Molecular Hydrogen Neuroprotection in Post-Ischemic Brain Injury

Subjects: Pathology

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Molecular hydrogen has gained the attention of both preclinical and clinical researchers. The death of pyramidal neurons in especially the CA1 area of the hippocampus, increased permeability of the blood-brain barrier, neuroinflammation, amyloid accumulation, tau protein dysfunction, brain atrophy, cognitive deficits and dementia are considered an integral part of the phenomena occurring during brain neurodegeneration after ischemia.

Keywords: brain ischemia ; neurodegeneration ; amyloid ; tau protein

1. Introduction

Molecular hydrogen is an odorless, colorless gas that is physiologically inert. Hydrogen is the lightest and most abundant element in the Earth's atmosphere. Furthermore, hydrogen is a biological gas that is produced in mammals by intestinal bacteria [1][2][3]. It is believed to be a new type of natural antioxidant with a low ability to react with most biomolecules, which is potentially therapeutic. The first use of hydrogen in humans was hydreliox, a breathing gas mixture of hydrogen, helium and oxygen that is used to prevent decompression sickness and nitrogen narcosis during very deep technical dives [4]. The therapeutic use of hydrogen was first demonstrated in 1975, showing that hyperbaric hydrogen caused marked regression of skin squamous carcinoma in mice [5]. In 2001, hydrogen was documented to have anti-inflammatory properties in experimental parasitic hepatitis [6]. Six years later, it was found that hydrogen was supposed to act as an antioxidant by selectively removing the neurotoxic hydroxyl radical and peroxynitrite from the parenchyma of the rat brain as a result of oxidative stress caused by ischemic brain injury [7]. Hydrogen has been shown to have many advantages as a neuroprotective gas. First, it can penetrate biomembranes, diffuse into the cytosol and organelles and cross the blood-brain barrier [7][8][9]. Secondly, the repeated administration of hydrogen does not cause tolerance [10]. Thirdly, different easy and convenient approaches to administer it are available [11][12]. Fourthly, hydrogen has a protective effect against many diseases, including peripheral and central nervous system diseases such as neuropathic pain, Alzheimer's disease, stroke, animal cerebral ischemia and neonatal hypoxic-ischemic brain injury [11][13][14][15][16][17][18][19][20][21][22][23]. Fifth, there are no documented serious side effects [13][24]. Sixth, in Japan, 2% molecular hydrogen inhalation has been approved for the clinical treatment of cerebral ischemia due to cardiac arrest [24][25][26][27][28]. The Chinese National Health and Medical Commission in 2020 recommended the use of inhaled hydrogen in addition to oxygen therapy for anti-cancer, anti-inflammatory and anti-oxidant treatments [29]. Hydrogen has been suggested as a new complementary therapy against stroke, which, e.g., reduces oxidative stress, neuroinflammation and apoptosis [22][30][31][32]. Despite many inaccuracies, the selective ability to scavenge free radicals and heal inflammation are still widely accepted mechanisms of the action of hydrogen [32]. Clinical trials have shown that hydrogen treatment is safe and effective in patients with asthma and chronic obstructive pulmonary disease [33][34].

It has been proposed to prevent and treat coronavirus disease by inhaling oxygen mixed with hydrogen (33.4% oxygen and 66.6% hydrogen) due to the important role of hydrogen in alleviating the worsening of lung function, emphysema, and acute or chronic inflammation [29][35][36]. Thus, molecular hydrogen is an interesting potential therapeutic gas for the prevention and treatment of various diseases, including neurological disorders.

2. In Animals

In mice with focal cerebral ischemia with reperfusion, molecular hydrogen significantly increases SOD and GSH-Px activity, reduces malondialdehyde levels and infarct volume, relieves cerebral edema, improves neurological outcomes and alleviates cognitive deficits (**Table 1**) [19][37][38]. In global cerebral ischemia caused by cardiac arrest in rats, hydrogen inhalation improves neurological outcomes, cognitive deficits and survival [20][39]. Hydrogen injection or inhalation after global cerebral ischemia due to cardiac arrest effectively controls neuronal death and microglia activation in the

hippocampus and lowers serum levels of S100b protein (**Table 1**) [8][31][40]. Inhalation of hydrogen or in combination with hypothermia has been shown to be superior to hypothermia alone in global cerebral ischemia from cardiac arrest in rats [31][40][41]. Molecular hydrogen has been shown to protect the permeability of the blood-brain barrier after focal and global cerebral ischemia (**Table 1**) [8][9]. Hydrogen has been shown to protect against oxidative stress, neuroinflammation, and prevents the ischemic site from turning into a hemorrhagic focus in rats with local cerebral ischemia (**Table 1**) [42]. Additionally, it has been shown that the intraperitoneal injection of hydrogen-rich saline has healing properties after transient global cerebral ischemia in rats [43]. Since most of the damage in the above model occurs between 6 and 24 h after ischemia, the effective hydrogen protection period was much less than the 6 h of recirculation, so the protective effect of hydrogen-rich saline in this situation is quite limited [43]. Hydrogen treatment of mice after bilateral closure of the common carotid artery improves cognitive abilities and induces anti-apoptotic and antioxidant effects [44]. In rats, up to 7 days after middle cerebral artery occlusion with reperfusion and administration of hydrogen, a reduction in infarct volume, ischemic penumbra hyperperfusion, neurological and behavioral disorders and white matter damage were observed (**Table 1**) [45]. It was documented that hydrogen therapy significantly improved the 7-day survival rate of mice after global brain ischemia, from 8.3 to 50% [46]. Histopathological analysis revealed that hydrogen therapy significantly attenuated neuronal injury and autophagy in the hippocampal CA1 area and also brain edema, after 24 h of reperfusion [46]. The beneficial effects of hydrogen therapy on post-ischemic brain injury were associated with significantly lower levels of oxidative stress markers: malondialdehyde and 8-hydroxy-2′-deoxyguanosine in the brain parenchyma [46]. Hydrogen inhalation following 10-min transient global cerebral ischemia in rats that survived 3 days attenuated cognitive impairment [47]. This neuroprotective effect was associated with decreased pyramidal neuronal death in the CA1 region of the hippocampus and inhibition of oxidative stress [47]. Hydrogen inhalation improved survival and neurological deficit after global ischemia caused by cardiac arrest in rats [31]. It also prevented the increase in left ventricular end-diastolic pressure and the increase in serum IL-6 levels, and reduced mortality [31][48][49]. Hydrogen treatment increased the level of interleukin-10, vascular endothelial growth factor and leptin [50]. In addition, a reduction in mortality in rats after cardiac arrest and an effect on the restoration of the bioelectrical activity of the brain was noted [50]. The survival rate at 4 h was 78% in the hydrogen group and 22% in the placebo group [50]. In another global model of cerebral ischemia due to cardiac arrest in rats, increased survival and inhibition of autophagy were observed [51]. Hydrogen inhalation for 4 days improves neurological outcomes and survival after global cerebral ischemia due to cardiac arrest in systemic hypertension rats and is superior to treatment with mild hypothermia [40]. The intraperitoneal injection of hydrogen into rabbits in cardiac arrest improved 3-day survival and neurological deficits, reduced neuronal damage, and inhibited neuronal apoptosis [52]. The intraperitoneal injection of hydrogen decreased the indicators of oxidative stress in the blood and the parenchyma of the hippocampus and increased the activity of the antioxidant enzyme [52]. Rats given hydrogen-rich water before and after occlusion of the middle cerebral artery, surviving up to 14 days after focal ischemia, showed reduced infarct volume and improved neurological outcomes [53]. In addition, hydrogen prevented ischemia-induced decreases in parvalbumin and hypocalcin, and also reduced neuronal cell death induced by toxic glutamate [53]. In addition, hydrogen lowered the increased levels of intracellular Ca^{2+} caused by glutamate toxicity [53].

Table 1. Neuroprotective effects of molecular hydrogen in experimental post-ischemic brain injury.

Ischemia	Animal	Strain	Treatment	Benefits	References
Focal	**Mice**	**C57B/L**	**Inhalation of 66.7% hydrogen/33.3% oxygen for 90 min post-ischemia.**	**Inhibition of microglial activity and regulation of microglial phenotype. Improvement of neurological outcome.**	**[19][37]**
Global	**Mice**	**C57BL/6J**	**Inhalation hydrogen (1.3%), oxygen (30%), and nitrogen (68.7%). 45 min of ischemia and 180 min of reperfusion, and 3 h/d, from 1 to 3 days post-ischemia.**	**Improved survival. Attenuation of neuronal injury, autophagy and brain edema.**	**[46]**
Global	**Rat**	**Wistar**	**2.1% hydrogen supplemented by room air ventilation for 4 h after ischemia.**	**Reduction changes of prooxidant enzyme and gap junction protein levels.**	**[54]**
Global	**Rat**	**Sprague-Dawley**	**Hydrogen-rich saline (5 mL/kg) was injected immediately post-ischemia.**	**Significant improvement of surviving cells. Reduction tissue damage, the degree of mitochondrial swelling, and the loss of mitochondrial membrane potential but also preservation the mitochondrial cytochrome c content.**	**[55]**

Ischemia	Animal	Strain	Treatment	Benefits	References
Global	Rat	Sprague-Dawley	I.V. hydrogen-rich saline (1 mL/kg, 4 mL/kg, or 6 mL/kg), HRS was given before hypoxia and during reoxygenation.	Inhibition of hippocampus endoplasmic reticulum stress and microvascular endothelial cells apoptosis via PI3K/Akt/GSK3β signaling pathway.	[56]
Global	Rat	Sprague-Dawley	Hydrogen-rich saline 5 mL/kg was intraperitoneally injected immediately and 6 h post-ischemia.	Significant improvement survival rate and neurological function. The beneficial effects associated with decreased levels of oxidative products, as well as the increased levels of antioxidant enzymes and accompanied by the increased activity of glucose-regulated protein 78, the decreased activity of cysteinyl aspartate specific proteinase-12 (caspase-12).	[57]
Global	Rat	Wistar	Inhalation of 2% hydrogen started immediately at the end of ischemia and lasted for 3 h.	Attenuation of cognitive impairment. Decreased pyramidal neuronal death in CA1 region of hippocampus.	[47]
Global	Rat	Sprague-Dawley	Hydrogen-rich saline was administered i.v. at 1 min before end of ischemia, followed by injections at 6 and 12 h post-ischemia.	Improves survival and neurological outcome.	[8]
Focal	Rat	Sprague-Dawley	6 mL/kg i.p. per rat before and after ischemia.	Reduction brain infarct volume and improvement of neurological function. Prevention the ischemia-induced reduction of parvalbumin and hippocalcin levels and also reduced the glutamate toxicity-induced death of neurons. Attenuation the glutamate toxicity-induced by elevate in intracellular calcium.	[53]
Focal	Rat	Sprague-Dawley	0.5 mL/kg/day saturated hydrogen saline (0.6 mmol/L) i.p. 3 days prior to ischemia and immediately during 24 h of reperfusion.	Significantly reduction the number of apoptotic cells, and the protein expression of p38 MAPK and caspase-3. These effects may be associated with the p38MAPK signaling pathway.	[58]
Focal	Rat	Sprague-Dawley	Hydrogen saline was injected i.p. (1 mL/100 g body weight) at designed time points 0, 3 or 6 h after reperfusion onset.	Reduction 8-hydroxyl-2′-deoxyguanosine, malondidehyde, interleukin-1β, tumor necrosis factor-α, and suppressed caspase 3 activity in ischemic brain.	[59]
Global	Rabbit	White	Before ischemia i.p. injection of hydrogen low dose (10 mL/kg) or high dose (20 mL/kg).	Improvement survival and neurological outcomes, reduction of neuronal damage and inhibition of neuronal apoptosis. Reduction indicators of oxidative stress in the blood and the hippocampus and increased activity of antioxidant enzyme.	[52]
Global	Swine	Yorkshire	Inhalation of hydrogen (2.40%) for a 24-h period during and after the ischemic injury.	Reduced neurological injury.	[60]

Subsequent studies found that rats that underwent global cerebral ischemia and were treated with hydrogen-rich saline had milder neuronal injury and a limited number of irreversibly damaged neurons in the brain [15]. Expression of miR-210, miR21 and NF-κB in the ischemic hippocampus at 6, 24 and 96 h was significantly reduced in the hydrogen-treated group [15]. Moreover, the number of Tregs cells after cerebral ischemia treated with hydrogen increased on days one and four after reperfusion [15]. These results indicate that the recovery from global cerebral ischemia in rats dosed with hydrogen-rich saline is most likely associated with an upregulation of Treg cell numbers [15]. Hydrogen significantly increased the number of surviving ischemic pyramidal neurons in the CA1 region of the hippocampus [15]. In addition, the neurobehavioral test confirmed that hydrogen reduced damage to the brain after ischemia [15]. This neuroprotective effect may be due to the extensive spread of hydrogen throughout the brain. Hydrogen has a good diffusion rate, can easily penetrate the blood-brain barrier and reach deep brain structures, and is also able to reach the site of injury before revascularization to remove toxic oxygen free radicals [61].

In behavioral studies of rats after focal cerebral ischemia, administration of lactulose, which induces endogenous hydrogen production in the intestine, resulted in higher neurological scores and shorter escape latency in the Morris test [62]. Morphological studies using 2,3,5-triphenyltetrazolium chloride showed a smaller infarct volume, Nissel staining showed relatively distinct and intact neuronal cells and TUNEL staining showed fewer apoptotic neurons [62]. In biochemical studies, lactulose decreased the content of malondialdehyde in the brain, the activity of caspase-3, the concentration of 3-nitrotyrosine and 8-hydroxy-2-deoxyguanosine and increased the activity of superoxide dismutase [62]. Orally administered lactulose activated expression of NF-E2 related factor 2 (Nrf2) in the brain [62]. The antibiotics suppressed the neuroprotective effects of lactulose by reducing hydrogen generation [62]. Lactulose administered intragastrically had a neuroprotective effect in post-ischemic brain injury in rats, which is attributed to the production of hydrogen via fermentation of lactulose by intestinal bacteria and activation of Nrf2 [62].

Studies that assessed the most effective timing of hydrogen administration after local cerebral ischemia in rats showed a post-ischemic time interval of up to 6 h during which significant reductions in infarct volume and brain edema were observed, and neurological outcomes improved [59]. At that time, after local cerebral ischemia, hydrogen decreased 8-hydroxyl-2′-deoxyguanosine (8-OHdG), reduced the content of malondialdehyde, interleukin-1β, tumor necrosis factor-α and suppressed caspase 3 activity [59]. These results indicate that hydrogen has a neuroprotective effect when administered during 6 h post-ischemia [59].

One study used hydrogen-saturated saline for focal cerebral ischemia in rats to test whether hydrogen-saturated saline reduces apoptosis of neuronal cells through the p38 MAPK-caspase-3 signaling pathway [58]. The obtained data showed that hydrogen reduced apoptotic neuronal cell death and infiltration of inflammatory cells in the brain cortex of rats post-ischemia [58]. In the hydrogen-treated group, there was a significant decrease in p38 MAPK protein expression compared to the untreated group [58]. It was concluded that hydrogen-rich saline could exert anti-apoptotic neuroprotective effects via the p38 MAPK signaling pathway [58]. It has also been found that, in acute post-ischemic brain injury in mice, hydrogen reduces the levels of Bax and TNFα and induces an anti-inflammatory response by regulating IL-2 and IL-10 [44].

3. In Humans

Studies in patients with acute focal cerebral ischemia have shown that administration of molecular hydrogen by inhalation or intravenous infusion is safe, hydrogen has been found in the blood, and there was no effect of hydrogen on physiological parameters [13][25][63]. Patients with local cerebral infarction who received hydrogen inhalation as part of their treatment had a reduced infarct size, improved neurological outcomes and the ability to perform daily activities compared to untreated patients (**Table 2**) [16]. In a human study of global cerebral ischemia due to cardiac arrest, inhalation of low concentration molecular hydrogen positively affected brain function without adverse events (**Table 2**) [25]. In Japan, a phase II clinical trial was conducted in patients with cerebral ischemia after cardiac arrest, finding a positive effect on neurological functioning and the safety of molecular hydrogen inhalation (**Table 2**) [25][27]. While no side effects of hydrogen have been detected in animal studies, potential side effects should still be investigated due to diarrhea reported by a small number of patients after receiving hydrogen [63].

Table 2. Neuroprotective effects of molecular hydrogen in clinical post-ischemic brain injury.

Ischemia	Number of Participants	Treatment	Benefits	Study	References
Focal	**50 patients**	**Inhalation 3% hydrogen gas (1 h twice a day) for initial 7 days.**	**Reduced infarct size, improved neurological outcome and daily living activity.**	**Randomized**	**[16]**
Global	**5 patients**	**2% hydrogen with oxygen was supplied via a respirator after admission to the intensive care unit for 18 h.**	**4 patients survived 90 days with a favorable neurological outcome.**	**Pilot study**	**[25]**
Global	**360 patients**	**2% hydrogen with 24 to 50% oxygen was supplied via mechanical ventilation after admission for 18 h.**	**The first multicenter randomized trial is underway to confirm the efficacy of hydrogen on neurological outcomes in comatose out-of-hospital cardiac arrest survivors.**	**Randomized, double-blind, placebo-controlled trial.**	**[26]**

Ischemia	Number of Participants	Treatment	Benefits	Study	References
Global	5 patients	Inhalation 2% hydrogen with titrated oxygen was initiated upon admission for 18 h.	Oxidative stress markers were reduced in cardiogenic post-cardiac arrest patients but were slightly elevated in the patient with sepsis. Inflammatory cytokine levels remained unchanged in cardiogenic post-cardiac arrest patients, whereas a dramatic reduction was observed in one patient with sepsis.	Pilot study	[27]

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