Recent advances in the neuroprotective effects of medical gases

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Abstract

Central nervous system injuries are a leading cause of death and disability worldwide. Although the exact pathophysiological mechanisms of various brain injuries vary, central nervous system injuries often result in an inflammatory response, and subsequently lead to brain damage. This suggests that neuroprotection may be necessary in the treatment of multiple disease models. The use of medical gases as neuroprotective agents has gained great attention in the medical field. Medical gases include common gases, such as oxygen, hydrogen and carbon dioxide; hydrogen sulphide and nitric oxide that have been considered toxic; volatile anesthetic gases, such as isoflurane and sevoflurane; and inert gases like helium, argon, and xenon. The neuroprotection from these medical gases has been investigated in experimental animal models of various types of brain injuries, such as traumatic brain injury, stroke, subarachnoid hemorrhage, cerebral ischemic/reperfusion injury, and neurodegenerative diseases. Nevertheless, the transition into the clinical practice is still lagging. This delay could be attributed to the contradictory paradigms and the conflicting results that have been obtained from experimental models, as well as the presence of inconsistent reports regarding their safety. In this review, we summarize the potential mechanisms underlying the neuroprotective effects of medical gases and discuss possible candidates that could improve the outcomes of brain injury.

Key words: hydrogen; hydrogen sulphide; hyperbaric oxygen; inert gases; nitric oxide; isoflurane; sevoflurane; traumatic brain injury; ischemia/reperfusion; subarachnoid hemorrhage

doi: 10.4103/2045-9912.260649

How to cite this article: Wang YZ, Li TT, Cao HL, Yang WC. Recent advances in the neuroprotective effects of medical gases. Med Gas Res. 2019;9(2):80-87.

Funding: This work was supported by the National Natural Science Foundation of China, No. 81400989 (to WCY).

Introduction

Central nervous system injuries are a leading cause of death and disability worldwide. In China, brain injury is one of the major causes of clinical mortality and long-term disability. With China's economic development, an increase in traffic accidents and brain trauma has been observed over the past few years. Stroke is another health burden in China as it accounts for 80% of deaths and 70% of disability-adjusted life-years lost. Additionally, the growth in the aging population of China has led to an increase in the occurrence of neurodegenerative diseases. Interestingly, brain injuries often share similar underlying pathophysiological mechanisms. Therefore, reducing neural damage through the use of neuroprotective agents will improve the patient prognosis.

Medical gases are increasingly used clinically because of their special physicochemical properties and convenience in use. Medical gases exert unique neuroprotective effects against brain injury. Administration of hyperbaric oxygen (HBO) has been successfully used for the treatment of some neurological disorders. Furthermore, hydrogen (H₂) is emerging as an antioxidant agent with neuroprotective properties. Hypercapnia, induced by a high concentration of carbon dioxide, has been demonstrated to be beneficial in the treatment of ischemic brain injuries. Hydrogen sulphide (H₂S) and nitric oxide (NO), which were once considered toxic, can act as signaling molecules with a promising role in brain protection. In addition, clinical studies have demonstrated that inhaled anesthetics, as well as rare gases, provide a certain degree of neuroprotection. In this review, we searched for neuroprotective studies on common medical gases in the past 5 years, and briefly summarized their application and mechanisms in various neurological diseases, with gas species as a classification criterion (Table 1). It can be seen that the various medical gases reviewed play a protective role in nerve injuries, and the molecular mechanism still has a broad space for exploration. Further, we will discuss the advantages of their use and challenge their wide clinical applications.

Hyperbaric Oxygen

HBO treatment refers to the inhalation of pure oxygen, or a high concentration of oxygen, in a high pressure environment to treat hypoxic conditions. HBO is the main treatment for carbon monoxide poisoning and decompression sickness. Recently, HBO has become an issue of concern for its beneficial effects in the treatment of brain injuries. Chen et al. and Wee et al. previously confirmed that inflammation plays an important role in the pathophysiology of traumatic brain injuries (TBI) in animal models. Following TBI, a lack of interleukin (IL)-10 counters the protective effect of HBO thereby increasing the degree of brain injury. Therefore, this anti-inflammatory cytokine (IL-10) plays a crucial role in mediating the neuroprotective effect of HBO. The immediate inhalation of HBO (2.0 atmosphere absolute (ATA), 1 ATA = 1.013 kPa, 100% O₂) after brain injury decreases apoptosis and reduces the expression of inflammatory mediators.

| Gas Species | Model | Application | Mechanism |
|-------------|-------|-------------|-----------|
| HBO         | TBI   | Treatment   | Neuroprotection |
| H₂S         | Stroke| Protection | Anti-inflammatory |
| NO          | Stroke| Protection | Anti-inflammatory |
| Isoflurane  | Stroke| Protection | Anti-inflammatory |
| Sevoflurane | Stroke| Protection | Anti-inflammatory |

In conclusion, despite the challenge of inconsistent reports regarding the safety and efficacy of medical gases, recent advances in the neuroprotective effects of medical gases have opened new perspectives for clinical applications. Further studies are needed to bridge the gap between experimental and clinical research, and thus improve the outcomes of brain injury.
| Medical gas                  | Condition                          | Mechanism of action | Reference   |
|----------------------------|------------------------------------|---------------------|-------------|
| Hyperbaric oxygen          | Traumatic brain injury             | IL-10, caspases-3, Bcl-2 | Chen et al. |
|                            |                                    | TNF-α, TGF, TGF-β1  |             |
|                            |                                    | NAA/Cr ratio, Cho/Cr ratio |             |
|                            | Middle cerebral artery occlusion   | Cleaved caspase-3   |             |
|                            | Cerebral malaria                   | Indoleamine 2,3-dioxygenase 1, AhR | Bastos et al. |
|                            | Posttraumatic stress disorder      | Glucocorticoid receptor | Lin et al. |
| Hydrogen                   | Ischemia/reperfusion               | Reactive oxygen species | Obsawa et al. |
|                            | Ischemia/reperfusion               | caspase-3, caspase-12 | Cai et al. |
|                            | Alzheimer’s disease                | JNK, NF-κB          | Wang et al. |
|                            | Traumatic brain injury             | Reactive oxygen species | Ji et al. |
|                            |                                    | IL-1β, IL-10, HMGB1 |             |
|                            | Subarachnoid hemorrhage            | NF-xB, NLRP3        | Shao et al. |
|                            | Cognitive impairment               | Estrogen, ERb, BDNF | Hou et al. |
|                            | Ischemia/reperfusion               | 8-OHdG, reactive oxygen species | Nagatani et al. |
| Carbon dioxide             | Hypoxia/ischemia                   | AQP4                | Yang et al. |
|                            | Ischemia/reperfusion               | cyt-c, cleaved caspase-3 | Tao et al. |
|                            |                                    | Bcl-2, Bax          |             |
| Hydrogen sulphide          | Middle cerebral artery occlusion   | AQP4, PKC           | Wei et al.  |
|                            | Subarachnoid hemorrhage            | AQP4, MMP-9         | Cao et al. |
|                            |                                    | IL-1β, CBS, 3MST    | Cui et al. |
|                            |                                    | Akt/ERK, BDNF-CREB  | Li et al.  |
|                            | Intracerebral hemorrhage           | P2X7R/NLRP3         | Zhao et al. |
|                            | Cognitive impairment               | Cleaved caspase-3   | Hu et al.  |
|                            |                                    | GluN2B, NMDAR       | Zhan et al. |
|                            | Traumatic brain injury             | Beclin-1-Vps54      |             |
|                            | Parkinson’s disease                | ROCK2, miR-135a-5p  | Liu et al. |
| Nitric oxide               | Subarachnoid hemorrhage            | Pial arteriole       | Terpolilli et al. |
|                            | Traumatic brain injury             | Resistance vessel, CBF |             |
|                            | Cerebral ischemia                  | Pial venule, arteriole | Terpolilli et al. |
|                            | Ischemia/reperfusion               | CBF                 | Li et al.  |
| Isoflurane                 | Ischemia/reperfusion               | JNK                 | Wang et al. |
|                            |                                   | BMP4/Smad1/5/8      | Yuan et al. |
| Sevoflurane                | Ischemia/reperfusion               | Notch               | Yin et al. |
|                            | Hypoxia/reoxygenation              | VEGF                | Restin et al. |
|                            | Ischemia/reperfusion               | Lysoosomal cathepsin B | Zhu et al. |
|                            | Cerebral ischemia                  | TLR-4/NF-κB         | Hwang et al. |
|                            |                                    | Microglia, macrophage | Dang et al. |
|                            | Hypoxia/ischemia                   | PI3K/Akt-mPTP       | Lai et al. |
|                            | Hemorrhage shock and resuscitation| GRP78, CHOP         | Hu et al.  |
| Helium                     | Hypoxia/ischemia                   | Ang-1, Tie-2, Flt-1 | Li et al.  |
| Argon                      | Hypoxia/ischemia                   | PI3K/Akt-HO-1       | Zhao et al. |
| Subarachnoid hemorrhage    |                                   | HO-1                | Höllig et al. |
cytokines. Moreover, HBO has been found to protect the integrity of the blood-brain barrier (BBB) and improve the patient prognosis. Lin et al. also demonstrated the positive impact of HBO administration on the behavioral and neurochemical outcomes of posttraumatic stress disorder. In mice, the continuous inhalation of HBO immediately after TBI reduces neural loss and increases the activity of astrocytes. Moreover, continuous HBO inhalation has been shown to exert a more significant neuroprotective effect than non-continuous inhalation.

Clinical trials have shown that inhalation of HBO (2.0 ATA, 100% O2) promotes the regeneration of cerebral blood vessels and the reconstruction of nerve fibers after TBI. In healthy volunteers, the inhalation of HBO significantly enhances the cognitive functions and ability to perform cognitive tasks compared to the performance following inhalation of normobaric air. In addition, long-term HBO therapy could improve post-concussion syndrome and post-traumatic stress disorder after moderate brain injury and may significantly reduce posttraumatic anxiety and suicide. Nevertheless, at present, the impact of HBO has been derived from small and uncontrolled studies or single case reports. Therefore, randomized double-blinded clinical trials are required to enable the wide clinical application of HBO.

**HYDROGEN**

H2 gas is chemically stable at room temperature. It has a small molecular weight and strong permeability, which enables its diffusion into the cells. In 1975, hyperbaric H2 therapy was proposed as a possible anticancer agent. However, the selective anti-oxidative effects of H2 were discovered more recently, in 2007. Ohsawa et al. reported that H2 significantly reduces the area of cerebral infarction by neutralizing toxic free radicals. Subsequent research, performed in experimental animals, found that H2 has anti-inflammatory, anti-apoptotic, and antioxidant properties. Additionally, H2 has been shown to have neuroprotective effects in cerebrovascular diseases and neurodegenerative diseases. Takeuchi et al. demonstrated that drinking hydrogen water could reduce the production of reactive oxygen species and inhibit the activation of matrix metalloproteinase-9 in the hippocampus, thereby reducing BBB damage and improving brain function. In a hypoxic-ischemic encephalopathy piglet model, treatment with H2 reduced oxidative stress and improved neural recovery.

Cerebral microvascular endothelial cells play an important role in regulating and maintaining the stability and balance of the brain neurovascular microenvironment. Consuming hydrogen water has been shown to prevent the apoptosis of cerebral microvascular endothelial cells through the down-regulation of the phosphatidylinositol 3-hydroxy kinase/protein kinase B/glycogen synthase kinase 3β pathway, leading to a decrease in the extent of secondary brain injury. Systemic and central nervous system inflammation induces microglial activation, causing neuronal injury. H2 inhibits microglial activation, thus protecting against brain trauma. In a rat model of subarachnoid hemorrhage, injection of H2 saline inhibits the nuclear factor-kappa B pathway and the nucleotide binding and oligomerization domain-like receptor family pyrin domain–containing three inflammatory, which subsequently reduces the systemic inflammatory response and promotes the neurological function, as well as behavioural recovery. Yoshi et al. reported that the observed neuroprotective effect of drinking hydrogen water could be associated with the secretion of ghrelin, a gastric hormone, in the stomach. However, the mechanism of H2 appears to differ between the various experimental models. For instance, H2 inhibits the immuno-inflammatory response by up-regulating the expression of regulatory T cells after cerebral ischemia/reperfusion injury. Activation of inflammatory mediators plays an important role in major depressive disorder. Hydrogen water inhibits the production of IL-1β and reactive oxygen species, reduces the inflammatory reaction, and subsequently decreases the depression behavioural scores. In a model of cerebral infarction, glutamate producesdependent neurotoxicity and increases the intracellular calcium level. The neuroprotective function of hydrogen water, in this case, was found to be mediated through a reduction in glutamate-induced neuronal cell death and inhibition of calcium ion influx. On the other hand, treatment with H2 failed to relieve brain edema or exert a neuroprotective function, although it did decrease the
expression of 8-hydroxy-2'-deoxyguanosine, in a rat model of intracerebral hemorrhage. This result may be attributed to the low H₂ concentration that was used in this study, or to the existence of a more complicated mechanism involving reactive oxygen species in intracerebral hemorrhage.⁷⁶ Therefore, the protective effects of H₂ may differ according to the dosage and/or animal model that are used. Nevertheless, H₂ is safe to the human body at a high concentration and it plays an anti-inflammatory, as well as an antioxidant, role in combating cerebral ischemia/reperfusion injury.¹³ Therefore, the protective effects of H₂ in TBI are dose- and time-dependent. Indeed, we observed that the inhalation of a high H₂ concentration exerts neuroprotective effects against TBI in diabetic mice (unpublished observations). Taken together, these findings indicate that the neuroprotective effect of H₂ must be replicated in clinical studies to enable its future application.

**Carbon Dioxide**

Carbon dioxide is a liposoluble gas that can cross the cell membrane and the BBB.⁷⁷ Therapeutic hypercapnia, through the inhalation of carbon dioxide, has been shown to exert beneficial biological functions.⁷⁸−⁸⁰ The use of hypercapnia in organ protection has been the focus of recent research especially its effect on the brain function.¹⁵,¹⁶ Hypercapnia significantly reduces the infarct size and improves the neuropa protection and memory functions in mice and rats.¹⁵,¹⁶,⁴⁶ More recently, hypercapnia protects rats against subarachnoid hemorrhage.¹⁹ The concentration of NO and inhalation time were positively correlated with its neuroprotective effects.⁵¹ At present, evidence has shown that the neuroprotective impact of H₂S could be mediated through the induction of the Akt-ERK pathway. Rho-associated protein kinase 2 through microRNA-mediated protection of nerve cells.⁸⁸ Future research should focus on uncovering the exact role of H₂S in the central nervous system with the aims of dissecting the signaling pathways involved.

**Nitric Oxide**

Like H₂S, NO has previously been considered to be a toxic chemical substance.⁶⁶ In the 1980s, the vasodilating factor secreted by vascular endothelial cells was identified as NO.⁷⁷ Recent reports have suggested that NO inhalation successfully reduces the size of the necrotic area and brain edema as well as reduces BBB permeability following subarachnoid hemorrhage or TBI.¹⁹,⁴⁹,⁵⁰ Thus, NO may improve neurological function and relieve secondary brain injury.⁴⁹ Additionally, NO inhalation may alleviate the spasm of pia mater arterioles,⁵⁰ improve the neurological score, and reduce the mortality rate in mice.¹⁹ The concentration of NO and inhalation time were positively correlated with its neuroprotective effects.⁵¹ The neuroprotective function of NO is mediated through the improvement of the cerebral blood flow without causing hypertension or other significant side effects.⁵¹ At present, evidence for the neuroprotective impact of NO is based on the results of animal experiments. Clinical studies are required to confirm the role of NO in TBI. Additionally, research studies examining experimental animal models will be instrumental in elucidating the neuroprotective mechanisms of hypercapnia and acidosis before conducting clinical trials.
the mechanism of action of NO as well as the toxicity and side effects of long-term use will influence the future therapeutic applications of NO.

**Volatile Anesthetic Gases**

**Isoflurane**

Isoflurane is a general anesthetic mainly used to start or maintain anesthesia. Following a cerebral ischemic event, microglial activation may induce neural apoptosis in the brain.53,88 Isoflurane has been found to inhibit the activation of microglia through the Notch pathway, therefore, producing a decrease in apoptosis.53 Additionally, Wang et al.20 and Yuan et al.52 demonstrated that isoflurane could alleviate the incidence of brain edema and reduce the area of reperfusion injury by down-regulating the expression of AQP4. Moreover, isoflurane inhalation up-regulates transforming growth factor-beta1 expression and down-regulates phospho-c-Jun N-terminal kinase expression, leading to an improvement in the ischemia/reperfusion injury outcome.20 However, in cases of severe brain injury, long-interval isoflurane inhalation may reverse its previous protective effect and aggravate brain injury.89 Therefore, future studies should focus on optimizing the ideal dose and time-frame for isoflurane inhalation to lay a solid foundation for the widespread application of isoflurane in the treatment of TBI.

**Sevoflurane**

To date, sevoflurane has been considered to be an ideal inhalation anesthetic, owing to its rapid induction and revival.57 In vitro experiments have demonstrated that sevoflurane can down-regulate the expression of vascular endothelial growth factor, maintain the function of the endothelial barrier, and play a key role in injury regulation.54 Cerebral ischemia often leads to the astrocyte activation and the formation of a glial scar.53 In addition, sevoflurane inhalation alleviates reactive astrocytic gelatinization, reduces the effect of glial scar formation, and inhibits the activation and release of lysosomal cathepsin B, which improves the outcome of cerebral ischemia.55 Sevoflurane may also attenuate the inflammatory response.56,88 However, this anesthetic neither relieves inflammation in the brain nor significantly inhibits the activation of microglia or astrocytes.55 Nevertheless, Dang et al.37 demonstrated that the neuroprotective impact of sevoflurane could be attributed to the activation of microglia/macrophage migration and, thus, the promotion of brain repair. Additionally, sevoflurane post-conditioning improves the cognitive performance in rats as well as promoting neural survival and decreasing apoptosis and cellular atrophy through the regulation of the PI3K/Akt pathway.58,90 Conversely, several studies have reported that sevoflurane exhibit neurotoxic effects.21,91-93 Inhalation of 7% sevoflurane in aged rats inhibits the expression of brain-derived neurotrophic factor, aggravates postoperative cognitive dysfunction and impairs the brain function.21 Moreover, sevoflurane-induced nerve injury is correlated with the used concentration.91 Therefore, future research should explore the neuroprotective mechanisms of sevoflurane and optimize the concentration that is selected for research. Nevertheless, the neuroprotective effect of sevoflurane provides unique opportunities for its application by clinical anesthesiologists in cases of TBI.

**Inert Gases**

**Helium**

Helium has a lower solubility in blood than nitrogen and is often mixed with oxygen to provide a breathing gas for divers.84 Angiogenesis is a natural defense mechanism that provides oxygen and nutrient supply to the injured brain.60 Li et al.60 demonstrated that helium exerts its neuroprotective effects by improving the neurovascular niche, as well as increasing the expression of anti-inflammatory cytokines and BNDF. However, Aehling et al.93 did not observe any beneficial effect of helium preconditioning or post-conditioning on neurologic function. However, it did reduce the level of apoptosis in a rat resuscitation model.95 Future studies will improve our understanding of the function of helium in neuroprotection.

**Argon**

The neuroprotective effects of argon have been validated in various brain injury models.60 Argon improves the general condition of rats and reduces mortality by inducing the expression of Heme oxygenase 1.51,62 Compared to the impact of argon alone, the combination of argon and hypothermia therapy significantly increases the expression of Heme oxygenase 1, reduces the infarct size, and provides effective protection against short-term and long-term brain injury.61 Although there are still many uncertainties regarding the effect and mechanism of argon therapy, its neuroprotective role in TBI is worth further exploration.

**Xenon**

Xenon is an ideal anesthetic. However, the widespread clinical application of xenon is hampered by the difficulty of its separation and its scarce availability. Nevertheless, the potential neuroprotective effect of xenon has been the focus of scientific research.97 Xenon alleviates oxidative stress, reduces N-methyl-D-aspartate receptor mediated neurodegeneration and exerts both neurotrophic as well as neuroprotective effects in cholinergic neurons.64,65 Additionally, xenon produces neuroprotection by inhibiting the activation of microglia and reducing the level of hippocampal neural damage.66 In Parkinson’s disease, xenon may protect and nourish dopamine neurons, thus inhibiting the potential damage to dopaminergic neurons and astrocytes.63 However, the feasibility of the widespread clinical application of xenon remains to be explored in future experiments.

**Perspectives**

The debate regarding the neuroprotective role of medical gases is still ongoing. To date, there are significant differences in the observed value of medical gases across different studies. However, the evidence from published studies suggests that each of the medical gases discussed in this review exert different degrees of brain protection in specific nerve injury models. It is worth mentioning that, although these gases have different uses in various types of brain injuries, the mechanisms by which these gases reduce neuronal injury at the intracellular
and intercellular level are similar. The major challenge that faces this field of research is the translation from preclinical to clinical training, i.e., the feasibility of the clinical administration of medical gases and their inclusion in individualized treatment plans. HBO should be considered to be a supportive therapeutic modality in TBI. The use of carbon dioxide in neuroprotective therapy is still at the experimental animal stage and, thus, there is an urgent need for more extensive research to determine its therapeutic value. The lack of precise methodology for the accurate estimation of H₂S and NO endogenous concentrations hinders their clinical use. Volatile anesthetic gases may not be effective as single therapeutic agents. However, their use might be beneficial during neuroprotective surgeries. The clinical administration of inert gases is hampered by high costs and difficulty of their extraction. H₂ is a popular gas with definite roles in disease prevention and treatment and has a high safety margin. These characteristics imply that H₂ may revolutionize the medical field in the future. Future research should aim to clarify the specific mechanisms that underlie the action of H₂. In conclusion, in this review we present recent insights into the therapeutic uses and possible applications of medical gases. Future research will focus on the precise function and molecular mechanism of each medical gas, which will lay a solid foundation for their widespread application in clinical practice.

Author contributions
Conception and literature search: YZW and TTL; drafting: YZW; revision: YZW, TTL, HLC, WCY. All authors read and approved the final version of the paper for publication.

Conflicts of interest
The authors declare no conflicts of interest.

Financial support
This work was supported by the National Natural Science Foundation of China, No. 81400989 (to WCY).

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Received: December 6, 2018
Accepted: April 15, 2019