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

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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 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
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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 no side effects related to hemodynamics and neurological function,9 so that it can be considered for clinical treatment. Originally 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.

NEUROPROTECTIVE EFFECTS OF HELIUM

There are already evidences showed that helium-preconditioning (He-PC) can reduce the damage caused by cerebral ischemia.10 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...
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 pores are 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 Induces Tolerance to Early or Late Cerebral Ischemia Reperfusion**

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 protective 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).\(^29\) Result suggests that the neuroprotective effect of He-PC may be related to the improvement of cerebrovascular ecological environment.\(^30\) 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.

### 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 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 future, we will bring more clinical research value and clinical application value of helium into our life.
future, helium gas will be widely used for clinical treatment and healthy care of the newborn.

**Author contributions**

Writing manuscript: RMD, HYL; revision: XL, HTS; drafting: DGW, ZW and GC. All the authors read and approved the final version of the manuscript for publication.

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The authors have no conflicts of interests to declare.

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