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Hydrogen as a novel and effective treatment of acute carbon monoxide poisoning

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SUMMARY

Hydrogen is a major component of interstellar space and the fuel that sustains the stars. However, it is seldom regarded as a therapeutic gas. A recent study provided evidence that hydrogen inhalation exerted antioxidant and anti-apoptotic effects and protected the brain against ischemia–reperfusion injury by selectively reducing hydroxyl radical and peroxynitrite. It has been known that the mechanisms underlying the brain injury after acute carbon monoxide poisoning are interwoven with multiple factors including oxidative stress, free radicals, and neuronal nitric oxide synthase as well as abnormal inflammatory responses. Studies have shown that free radical scavengers can improve the neural damage. Based on the findings abovementioned, we hypothesize that hydrogen therapy may be an effective, simple, economic and novel strategy in the treatment of acute carbon monoxide poisoning.

Introduction

Hydrogen is the simplest and most essential chemical element, composing nearly 75% of the universe's elemental matter. It is a colorless, tasteless, odorless, non-irritating and highly flammable diatomic gas which has been used in the fossil fuel processing and ammonia production. Hydrogen is seldom regarded as an important candidate in medicine, especially as a therapeutic gas. However, a recent study showed that hydrogen inhalation exhibited antioxidant and anti-apoptotic activities which protected the brain against ischemia–reperfusion injury by selectively reducing hydroxyl radical (·OH) and peroxynitrite ($ONOO^-$) [1]. This study indicated that hydrogen, a highly diffusible molecular, may be a novel anti-oxidative agent which can specifically target intracellular sources of reactive oxygen species (ROS).

ROS and reactive nitrogen species (RNS) including ·OH, superoxide anion (O^{2-}), hydrogen dioxide (H_2O_2), nitric oxide (NO), $ONOO^-$, have been confirmed to play critical roles in the cell damage after stroke, myocardial ischemia–reperfusion injury, transplantation injury and other injuries. Many efforts have been conducted to restore the blood flow to the ischemic tissues after stroke or a heart attack. However, it is still difficult to relieve this pathological cascade of oxidative damage after reperfusion injury [2].

Ohsawa and colleagues [1] presented that hydrogen selectively reduces the toxic ·OH to H_2O, and has antioxidant and anti-apoptotic properties affording neuroprotection in the setting of ischemia–reperfusion injury. Their findings support a novel hypothesis that hydrogen might act as a gaseous oxygen radical scavenger that prevents neural death. Other researchers have showed that hydrogen can also improve myocardial, hepatic ischemia–reperfusion injury, neonatal hypoxia–ischemia, Parkinson's disease, oxidative stress induced cognitive decline, etc. [3–7].

However, no study has been conducted to investigate the effects of hydrogen in the treatment of acute carbon monoxide (CO) poisoning, in which ROS also play pivotal roles.

Acute carbon monoxide poisoning

Acute CO inhalation is the leading cause of death relevant to gas poisoning in the world since increasing use of carbon-based fuels. Autopsy has revealed that CO poisoning injures several brain regions, including the cerebral cortex, globus pallidus, caudate putamen, hippocampus and striatum [8–10]. Furthermore, neuropsychiatric abnormalities, including Parkinsonism and dementia, with abnormal images of those brain regions in computed tomography (CT) and/or magnetic resonance imaging (MRI), have been reported in survivors from acute CO poisoning [11–14]. Delayed neurological syndrome (DNS), typically character of which is the lucid interval before the appearance of neuropsychiatric abnormalities, are commonly observed after acute CO poisoning.

It has still been a barrier for medical person because of poor early detection and disappointing prognosis. The specific mechanisms underlying the brain damage including DNS after CO poisoning are still poorly understood. However, numerous studies have indicated significantly increased production of ROS, which are of crucial relevance in the pathophysiology of CO intoxication [10,15–17]. Although ROS are probably intended to fight against invaded pathogens, they seem to produce substantial collateral damage resulting in DNA strand breaks, and lipid and protein

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oxidation [18–20]. The brain is highly vulnerable to oxidative stress in comparison with other organs due to high metabolic rate to meet the need of the brain for energy, which leads to the increased production of ROS. Once the defense against these ROS is insufficient, these ROS may inevitably cause oxidation of unsaturated fatty acids resulting in lipid peroxidation [21,22]. Enhancement in the ROS generation following brain insults, including cerebral ischemia/hypoxia, brain trauma, and CO poisoning, may disrupt the balance between ROS generation and the defense system, accelerating the neural injury resulting in extension of the injury or a more severe outcome [23,24,10].

Numerous strategies have been applied in the treatment of CO poisoning including aggressive supportive care, application of free radical scavengers, monoamine oxidase inhibitors, and N-methyl-D-aspartate blockers, as well as hyperbaric oxygen (HBO) therapy. Furthermore, general agreement that HBO therapy can reduce the neurologic morbidity and mortality, and partially ameliorate the impaired neurofunction has also been achieved [25–27]. The main mechanisms underlying the beneficial effects of HBO on acute CO poisoning is by accelerating the dissociation of CO from hemoglobin. However, there are still controversial over the effectiveness of HBO treatment on severe CO poisoning [28,29]. More attention should be paid to the adverse effects of HBO therapy. Theoretically, the increase availability of oxygen due to oxygen therapy may lead to the augmented formation of oxygen radicals. Studies have reported increased production of ROS in human blood and rat brain after HBO treatment [30,31]. Li et al. also found that HBO may result in convulsion through up-regulating nitric oxide synthases (NOS) [32].

Despite a variety of neuroprotective agents have been widely studied in the past decades, no agent is found to meet the criteria of an optimal neuroprotectant. Various researchers have engaged in identifying novel, nontoxic, effective, and convenient compounds to protect against tissue injuries caused by acute CO poisoning.

Hypothesis

Our hypothesis is that hydrogen may be a promising, effective and specific treatment of acute CO poisoning. Our hypothesis is on the ground of the theory that molecular hydrogen can selectively decrease $^{\cdot}OH$ and $ONOO^-$ [1]. Given $^{\cdot}OH$ and $ONOO^-$ are much more reactive than other ROS, we have reason to believe that hydrogen will act in response with only the strongest toxic oxidants.

This is beneficial for medical procedures in that molecular hydrogen is so mild that it does not disturb metabolic oxidation–reduction reactions or not disrupt ROS involved in cell signaling [1,2]. In addition, it can penetrate biomembranes and diffuse into the cytosol, mitochondria and nucleus. Therefore, hydrogen may protect nuclear DNA damage and mitochondrial membrane permeabilization. Furthermore, it can react with low density toxic ROS in that its relative concentration is quite high. Also as a potential treatment, hydrogen has distinct advantages over pharmaceutical drugs: it easily diffuses across the blood–brain barrier to reach target tissues, may act via multiple pathways. Last but not least, the tissue compatibility of hydrogen is stronger than many other antioxidant because it is an endogenous substance [33].

Since it has been known that the mechanisms underlying the brain injury after acute CO poisoning are interwoven with multiple factors including oxidative stress, free radicals, and neuronal nitric oxide synthase as well as abnormal inflammatory responses, and hydrogen can protect cells from oxidative damage through selectively scavenging $^{\cdot}OH$ and $ONOO^-$ [1], we hypothesize that hydrogen can be potentially effective for acute CO poisoning. That is to say, hydrogen may be a promising novel neuroprotectants. We believe that in vitro and in vivo work for hydrogen on neuroprotection against acute CO poisoning should commence as soon as possible.

Conflicts of interest statement

None declared.

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