Neuroprotective effect of helium after neonatal hypoxic ischemia: a narrative review

Ru-Ming Deng[1], Hai-Ying Li[1], Xiang Li[1], Hai-Tao Shen[1], De-Gang Wu[2,*], Zhong Wang[1,*], Gang Chen[1]
1 Department of Neurosurgery & Brain and Nerve Research Laboratory, the First Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China
2 Department of Neurosurgery, Yijishan Hospital of Wan-nan Medical College, Wuhu, Anhui Province, China

*Correspondence to: De-Gang Wu, MD, 20184132150@stu.suda.edu.cn; Zhong Wang, MD wangzhong761@163.com.
orcid: 0000-0002-7342-0845 (Zhong Wang); 0000-0002-2816-9305 (De-Gang Wu)

Abstract

Neonatal hypoxic ischemia is one of the leading causes of permanent morbidity and mortality in newborns, which is caused by difficulty in supplying blood and oxygen to brain tissue and is often associated with epilepsy, cerebral palsy, death, short-term or long-term neurological and cognitive impairment. In recent years, the clinical therapeutic effects of noble gases have been gradually discovered and recognized. Numerous studies have shown that noble gases have unique neuroprotective effects to restore damaged nerve and relieve symptoms in patients. Although research on the neuroprotective mechanisms of xenon and argon has yielded a lot of results, studies on helium have stalled. Helium is a colorless, odorless, monoatomic inert gas. The helium has no hemodynamic or neurocognitive side effects and can be used as an ideal pre-adaptor for future clinical applications. In recent years, studies have shown that heliox (a mixture of helium and oxygen) pretreatment can protect the heart, brain, liver and intestine from damage in several animal models, where a variety of signaling pathways have been proved to be involved. There are numerous studies on it even though the mechanism of helium for protecting newborns has not been fully elucidated. It is urgent to find an effective treatment due to the high death rate and disability rate of neonatal hypoxic ischemia. It is believed that helium will be approved safely and effectively for clinical use in the near future.

Key words: cerebral infarction area; heliox; helium; helium preconditioning; hypoxic ischemia; inflammation; middle cerebral artery obstruction; neuroprotective

doi: 10.4103/2045-9912.314332
How to cite this article: Deng RM, Li HY, Li X, Shen HT, Wu DG, Wang Z, Chen G. Neuroprotective effect of helium after neonatal hypoxic ischemia: a narrative review. Med Gas Res. 2021;11(3):121-123.

Introduction

Neonatal hypoxic ischemia (HI) is the most important cause of irreversible nerve injury and death in newborns.[1,2] The incidence of this disease affects 4 of 1000 full-term infants.[3] Newborns who survive develop varying degrees of neurological defects, from mild cognitive impairment to severe cerebral palsy.[4] A large number of newborn babies are under great health threat of this disease. The pathogenesis of HI is so complexed that it has not been completely illustrated. So far, existing studies have shown that the pathogenesis of HI is caused by multiple mechanisms. Firstly, innate immune response plays an important role in mediating the injury of acute neonatal hypoxic ischemic encephalopathy. Mitochondrial dysfunction is characterized by increased mitochondrial swelling and permeability, producing a large number of reactive oxygen species, lead to oxidative stress and cell death.[5,6] Secondly, the activation and proliferation of astrocytes also played a key role.[7] After HI, astrocytes are activated and proliferated, after then transformed into glial fibrillary acidic protein, which is highly expressed in the damaged area and forms glial scar, leading to long-term damage of the nervous system and cognitive dysfunction. Although a lot of studies have been conducted to investigate treatment strategies of HI, including therapeutic hypothermia, anticonvulsant, melatonin and stem cells,[8] no effective treatment has been approved in existing studies.

Chemical and Physical Characteristics of Helium

Helium is a kind of colorless, odorless, non-toxic inert gas and has no side effects related to hemodynamics and neurological function,[9] so that it can be considered for clinical treatment. Originally heliox (a mixture of oxygen and helium) was used to treat patients with airway disease, especially those with chronic obstructive pulmonary disease and asthma.[10,11] In recent years, with the development of modern medical research, heliox pretreatment has been proved to protect the heart,[12] brain, liver,[13] intestinal tract[14] and a variety of signaling pathways have been proved to be involved in this process.

Neuroprotective Effects of Helium

There are already evidences showed that helium-preconditioning (He-PC) can reduce the damage caused by cerebral ischemia.[15] The biological effects of gases have been considered to be direct or indirect effects on cytoplasmic and membrane-bound (specific) proteins. However, there are few studies on the effects of helium on the brain. Therefore, this paper comprehensively describes the existing studies on the protective effects of helium on the brain.

Helium-Preconditioning Reduces Cerebral Infarction Area

Helium was proposed in the 1930s as a treatment gas, but specific basic research is relatively limited. It is usually used in the form of heliox, which is a kind of mixed gas that is composed

by 70% helium and 30% oxygen.[16] A study has shown that inhalation of heliox at 24 hours after middle cerebral artery obstruction can effectively improve neurological function and reduce the size of infarction.[17] In a study of HI in newborn rats, it can be found that He-PC has a neuro-protective effect, which is manifested as decreased infarction area, increased expression of antioxidant enzyme, decreased apoptotic cells, improved neurological function and decreased brain atrophy. And this neural protection function that may be associated with nitric oxide (NO), research has shown that He-PC can induce the production of NO in the brain, reduces cerebral infarction area, increases nuclear factor E2-related factor 2 antioxidant enzyme expression and DNA binding activity, reduces the number of apoptotic cells, and improves nerve function and brain atrophy. Treating with non-selective NO synthetase inhibitors before He-PC, Helium neural protection will be significantly reduced, which showed NO play a crucial role in the brain protection of helium, and the other experimental results show that the Nω-nitro-L-arginine methyl ester did not reduce the proportion of infarction or improve nerve function.[18] Therefore, we speculated that the decreased protective effect of He-PC might be related to the inhibition of NO.

Helium-Preconditioning Induces Tolerance to Early or Late Cerebral Ischemia Reperfusion

Most noble gases have anesthetic effects, but helium does not.[19,20] So far decades it was thought that helium had no pharmacological effect, but was a kind of drug. Helium has a very low blood-gas partition coefficient and is practically insoluble in blood at 1 atmospheric pressure.[21] Both He-PC and Xenon-preconditioning can induce tolerance to early or late cerebral ischemia reperfusion. The mechanisms are: pro-survival signaling kinases are activated and mitochondrial permeability transition is suppressed,[22] the blocking of glycogen synthase kinase,[23] induction of endothelial NO synthase synthesis,[24] in addition, activation of morphine receptors[25] in early preconditioning and activation of cyclooxygenase-2 in late preconditioning.[26] These mechanisms may have something to do with He-PC protecting the brain. In addition, we hypothesized that the reperfusion injury signal kinase pathway and opioid receptor-mediated mechanisms may also be involved in He-PC-induced neuroprotection.

Helium-Preconditioning Alleviates Inflammation Response

Neonatal hypoxic ischemic disease is a devastating disease that can lead to brain damage and neurodevelopmental defects.[27,28] Currently, there are few therapeutic methods to improve neonatal neurodevelopment, so it is urgent to find intervention measures to reduce perinatal HI. In recent years, the protect role of He-PC in different organs has been verified in the *in vivo* or *in vitro* experiments, as mentioned earlier, He-PC can improve nerve behavior after brain injury of, in addition, we also found that He-PC can reduce proinflammatory factor (interleukin-1β, tumor necrosis factor-α), and increase the release of inflammatory factor (interleukin-10), as well as stimulate growth/neurotrophic factors (brain-derived neurotrophic factor and nerve growth factor).[18] Result suggests that the neuroprotective effect of He-PC may be related to the improvement of cerebrovascular ecological environment.[10] Angiogenesis is a defense mechanism in the brain that helps deliver nutrients and oxygen to repair damaged brain tissue,[29] and also associated with nerve repair.[30] However, the current limitation is that the specific mechanism of angiogenesis after He-PC has not been further investigated. The mechanism of helium-induced neuroprotection is unclear. First, a pro-survival protein theory suggests that the neuroprotection of helium is mediated by the activation of a series of pro-survival proteins.[31] Second, helium's high thermal conductivity leads to a lower body temperature when the body is buried in helium, which may lead to a reduced metabolism and energy expenditure.[32] The mechanism of helium-induced organ protection remains unclear. The neuroprotective mechanism provided by noble gases may be the result of up-regulation of genes and synthesis of Bcl-2 and Bcl-xl. Direct molecular targets for inert gases are poorly understood, especially because these drugs may affect both intracellular and extracellular effectors. As a preconditioning agent, helium reduces infarct area by activating pre-survival kinases[33] and mitochondrial adenosine-5-triphosphate regulated potassium channels and calcium-sensitive potassium channels,[22] ultimately inhibiting the opening of mitochondrial permeability transition pores. Although helium has morphological and behavioral protective effects on moderate hypoxic ischemic injury, it has no protective effects on severe hypoxic ischemic injury and has adverse effects on physiological development Table 1.

Future Directions

HI is an extremely harmful disease to the newborns, which has brought heavy health disorders to children all over the world. In recent years, although researches on protective noble gases emerge endlessly, little is reported on the neuroprotective effect of helium. Helium has certain clinical value as a noble gas with organic protection properties, and we believe that in the near

Table 1: The neuroprotective effects of helium

	Experimental subject	Conclusion
Neonatal cerebral hypoxic ischemia	Rat	Helium preconditioning reduces infarct area, protects neurons and reduces nerve defects in rats at the early stage of hypoxic-ischemic injury
Traumatic brain injury	Mouse	Helium can effectively reduce cell death after injury.
Middle cerebral artery obstruction	Rat	Inhaling the mixture gas of helium and oxygen can reduce the infarct area and effectively reduce the neurological deficit
Oxygen-glucose deprivation	Neuron	Compared with the nitrogen group, the cell damage was more severe in the helium group during and after hypoxia

future, helium gas will be widely used for clinical treatment and healthy care of the newborn.

Author contributions
Manuscript writing: RMD, HYL; revision: XL, HTS; drafting: DGW, ZW and GC. All the authors read and approved the final version of the manuscript for publication.
Conflicts of interest
The authors have no conflicts of interests to declare.
Financial support
None.

References

1. Mirza MA, Ritzel R, Xu Y, McCullough LD, Liu F. Sexually dimorphic outcomes and inflammatory responses in hypoxic-ischemic encephalopathy. *J Neuroinflammation.* 2015;12:32.
2. Chen Z, Hu Y, Lu R, Ge M, Zhang L. MicroRNA-374a-5p inhibits neuroinflammation in neonatal hypoxic-ischemic encephalopathy via regulating NLRP3 inflammasome targeted Smad6. *Life Sci.* 2020;252:117664.
3. Gamdzyk M, Doycheva DM, Araujo C, et al. cGAS/STING pathway activation contributes to delayed neurodegeneration in neonatal hypoxia-ischemia rat model: possible involvement of LINE-1. *Mol Neurobiol.* 2020;57:2600-2619.
4. Odorcyk FK, Duran-Carabali LE, Rocha DS, et al. Differential glucose and beta-hydroxybutyrate metabolism confers an intrinsic neuroprotection to the immature brain in a rat model of neonatal hypoxia ischemia. *Exp Neurol.* 2020;330:113317.
5. Jiang H, Fang J, Xing J, et al. Tilianin mediates neuroprotection against ischemic injury by attenuating CaMKII-dependent mitochondrion-mediated apoptosis and MAPK/NF-κB signaling. *Life Sci.* 2019;216:233-245.
6. Silachev DN, Plotnikov EY, Pevzner IB, et al. Neuroprotective effects of mitochondria-targeted plastoquinone in a rat model of neonatal hypoxic ischemic brain injury. *Molecules.* 2018;23:1871.
7. Liu F, McCullough LD. Inflammatory responses in hypoxic ischemic encephalopathy. Acta Pharmacol Sin. 2013;34:1121-1130.
8. Bennet L, Tan S, Van den Heuij L, et al. Cell therapy for neonatal hypoxia-ischemia and cerebral palsy. *Ann Neurol.* 2012;71:589-600.
9. Yamamura E, Matsuda K, Kikuchi H, et al. A case of suicide by helium gas. *Chudoku Kenkyu.* 2016;29:355-359.
10. Li Y, Zhang P, Liu Y, Liu W, Yin N. Helium preconditioning protects the brain against hypoxia/ischemia injury via improving the neurovascular niche in a neonatal rat model. *Behav Brain Res.* 2016;314:165-172.
11. Ding YP, Zhang JY, Feng DX, Kong Y, Xu Z, Chen G. Advances in molecular mechanism of cardioprotection induced by helium. *Med Gas Res*. 2017;7:124-132.
12. Oei GT, Huhn R, Heinen A, et al. Helium-induced cardioprotection of healthy and hypertensive rat myocardium in vivo. *Eur J Pharmacol.* 2012;684:125-131.
13. Zhang R, Zhang L, Manaenko A, Ye Z, Liu W, Sun X. Helium preconditioning protects mouse liver against ischemia and reperfusion injury through the PI3K/Akt pathway. *J Hepatol.* 2014;61:1048-1055.
14. Du L, Zhang R, Luo T, Nie M, Bi J. Effects of helium preconditioning on intestinal ischemia and reperfusion injury in rats. *Shock.* 2015;44:365-370.
15. Liu Y, Xue F, Liu G, et al. Helium preconditioning attenuates hypoxia/ischemia-induced injury in the developing brain. *Brain Res.* 2011;1376:122-129.
16. Moraa I, Sturman N, McGuire TM, van Driel ML. Heliox for croup in children. *Cochrane Database Syst Rev.* 2018;10:CD006822.
17. Pan Y, Zhang H, VanDeripe DR, Cruz-Flores S, Panneton WM. Heliox and oxygen reduce infarct volume in a rat model of focal ischemia. *Exp Neurol.* 2007;205:587-590.
18. Li Y, Liu K, Kang ZM, Sun XJ, Liu WW, Mao YF. Helium preconditioning protects against neonatal hypoxia-ischemia via nitric oxide mediated up-regulation of antioxidases in a rat model. *Behav Brain Res.* 2016;300:31-37.
19. Lango T, Morland T, Brubakk AO. Diffusion coefficients and solubility coefficients for gases in biological fluids and tissues: a review. *Undersea Hyperb Med*. 1996;23:247-272.
20. Höllig A, Rossaint R, Coburn M. Is helium eclipsing current thromboembolic stroke therapy? *Crit Care Med.* 2016;44:1257-1258.
21. Ogura K, Takahashi W, Morita Y. A case of hypoxic encephalopathy induced by the inhalation of helium that resolved with no neurological complications: a case report and analysis of similar cases. *Acute Med Surg*. 2019;6:308-311.
22. Heinen A, Huhn R, Smeele KM, et al. Helium-induced preconditioning in young and old rat heart: impact of mitochondrial Ca(2+) -sensitive potassium channel activation. *Anesthesiology.* 2008;109:830-836.
23. Pagel PS, Krolikowski JG, Pratt PF, Jr., et al. Inhibition of glycogen synthase kinase or the apoptotic protein p53 lowers the threshold of helium cardioprotection in vivo: the role of mitochondrial permeability transition. *Anesth Analg*. 2008;107:769-775.
24. Pagel PS, Krolikowski JG, Pratt PF, Jr., et al. The mechanism of helium-induced preconditioning: a direct role for nitric oxide in rabbits. *Anesth Analg.* 2008;107:762-768.
25. Pagel PS, Krolikowski JG, Amour J, Warltier DC, Weihrauch D. Morphine reduces the threshold of helium preconditioning against myocardial infarction: the role of opioid receptors in rabbits. J *Cardiothorac Vasc Anesth.* 2009;23:619-624.
26. Huhn R, Heinen A, Weber NC, et al. Helium-induced late preconditioning in the rat heart in vivo. *Br J Anaesth.* 2009;102:614-619.
27. Huang J, Lu W, Doycheva DM, et al. IRE1α inhibition attenuates neuronal pyroptosis via miR-125/NLRP1 pathway in a neonatal hypoxic-ischemic encephalopathy rat model. *J Neuroinflammation*. 2020;17:152.
28. Deng K, Li Y, Xiao M, et al. Lycium ruthenicum Murr polysaccharide protects cortical neurons against oxygen-glucose deprivation/reperfusion in neonatal hypoxic-ischemic encephalopathy. *Int J Biol Macromol.* 2020;158:562-568.
29. Beck H, Plate KH. Angiogenesis after cerebral ischemia. *Acta Neuropathol.* 2009;117:481-496.
30. Ruan L, Wang B, ZhuGe Q, Jin K. Coupling of neurogenesis and angiogenesis after ischemic stroke. *Brain Res.* 2015;1623:166-173.
31. Zhuang L, Yang T, Zhao H, et al. The protective profile of argon, helium, and xenon in a model of neonatal asphyxia in rats. *Crit Care Med.* 2012;40:1724-1730.
32. Singer D. Why 37 degrees C? Evolutionary fundamentals of thermoregulation. *Anaesthesist.* 2007;56:899-902, 904-896.
33. Pagel PS, Krolikowski JG, Pratt PF Jr, et al. Reactive oxygen species and mitochondrial adenosine triphosphate-regulated potassium channels mediate helium-induced preconditioning against myocardial infarction in vivo. *J Cardiothorac Vasc Anesth.* 2008;22:554-559.

Date of submission: March 13, 2020
Date of decision: March 24, 2020
Date of acceptance: April 6, 2020
Date of web publication: April 27, 2021