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 necessany 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

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Introduction

Central nervous system injuries are a leading cause of death and disability worldwide.[1] In China, brain injury is one of the major causes of clinical mortality and long-term disability.[2] With China's economic development, an increase in traffic accidents and brain trauma has been observed over the past few years.[2-4] Stroke is another health burden in China as it accounts for 80% of deaths and 70% of disability-adjusted life-years lost.[5] Additionally, the growth in the aging population of China has led to an increase in the occurrence of neurodegenerative diseases.[6,7] Interestingly, brain injuries often share similar underlying pathophysiological mechanisms.[1] Therefore, reducing neural damage through the use of neuroprotective agents will improve the patient prognosis.[8,9]

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.[10,11] Furthermore, hydrogen (H_2) is emerging as an antioxidant agent with neuroprotective properties.[12-14] Hypercapnia, induced by a high concentration of carbon dioxide, has been demonstrated to be beneficial in the treatment of ischemic brain injuries.[15-17] Hydrogen sulphide (H_2S) and nitric oxide (NO), which were once considered toxic, can act as signaling molecules with a promising role in brain protection.[18,19] In addition, clinical studies have demonstrated that inhaled anesthetics, as well as rare gases, provide a certain degree of neuroprotection.[20,21] 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.[67] HBO is the main treatment for carbon monoxide poisoning and decompression sickness.[68] Recently, HBO has become an issue of concern for its beneficial effects in the treatment of brain injuries.

Chen et al.[22] and Wee et al.[23] 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.[22] 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% O_2) after brain injury decreases apoptosis[25] and reduces the expression of inflammatory

Table 1: Neuroprotective effects of medical gases and the related mechanisms

Medical gas	Condition	Mechanism of action	Reference
Hyperbaric oxygen	Traumatic brain injury	IL-10, caspases-3, Bcl-2	Chen et al.[22]
		TNF-a, TGIF, TGF-β1	Wee et al.[23]
		NAA/Cr ratio, Cho/Cr ratio	Zhang et al.[24]
	Middle cerebral artery occlusion	Cleaved caspase-3	Lu et al.[25]
	Cerebral malaria	Indoleamine 2,3-dioxygenase 1, AhR	Bastos et al.[26]
	Posttraumatic stress disorder	Glucocorticoid receptor	Lin et al.[11]
Hydrogen	Ischemia/reperfusion	Reactive oxygen species	Ohsawa et al.[12]
	Hypoxia/ischemia	caspase-3, caspase-12	Cai et al.[27]
	Alzheimer's disease	JNK, NF-κB	Wang et al.[28]
	Traumatic brain injury	Reactive oxygen species	Ji et al.[29]
		IL-1β, IL-10, HMGB1	Tian et al.[30]
	Subarachnoid hemorrhage	NF-κB, NLRP3	Shao et al.[31]
	Cognitive impairment	Estrogen, ERb, BDNF	Hou et al.[32]
	Ischemia/reperfusion	8-OHdG, reactive oxygen species	Nagatani et al.[33]
		Tregs, miR-21, miR-210	Li et al.[34]
	Intracerebral hemorrhage	Reactive oxygen species	Manaenko et al.[35]
	Spontaneously hypertensive stroke-prone	Reactive oxygen species, MMP-9	Takeuchi et al.[36]
	Brain injury	PI3K/Akt/GSK3β	Chen et al.[37]
	Parkinson's disease	ghrelin	Yoshii et al.[38]
	Major depressive disorder	IL-1β, reactive oxygen species	Zhang et al.[39]
Carbon dioxide	Hypoxia/ischemia	AQP4	Yang et al.[15]
	Ischemia/reperfusion	cyt-c, cleaved caspase-3	Tao et al.[17]
		Bcl-2, Bax	Tao et al.[17]
		AQP-4, caspase-3	Zhou et al.[40]
Hydrogen sulphide	Middle cerebral artery occlusion	AQP4, PKC	Wei et al.[18]
	Subarachnoid hemorrhage	AQP4, MMP-9	Cao et al.[41]
		IL-1β, CBS, 3MST	Cui et al.[42]
		Akt/ERK, BDNF-CREB	Li et al.[43]
	Intracerebral hemorrhage	P2X7R/NLRP3	Zhao et al.[44]
	Cognitive impairment	Cleaved caspase-3	Hu et al.[45]
		GluN2B, NMDAR	Zhan et al.[46]
	Traumatic brain injury	Beclin-1-Vps34	Zhang et al.[47]
	Parkinson's disease	ROCK2, miR-135a-5p	Liu et al.[48]
Nitric oxide	Subarachnoid hemorrhage	Pial arteriole	Terpolilli et al.[19]
	Traumatic brain injury	Resistance vessel, CBF	Terpolilli et al.[49]
	Cerebral ischemia	Pial venule, arteriole	Terpolilli et al.[50]
	Ischemia/reperfusion	CBF	Li et al.[51]
Isoflurane	Ischemia/reperfusion	JNK	Wang et al.[20]
		BMP4/Smad1/5/8	Yuan et al.[52]
	Cerebral ischemia	Notch	Yin et al.[53]
Sevoflurane	Hypoxia/reoxygenation	VEGF	Restin et al.[54]
	Ischemia/reperfusion	Lysosomal cathepsin B	Zhu et al.[55]
	Cerebral ischemia	TLR-4/NF-κB	Hwang et al.[56]
		Microglia, macrophage	Dang et al.[57]
	Hypoxia/ischemia	PI3K/Akt-mPTP	Lai et al.[58]
	Hemorrhage shock and resuscitation	GRP78, CHOP	Hu et al.[59]
Helium	Hypoxia/ischemia	Ang-1, Tie-2, Flt-1	Li et al.[60]
Argon	Hypoxia/ischemia	PI3K/Akt/HO-1	Zhao et al.[61]
	Subarachnoid hemorrhage	HO-1	Höllig et al.[62]

Table 1: Continued

Medical gas	Condition	Mechanism of action	Reference
Xenon	Parkinson's disease	Astrocytes	Lavaur et al.[63]
	Ischemic/anoxic	Cholinergic traits	Lavaur et al.[64]
	Traumatic brain injury	NMDAR, TREK-1	Harris et al.[65]
	Subarachnoid hemorrhage	Microglial	Veldeman et al.[66]

Note: IL-10: Interleukin-10; TNF-a: tumor necrosis factor-a; TGIF: transforming growth interacting factor; TGF-β1: transforming growth factor-beta1; NAA: nonessential amino acid; Cr: creatinine; Cho: cholesterol; AhR: aryl hydrocarbon receptor; JNK: c-Jun N-terminal kinase; NF-κB: nuclear factor-kappa B; IL-1β: interleukin-1β; HMGB1: high mobility group box 1 protein; NLRP3: receptor family pyrin domain-containing 3; ERb: estrogen receptor b; BDNF: brain-derived neurotrophic factor; 8-OHdG: 8-hydroxy-2 deoxyguanosine; miR: microRNA; Tregs: regulatory T cells; MMP-9: matrix metalloproteinase-9; PI3K: phosphatidylinositol 3-hydroxy kinase; Akt: protein kinase B; GSK3β: glycogen synthase kinase 3β; AQP4: aquaporin 4; cyt-c: cytochrome c; PKC: protein kinase C; CBS: cystathionine beta-synthase; 3MST: 3-mercaptopyruvate sulfur transferase; ERK: extracellular regulated protein kinases; CREB: cyclic adenosine monophosphate-response element binding protein; P2X7R: P2X7 receptor; GluN2B: phospho-NMDA receptor 2B; NMDAR: N-methyl-D-aspartate receptor; Vps34: phosphatidylinositol 3-kinase; ROCK2: Rho-associated protein kinase 2; CBF: cerebral blood flow; BMP4: bone morphogenetic protein 4; Smad: mothers against decapentaplegic homolog; VEGF: vascular endothelial growth factor; TLR-4: Toll-like receptor 4; mPTP: mitochondrial permeability transition pore; GRP78: glucose-regulated protein-78; CHOP: C/EBP-homologous protein; Ang-1: angiopoietin-1; Tie-2: tyrosine kinase with immunoglobulin and epidermalgrowth factor homology domains-2; Flt-1: vascular endothelial growth factor receptor 1; HO-1: heme oxygenase 1; TREK-1: TWIK-related K^+ channel 1.

cytokines.[23,24,26] Moreover, HBO has been found to protect the integrity of the blood-brain barrier (BBB) and improve the patient prognosis.[24,69] Lin et al.[11] 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.[10] Moreover, continuous HBO inhalation has been shown to exert a more significant neuroprotective effect than non-continuous inhalation.[10]

Clinical trials have shown that inhalation of HBO (2.0 ATA, 100% O_2) promotes the regeneration of cerebral blood vessels and the reconstruction of nerve fibers after TBI.[9] 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.[70] In addition, long-term HBO therapy could improve post-concussion syndrome and post-traumatic stress disorder after moderate brain injury and may significantly reduce post-traumatic 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

H_2 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 H_2 therapy was proposed as a possible anticancer agent.[71] However, the selective anti-oxidative effects of H_2 were discovered more recently, in 2007.[12] Ohsawa et al.[12] reported that H_2 significantly reduces the area of cerebral infarction by neutralizing toxic free radicals. Subsequent research, performed in experimental animals, found that H_2 has anti-inflammatory,[69,72] anti-apoptotic,[27,73] and antioxidant[28] properties. Additionally, H_2 has been shown to have neuroprotective effects in cerebrovascular diseases and neurodegenerative diseases.[32,33,35] Takeuchi et al.[36] 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 H_2 reduced oxidative stress and improved neural recovery.[74]

Cerebral microvascular endothelial cells play an important role in regulating and maintaining the stability and balance of the brain neurovascular microenvironment.[37] 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 (PI3K/Akt/Gsk3β) pathway, leading to a decrease in the extent of secondary brain injury.[37] Systemic and central nervous system inflammation induces microglial activation, causing neuronal injury. H_2 inhibits microglial activation, thus protecting against brain trauma.[30] In a rat model of subarachnoid hemorrhage, injection of H_2 saline inhibits the nuclear factor-kappa B pathway and the nucleotide binding and oligomerization domain-like receptor family pyrin domain–containing three inflammasomes, which subsequently reduces the systemic inflammatory response and promotes the neurological function, as well as behavioural recovery.[31] Yoshii et al.[38] 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 H_2 appears to differ between the various experimental models. For instance, H_2 inhibits the immuno-inflammatory response by up-regulating the expression of regulatory T cells after cerebral ischemia/reperfusion injury.[34] Activation of inflammatory mediators plays an important role in major depressive disorder.[39] Hydrogen water inhibits the production of IL-1β and reactive oxygen species, reduces the inflammatory reaction, and subsequently decreases the depression behavioural scores.[39] In a model of cerebral infarction, glutamate producesdose-dependent neurocytotoxicity and increases the intracellular calcium level.[75] The neuroprotective function of hydrogen water, in this case, was found to be mediated through a reduction in glutamate-induced neural cell death and inhibition of calcium ion influx.[75] On the other hand, treatment with H_2 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 H_2 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 H_2 may differ according to the dosage and/or animal model that are used. Nevertheless, H_2 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 H_2 in TBI are dose- and time-dependent. Indeed, we observed that the inhalation of a high H_2 concentration exerts neuroprotective effects against TBI in diabetic mice (unpublished observations). Taken together, these findings indicate that the neuroprotective effect of H_2 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 neuropathologic score (neurosensitivity, reflex, and exercise behaviour) in a model of cerebral ischemic injury.[16] In addition, hypercapnia enhances the spatial memory and improves the sensorimotor impairment by regulating apoptosis, through an up-regulation of Bcl-2 and a down-regulation of Bax.[17] In a control case study, controlled transient hypercapnia increased the cerebral blood flow and cerebral oxygen saturation and reduced the possibility of secondary cerebral infarction in patients without adverse reactions.81 In a rat model of global cerebral ischemia/reperfusion, Zhou et al.[40] reported that moderate hypercapnia (partial pressure of carbon dioxide ($PaCO_2$) 80–100 mmHg) had significantly improved neuroprotective effects compared to those of mild hypercapnia ($PaCO_2$ 60–80 mmHg); whereas severe hypercapnia ($PaCO_2$ 100–120 mmHg) increased the severity of brain injury. In agreement with these findings, Yang et al.[15] reported that mild-to-moderate hypercapnia ($PaCO_2$ 60–80 mmHg and $PaO_2 > 50$ mmHg) was the optimal concentration range for neuroprotective effects. At this level, hypercapnia significantly reduces the BBB permeability as well as the brain water content, the expression of Aquaporin-4 (AQP4) and neural apoptosis.[15] Conversely, hypercapnia in combination with lower oxygen pressure ($PaO_2 < 50$ mmHg) may aggravate BBB destruction and edema due to cerebral ischemia/hypoxia. Therefore, the protective effect of carbon dioxide in the brain is determined by the degree of hypercapnia as well as the partial pressure of oxygen.[15] In our experience, we have confirmed that hypercapnia (3 hours with $PaCO_2$ levels of 80–100 mmHg) reduces brain edema, improves the BBB function, reduces the lesion volume, and improves the neurological outcome in a rat model of fluid percussion injury (unpublished observations). Taken together, these results suggest that there is a potential neuroprotective role for "therapeutic hypercapnia" after brain injury. However, confirming these results through the use of experimental animal models will be instrumental in elucidating the neuroprotective mechanisms of hypercapnia and acidosis before conducting clinical trials.

Hydrogen Sulphide

Hydrogen sulphide (H_2S), an endogenous gaseous signalling conduction factor, was considered to be a toxic substance for quite a long period of time. However, recent studies have confirmed that low doses of H_2S play an important role in the functioning of normal physiological processes.[82-84] In fact, H_2S was found to be widely involved in physiological and pathophysiological processes in the brain as well as the peripheral tissues.[82] Following brain injury accompanied with brain edema, the expression of AQP4 increases remarkably.[18,41] Accumulating evidence has shown that the neuroprotective impact of H_2S is mediated by its ability to increase the expression of protein kinase C and decrease the expression of matrix metalloprotein-9 through the inhibition of AQP4 expression, which in turn leads to the suppression of glial cell activation and the release of pro-inflammatory factors.[18,41,44] In rats, H_2S relieves cerebral vasospasm, protects neurons, preserves endothelial function, reduces cerebral edema, and inhibits apoptosis as well as the inflammatory response.[42,44] Additionally, Zhang et al.[47] demonstrated that the administration of H_2S attenuates apoptosis, inhibits the activation of autophagy and improves motor function following TBI. H_2S could also improve the learning and cognitive ability as well as preserving the memory functions after brain injury.[46] Taken together, these results indicate that H_2S can improve the sequelae of brain injury, including long-term disability.[43,85] Li et al.[43] suggested that the neuroprotective impact of H_2S could be mediated through the induction of the Akt-ERK pathway. Rho-associated protein kinase 2 is a key factor that promotes neurodegeneration in Parkinson's disease.[48] H_2S could reduce the expression of Rho-associated protein kinase 2 through microRNA-mediated protection of nerve cells.[48] Future research should focus on uncovering the exact role of H_2S in the central nervous system with the aims of dissecting the signaling pathways involved.

Nitric Oxide

Like H_2S, NO has previously been considered to be a toxic chemical substance.[86] In the 1980s, the vasodilating factor secreted by vascular endothelial cells was identified as NO.[87] 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] 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 hypotension 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

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 anaesthetic, owing to its rapid induction and revival.[55] *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.[55] 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.[88] Nevertheless, Dang et al.[57] 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.[94] 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.[95] did not observe any beneficial effect of helium preconditioning or post-conditioning on neurological 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.[96] Argon improves the general condition of rats and reduces mortality by inducing the expression of Heme oxygenase 1.[61,62] 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 H_2S 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. H_2 is a popular gas with definite roles in disease prevention and treatment and has a high safety margin. These characteristics imply that H_2 may revolutionize the medical field in the future. Future research should aim to clarify the specific mechanisms that underlie the action of H_2. 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.

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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
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