinson's disease.

A decline in cognitive function is often considered a precursor to the development of serious neurodegenerative conditions such as Alzheimer's, senile dementia and Parkinson's disease.

Research Highlight: Rheumatoid Arthritis (RA)

Rheumatoid Arthritis is an autoimmune version of arthritis. It affects not only joints, but can affect the entire body, especially the respiratory and cardiovascular systems.

Patients have high levels of inflammation and ROS. The hydroxyl radical has been suggested to be involved in the pathogenesis of RA.

Twenty patients with RA drank 530 ml of water containing 4 to 5 ppm molecular hydrogen every day for 4 weeks. After a 4-week wash-out period, the patients drank the high H₂ water for another 4 weeks.

Patients who drank the high H₂ water had marked reduction in disease activity, and a significant decrease in hydroxyl radical levels and inflammation.

All the 5 patients with early RA (duration less than 12 months) achieved remission, and 4 of them became symptom-free at the end of the study.

One of the main theories on the development of neurodegenerative disease revolves around oxidative damage. For example, Parkinson's disease symptoms are mediated by a decrease in the level of the neurotransmitter dopamine, and a reduction in dopamine receptors. Reduction in both the number of dopamine receptors and their function is largely due to oxidative damage. In order to minimise the decrease in receptors, an antioxidant needs to be able to easily cross the blood brain barrier. Due to its ability to easily cross the blood brain barrier, Molecular Hydrogen is an ideal consideration to assist the health and well being of those with Parkinson's disease.

Administration of saturated hydrogen water (approx. 0.8 mM) led to symptomatic improvement in PD patients. Administration of hydrogen water at about 0.05% saturation successfully maintained dopaminergic neurons in Parkinson's disease model mice.

In Parkinson's disease, mitochondrial dysfunction and the associated oxidative stress are major causes of dopaminergic cell loss in the substantia nigra. A study examined effects of 50%-saturated molecular hydrogen in drinking water in a rat model of Parkinson's disease. Molecular hydrogen prevented both the development and progression of the nigrostriatal degeneration and prevented the dopaminergic cell loss. Suggesting that hydrogen water is likely able to retard the development and progression of Parkinson's disease.

Another factor in the progression of Parkinson's disease is a decrease in the levels of Ghrelin. Ghrelin is a hormone that is released from the stomach and its major role is associated with appetite. However it also has a neuroprotective effect, especially in the substantia nigra. Drinking hydrogen rich water has been shown to induce the release of ghrelin.

Alzheimer's Disease

Alzheimer's disease is the most common form of dementia. Symptoms include confusion, long term memory loss, mood swings and irritability. As the disease progresses there is loss of bodily functions and eventually death.

The development of Alzheimer's disease is linked to the deposition of amyloid-b ($A\beta$) plaques in the brain. In addition, oxidative stress is extensive in those AD brain areas in which $A\beta$ is abundant and leads to neuronal lipid peroxidation, protein oxidation and DNA oxidation by means that are inhibited by free-radical antioxidants.

Parkinson's Disease and Dopamine

Parkinson's disease is a neurodegenerative disease that results from the death of dopamine generating cells in part of the brain called the substantia nigra.

The substantia nigra is involved in control of movement and development of memory.

Dopamine is a neurotransmitter (brain chemical) that is needed for movement, memory, mood and motivation.

Thus a reduction in dopamine and loss of the receptors results in the symptoms seen in Parkinson's disease such as loss of control of movement, rigidity and difficulty walking.

As the disease progresses there is also a decrease in thinking, behavioural problems and often dementia.

Development has also been linked to neuro-inflammation caused by aggregation of amyloid plaques. Molecular Hydrogen has been shown to inhibit signalling pathways in animal models of amyloid-beta-induced Alzheimer's disease and in the rat model of Alzheimer's disease, hydrogen-rich saline prevented β -amyloid-induced neuro inflammation and oxidative stress and improved memory.

Alzheimers is increasingly being referred to as Type 3 Diabetes.

As such treatments that address the precursors to the development of diabetes should be considered as part of a preventive strategy for Alzheimer's.

Stress Induced Cognitive Decline

Persistent high levels of stress are associated with cognitive decline. In humans this is often psychological stress, but in animals physical stress is used to simulate human stress.

Chronic physical restraint stress on mice increased levels of oxidative stress in the brain, and impaired learning and memory. Consumption of hydrogen water suppressed the increase in oxidative stress in the brain, and prevented cognitive impairment.

Abnormal Cell Division

Abnormal cell division is the start of cancerous changes in tissue.

We can't state that Molecular hydrogen can prevent or treat cancer; but it may be beneficial in helping the well-being of someone with cancer.

The tumor micro-environment has an important role to play in abnormal cell progression and metastasis. A series of recent studies have shown that the production of hydrogen peroxide, by abnormal cells, may provide the necessary "fertilizer," by driving accelerated ageing, DNA damage, inflammation and cancer metabolism. By secreting hydrogen peroxide, cancer cells

Inflammatory Neurodegeneration

Inflammatory neurodegeneration is neuronal degeneration due to inflammation, and is thought to contribute to neuronal loss in infectious, ischemic, traumatic and neurodegenerative brain pathologies.

Hydrogen water was found to improve the outcome of lipopolysaccharide (LPS)-induced neuroinflammation and promote recovery.

These effects are associated with a shift towards anti-inflammatory gene expression profile.

In addition, molecular hydrogen increases the amplitude, but shortens the duration and promotes the extinction of neuroinflammation.

and fibroblasts are mimicking the behavior of immune cells driving local and systemic inflammation, via the innate immune response (NFκB).

Thus, we should consider using various therapeutic strategies (such as catalase and/or other anti-oxidants) to neutralize the production of cancer-associated hydrogen peroxide, thereby preventing tumor evolution and metastasis.

Molecular hydrogen removes excess hydrogen peroxide from the body by increasing the enzymes (catalase) that scavenge the hydrogen peroxide radicals. Thus hydrogen therapy may be a useful therapeutic consideration for the prevention of abnormal cell division.

Research over the past several years has indicated close associations among reactive oxygen species, chronic inflammation, and cancer. ROS induces chronic inflammation by the induction of COX-2, inflammatory cytokines (TNFα, interleukin 1 (IL-1), IL-6), chemokines (IL-8, CXCR4) and pro-inflammatory transcription factors (NF-κB). These chemokines and chemokine receptors, in turn, promote invasion and metastasis of various tumour types.

Hydrogen has been shown to modulate the release of a number of inflammatory mediators, including:

- COX-2,
- inflammatory cytokines (TNFα, interleukin 1 (IL-1), IL-6),
- chemokines (IL-8, CXCR4) and
- pro-inflammatory transcription factors (NF-κB)

The side effects of traditional cancer treatments are predominantly due to oxidative damage and inflammation. In some studies, hydrogen has been shown to reduce the side effects of some chemotherapeutic agents, and radiation therapy without decreasing the effectiveness of these treatments.

Inflammation caused by the surgical removal of tumours has been shown to increase cancer cell division and metastasis. Thus anti-inflammatory treatment should be a part of any cancer treatment plan.

Hydrogen as an effective and safe anti-inflammatory could be considered as a treatment option.

Molecular Hydrogen should be considered as part of the treatment plan for conditions associated with or developing from inflammation and oxidative stress. This includes metabolic syndrome and its associated conditions, chronic pain, decreases in cognitive function and abnormal cell division.

Though no therapeutic agent can be said to be completely free of side effects, the side effects seen from Molecular hydrogen seen thus far have been associated with mild detoxification reactions such as a mild headache and loose bowel motions.

ⁱ I:\HYDROGEN\HYDROGEN TECH SHEET PART 1.doc REFERENCES AVAILABLE ON REQUEST