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Molecular hydrogen, a therapeutic gas with antioxidant effects, general aspects and mechanisms

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Abstract
Background. There is an increasing scientific interest in molecular hydrogen (H2) worldwide. Over the last 13 years, over 500 scientific articles have been published about molecular H2.
Aims. The aim of this paper is to present some introductory information on H2 from the perspective of its antioxidant mechanisms and actions.
Methods. The method is based on the structure of a mini narrative review.
Results. Research presents the physiological effects of H2, with beneficial results on both animals and human subjects. Due to the rapid diffusion in the circulation of blood and cells, H2 is a new type of natural antioxidant with potential therapeutic benefits.
Conclusions. H2 could be considered the ideal antioxidant.
Keywords: Molecular hydrogen, therapeutic gas, antioxidant mechanisms, antioxidant effects.

Introduction – Features

Molecular H2 is a colorless, insipid, odorless and minimal molecule, with high flammability (Huang et al., 2010), a non -polar and diatomic compound with low molecular weight, with strong cell protection effects both in plants and mammals (Iida et al., 2016).

H2 can be explosive, but it does not explode if it is <10% when mixed with air or O2 (Kurokawa et al., 2019). The chemical property of H2 is that it burns with O2 to form water.

It has been found that H2 does not exist almost at all in arterial and venous blood, heart, liver and other tissues in normal rats (Chen et al., 2017). Mammal cells cannot produce H2 due to the deficiency of hydrogenases, however human bacteria produce H2 (Hylemon et al., 2018). It has been shown that exposure to H2 gas for 72 hours does not affect any of the physiological parameters (Cole et al., 2021).

H2 - Administration

There are several administration variants that can have different effects (Xin et al., 2014).

a) Inhalation H2

H2 inhalation is the simplest therapeutic method. H2 inhaled is broadcast by plasma alveoli and is transported by blood to the body. There are various forms of inhalation of H2, which lead to different results, such as nasal masks or tubes.

This method of administration increases H2 dissolved in arterial blood, but H2 levels in venous blood are lower than in arterial blood (Ohsawa et al., 2007).

As an inconvenience, the concentration of H2 in the blood and tissues (Fukuda et al., 2007), as well as the antioxidant effect of H2, depends on the time and concentration of H2 inhalation.

b) Ingestion in the liquid form - water with H2

The consumption of drinking water that contains H2 is a safe and easily administered way, and from this aspect it can be more beneficial. Another advantage is that it can be frequent. It has been shown that 41% of H2 ingested by rich water in H2 is kept in the body (Shimouchi et al., 2012).

However, due to the fact that the solubility in water is low, the ingestion cannot be guaranteed in sufficient concentration of H2.

c) Bathing in water with H2

Due to the ability of H2 to diffuse through the cell membrane , this method of use has evolved to therapeutic applications.

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The water in the H2-enriched water has been shown to have positive effects in the treatment of skin diseases (Asada et al., 2019), also in the preservation of grafts. Thus, a study in which the excised grafts were submerged in saturated water rich in H2 has shown effects of mitigating the lesion (Noda et al., 2013) by inhibiting excessive inflammation and oxidative stress (Qian et al., 2021).

d) Injection of H2 saline solution

This is an invasive method, which could become dangerous if H2 is injected directly into the skin or vein. The injection can be subcutaneous (Zhang et al., 2018), intravenous or intraperitoneal.

It has been shown that the luminaled saline injection rich in H2 can be a new and promising way in a model of ischemic lesion/reperfusion of the small intestine (Shigeta et al., 2015).

The injection of the subarachnoid cavity with H2 -rich saline solution has useful effects in brain and spinal cord disorders (Wang et al., 2015).

e) Irrigation with solutions containing H2

For example, ocular irrigation at Cu H2 has been proven beneficial (Igarashi et al., 2016). For example, the eye drops containing H2 reduced the level • OH - (Oharazawa at al., 2010).

Comparisons between methods

By inhalation, H2 diffuses at the same time with blood transport (Sano et al., 2020).

In the inhalation, H2 delivery to tissues is done almost at the same time, while by ingesting water with H2, the delivery time of H2 is longer (Sobue et al., 2015).

H2 inhalation causes a slower increase in H2 concentration than that obtained by intraperitoneal, intravenous or oral administration.

Thus, different H2 administration routes must be taken into account according to the user's needs to guarantee the best acceptable benefits.

H2 – Research

Experimental research

The first use of H2 in experimental medicine was published more than 40 years ago, when following the administration of H2 hyperbaric to obtain the marked regression of the tumors in Șiceci (Dole et al., 1975). Since then, most studies that have highlighted the beneficial effects of H2 on the various biochemical indicators of oxidative stress and/or antioxidant capacity in serum and urine have been experimental, but there are also studies that have evaluated clinical characteristics and/or benefits of H2 in humans. The effects of H2 have been widely studied and documented for a variety of experimental pathological models and situations (Ohno et al., 2012).

Clinical research

Although H2 research in the clinical environment is quite new, so far, the effectiveness H2 has been evaluated in several living situations or human suffering.

a) For example, in 1994 (Abraini et al., 1994), the first application of H2 was published in humans to alleviate some of the symptoms of high pressure nerve syndrome at depth divers.

b) Significant effects in human studies have been observed especially in mediated diseases based on oxidative stress, such as chronic inflammation in patients with hemodialysis (Nakayama et al., 2010).

In the case of clinical studies, some limitations have been noted:

a) Most studies have evaluated the effects following the administration H2 in the short -term - 8 weeks or less

b) Samples were relatively low in size

c) The lack of a dose-response relationship may suggest the absence of a causal relationship

Although most often the amount of H2 administered in clinical patients has not been standardized, this fact has not influenced the extent of the effects.

It is desirable that studies elucidate many problems of H2 therapy, including the dose-response curve and long-term clinical effects in a multitude of pathologies, using randomized controlled prospect and systematic finding of the best available evidence.

H2 - Effects

H2 has variety of effects: anti-allergic, anti-apoptotic, anti-inflammatory and antioxidant representing a potential therapeutic benefit for both prophylaxis and remediation (Ge et al., 2017). So far, no cytotoxicity has been reported following the administration of H2 (Zhou et al., 2019).

Beneficial effects of human administration were also found in:

a) Respiratory damage - asthma (Wang et al., 2020)

b) Ccardiac damage (Tamura et al., 2020)

c) Muscle impairment - inflammatory and mitochondrial myopathies (Ito et al., 2011)

d) Joint damage – rheumatoid arthritis (Ishibashi et al., 2012).

e) Neurological impairment - Parkinson's disease (Yoritaka et al., 2013)

f) Urological impairment (Matsumoto et al., 2013)

g) Metabolic impairment - metabolic syndrome (Nakao et al., 2010), diabetes (Kajiyama et al., 2008)

h) Post -traumatic impairment - inflammation caused by sports (Ostojic et al., 2014)

H2 is also very useful to ensure immune protection, as shown by studies:

a) H2, by regulating the proliferation of immune cells, balances the over -stimulation or immunodeficiency of the immune system (Chen et al., 2017; Xu et al., 2018).

b) The administration of H2 improves the activity of the CD4+ and CD8+ (Zhao et al., 2014) cells.

c) H2 reduces the manifestations of type I hypersensitivity, from allergic rhinitis (Huang et al., 2019), reversing the Th1/Th2 ratio (Xu et al., 2018)

d) The high consumption of H2 influences anti-inflammatory cytokine IL-4, which leads to the reduction of acute renal lesions (Yao et al., 2019),

e) H2 administration reduces inflammation from rheumatoid arthritis (Meng et al., 2016)

f) The consumption of H2-APA for four weeks by healthy adults causes the reduction of inflammation (Sim et al., 2020).

The most recent and remarkable benefit has been proven in Coronavirus-2019 disease-O2 inhalation mixed with H2 has led to the improvement of pulmonary function, emphysema and inflammation (Guan et al., 2020).

H2 - General Mechanisms of Action

The research carried out so far shows that H2 is involved in different signaling paths or physiological functions, has many actions, influences most of the systems in the body and mediates various beneficial effects. Examples:

a) H2 passes through the blood-brain barrier, although most antioxidants cannot perform this action.

b) It is able to diffuse rapidly through the membrane compartments, obtaining direct access to the cytosol, mitochondria and nucleus (Ohsawa et al., 2007) and reduces hydroxyl radicals.

c) H2 can play an anti -inflammatory and antioxidative role:

a. By direct impairment of the transport of mitochondrial electrons, neutralizing oxidative stress to alleviate mitochondrial damage

b. Bby balancing the homeostasis of the intracellular environment and influencing the transcript of key proteins in regulating inflammation (Ostojic, 2015).

An experimental study has shown that the administration of water containing H2 dissolved leads to (Cardinal et al., 2010):

a) the sustained increase in the level of H2 in the kidneys and serum, without any accumulation in time;

b) the functional improvement of the renal allograph over a 60-day tracking period;

c) a decrease in several inflammation markers, including cells that infiltrate the graft, proinflammatory cytokines and activate the mitogenic kinase protein;

d) decreased level of lipid peroxides and peroxinitrite in tissues

H2 - Antioxidant

Mitochondria produce 90% of the energy in the form of ATP, a process that is based on oxidative phosphorylation and which is accompanied by the generation of ROS (Annesley & Fisher, 2019). In this process, Coenzyme Q (CoQ) plays an important role in the electron transfer chain at the mitochondrial level (Gutierrez-Mariscal et al., 2020).

Oxidative stress is due to the imbalance between ROS and the antioxidant system is based on many conditions in the body (Burton & Jauniaux, 2011). For example, excessive red -induced mitochondrial damage is an important cause of many neurodegenerative diseases.

An ideal antioxidant is expected to alleviate excess oxidative stress, but not to disturb redox homeostasis.

Results of antioxidant action

We exemplify some of the effects:

a) H2 provides protection against oxidative reperfusion lesion in vitro and in vivo (Ohsawa et al., 2007).

b) H2 improves mitochondrial dysfunction and potential cell dysfunction regeneration (Yoshida et al., 2012).

c) H2 could protect against cell death (Iuchi et al., 2019).

d) Following the administration of H2 1.3% by inhalation, for 2 weeks in mice with vasculitis, it was found to reduce tissue damage (Kiyoi et al., 2020).

e) Following the administration of H2, the significant increase in the concentration of COQ9 (Gvozdjakova et al., 2020) was found.

f) H2 removal in diabetics reduces retinal injury (Liu et al., 2013).

g) By the antioxidant action, H2 provides neuroprotection (Wu et al., 2018) and is useful in Parkinson's disease therapy (Hirayama et al., 2018).

h) It has been observed that the biological and antioxidant effects of H2 remain even after H2 has been removed from the body (Dixon et al., 2013).

Antioxidant mechanisms

More ways have been described by which H2 determines the antioxidant effect:

a) A possible antioxidant mechanism of H2 is the direct removal of the hydroxyl radical (Lebaron et al., 2019).

b) H2 also prevents the production of hydroxyl radicals in the presence of catalytic active metals (Huang, 2016).

c) H2 can enter the cell through the cell membrane and then neutralizes the particles that intervene in the oxidative phenomenon (Ohta, 2014).

d) H2 can protect against cellular damage by improving the mitochondrial function (Liu et al., 2016).

e) In addition, H2 reduces the increase of the permeability of the cell membrane (Iuchi et al., 2019) and regulates the potential imbalance of the damaged mitochondrial membrane.

f) It has been found that H2 increases the activity superoxide dismutase and reduces the level of malondialdehyde (Gharib et al., 2001)

g) H2 significantly reduces reactive intracellular (ROS) reactive (ROS), promotes the expression of dismutase (SOD) and glutathione (GSH) and regulates the expression of NADPH oxidase (Su et al., 2019; Zhao et al., 2019).

h) H2 reduces the expression of inflammatory cytokines, which leads to the stopping of infiltration in the inflammatory place with phagocytes, with the consequence of stopping the subsequent release of the reactive species (Dixon et al., 2013; Ge et al, 2017), which explains the therapeutic effect of H2 in acute or chronic inflammatory diseases; also, H2 can inhibit the transcript of inflammation regulation proteins

i) H2 stimulates mitochondrial autophagia, ATP generation source (Wu et al., 2018).

j) 2% H2 administration for 3 hours leads to stimulating the elimination of damaged or dysfunctional mitochondria, called mitophagia (Yan et al., 2019).

Reported to the type and duration of action, H2 has four categories of intervention

a) Direct actions, by selective removal of reactive species (Ohsawa et al., 2007) and suppressing the chain reactions of free radicals for lipid peroxidation (Iuchi et al., 2016) and

b) Indirect actions by inducing the expression of antioxidant enzymes

c) Immediate actions consisting of:

a. Partial reduction of nitrites, by lowering the level of nitrotirosine (Zhang at al., 2015)

b. Direct cleaning of • OH, by neutralization • OH Ionizing radiation result (Qian et al., 2010)

d) Long -term actions consisting of:

a. Chronic regulation of gene expression and signal transduction, by inhibiting the MIR-200 expression in HT-22 cells produced by hypoxia and reoxification (Wei at al., 2015).

b. Adjusting the signaling path determined by lipopolysaccharides (Liu et al., 2013) and reduction of kinase protein

Conclusions

1. H2 has multiple beneficial actions in the body, proved in particular through animal studies, but in the last brush and by clinical studies, which are increasing numerically.

2. The administration of H2 can be done by several methods, the most commonly used being the inhalation, and the most practical, the water consumption with H2.

3. The antioxidant action of H2 is based on complex protective mechanisms, and the resulting effects can ensure many benefits of use.

4. Due to the numerous protective actions, H2 is considered the right candidate for the role of ideal antioxidant.

Conflict of interests

Nothing to declare.

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