

Hyperoxia preconditioning: the next frontier in neurology?

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Oxygen is indispensable for all aerobic organisms and has become one of the most widely used therapeutic agents. Currently, oxygen not only is applied in the treatment of diseases, but becomes a modality for the prevention of some diseases. Hyperoxia preconditioning with normobaric or hyperbaric oxygen has been found to be protective in some diseases in several animal models and clinical trials. Currently, investigators pay increasing attention to the application of hyperoxia preconditioning in the prevention of common neurological diseases, and encouraging effectiveness has been achieved. In the present short review, we briefly described the development, application and mechanisms of hyperoxia preconditioning in the neurology, and the issues in future application of hyperoxia preconditioning were also proposed.

Keywords: Hyperoxia preconditioning, Antioxidation, Apoptosis, Autophagy, Hypoxia inducible factor

Introduction

Oxygen is indispensable for all aerobic organisms. To date, oxygen has been one of the most widely used therapeutic agents. In the true sense of the word, it is a drug with specific biochemical and physiologic functions, a distinct range of effective doses, and well-defined adverse effects at high doses.¹

In almost all diseases resulting from tissue hypoxia, administration of oxygen in either normobaric or hyperbaric environment is feasible. Actually, oxygen has been applied in the treatment of a variety of diseases in clinical practice although the first application of oxygen as a therapeutic strategy is not known.² A critical mechanism of oxygen treatment is attributed to its ability to increase the oxygen content in the blood and subsequent elevation of oxygen supply to hypoxic tissues. Of course, the beneficial effects of oxygen treatment are exerted via numerous mechanisms including the improvements of hemodynamics, energy metabolism, inflammation, delayed cell death, vascular permeability, etc.³

With the progression of medicine, disease prevention is introduced. Generally, prevention includes a wide range of activities, known as 'interventions' and can be grouped into three categories. Primary prevention is to protect healthy people from developing a

disease or experiencing an injury in the first place; secondary prevention is usually done after an illness or serious risk factors have already been diagnosed; tertiary prevention focuses on helping people manage complicated, long-term health problems aiming to prevent further physical deterioration and maximize quality of life.⁴ Primary prevention is preferred for the majority of subjects and can be achieved in a variety of ways, such as preventing environmental exposures, improving human resistance to diseases, or education to diminish risk-taking behaviors. Of course, prevention of detrimental consequence of surgery or other treatments has also been investigated.⁵

To date, preconditioning has been introduced as a strategy for the prevention of diseases or alleviation of disease severity. Preconditioning is a process by which an organism's exposure to a stress/stimulus allows it be more resilient against subsequent fatal stimulus. Currently, a large number of strategies have been developed for preconditioning such as lipopolysaccharide,⁶ heat,⁷ seizure,⁸ hypoxia,⁹ and hyperoxia [especially hyperbaric oxygen (HBO)].^{10,11} In this review, we described the mechanisms and application of hyperoxia preconditioning in neurology and its potential mechanisms.

Development of Preconditioning

In 1964, Dahl and Balfour¹² found that rats subjected to a brief anoxia could survive 90 seconds in a second

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anoxia, compared to a 60-second survival time of control animals. In this study, they speculated that energy metabolism played an important role in prolonging the survival time. This effect was later confirmed in adult brain slices with pre-exposure to a short (5 minutes) anoxic episode which could recover from a subsequent, longer anoxic insult.¹³ In 1982, Geft *et al.*¹⁴ introduced brief periodic coronary occlusions up to 18 times by inflating and deflating the balloon for periods of 15, 10 or 5 minutes, followed by 15-minute periods of reperfusion. Their findings suggested that intermittent reperfusion had a beneficial effect and could prevent necrosis, even when total occlusion time exceeded 200 minutes. It was not until 1986 that Murry *et al.*¹⁵ proposed the concept of preconditioning and confirmed the protective effects of ischemia preconditioning on myocardial ischemia (four cycles of 5 minutes occlusion/5 minutes reperfusion). In a landmark paper of Kitagawa *et al.*,¹⁶ they documented the ability of brief bilateral carotid occlusion to protect gerbil hippocampal CA1 pyramidal neurons from more prolonged global ischemia, and these authors coined the term 'ischemic tolerance' to describe this phenomenon. To date, the protective effects of ischemic preconditioning have been confirmed in numerous organs including the heart,¹⁷ brain,¹⁸ lung,¹⁹ kidney,²⁰ and liver.²¹ Furthermore, not only early ischemia preconditioning, but delayed ischemia preconditioning,^{21,22} and not only 'in situ' preconditioning but remote ischemia preconditioning²³ have been investigated in these organs. Available evidence consistently supports the organ-protective effects of ischemia preconditioning.

Development of Hyperoxia Preconditioning

In 1986, Martin and Howard²⁴ found pretreatment with endotoxin and hyperoxia ($98 \pm 2\%$ oxygen for 48 hours) could reduce the inflammatory response in paraquat-induced neutrophil alveolitis. Four years later, D'Brot and Ahmed²⁵ indicated that prior exposure to alveolar hyperoxia could prevent hypoxia-induced enhancement of bronchial reactivity to carbachol and histamine, in which a cyclooxygenase (COX) dependent mechanism was proposed. In 1996, a Japanese group demonstrated that repeated HBO (100% oxygen at 2 atmosphere absolute [ATA] for 1 hour each) could increase the tolerance of the brain against ischemic neuronal damage, in which the induction of heat shock protein (HSP) 72 played an important role.²⁶ Since then, the protective effects of hyperoxia preconditioning, especially the HBO preconditioning, have been investigated in various animal models.

Compared with hypoxic preconditioning, hyperoxia preconditioning (HBO and normobaric hyperoxia) is more safe and available in clinical practice.

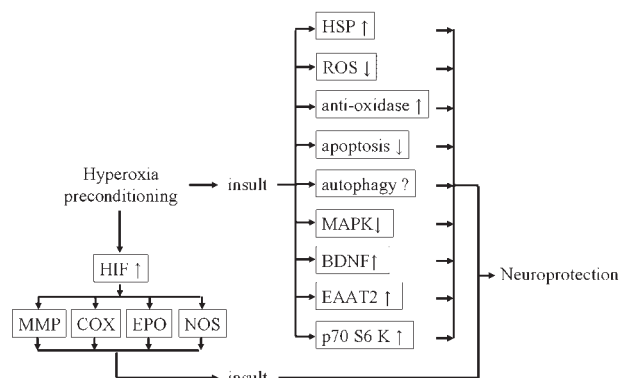


Figure 1 Potential mechanisms underlying the protective effects of hyperoxia preconditioning. Hyperoxia preconditioning may induce the HIF expression or activate HIF, which then induce the expression of its down stream genes. This is found to attribute to the neuroprotection against subsequent insult. In addition, following insult, the levels of HSP, antioxidants, brain-derived neurotrophic factor (BDNF), EAAT2, and p70 S6 K are increased but the levels of ROS, apoptosis and mitogen activated protein kinase (MAPK) are reduced in the presence of hyperoxia preconditioning when compared with those under the conditions without hyperoxia preconditioning. However, the available findings fail to confirm the neuroprotection of autophagy following hyperoxia preconditioning.

To date, the neuroprotective effects of hyperoxia have been investigated in various models, including global ischemia,²⁷ forebrain ischemia,²⁸ surgical brain injury,²⁹ ischemia-reperfusion injury,³⁰ neonatal hypoxia-ischemia,³¹ intracerebral hemorrhage,³² and spinal cord ischemia.³³ A majority of these studies are conducted in animals, and clinical implications of hyperoxia preconditioning in human neurological disease are required to be further studied.

Mechanisms Underlying the Neuroprotective Effects of Hyperoxia Preconditioning

To date, numerous studies have been conducted to investigate the mechanisms underlying the neuroprotective effects of hyperoxia preconditioning and some potential mechanisms have been identified in different animal models and clinical trials (Fig. 1). Although some mechanisms were discovered in distinct studies, there might be crosstalk among these mechanisms.

Induction of heat shock proteins

Several studies have suggested that the protective effects of hyperbaric oxygen preconditioning are attributed to the induction of HSPs.^{26,32} HSPs are a class of functionally related proteins of which the expressions are increased when cells are exposed to elevated temperatures or other stresses. HSPs function as intra-cellular chaperones for other proteins and play an important role in the protein-protein interactions such as folding and assisting in the establishment of proper protein conformation (shape) and prevention of unwanted protein aggregation. By helping to stabilize partially unfolded proteins, HSPs aid in

transporting proteins across membranes within the cells.³⁴ Some members of HSP family are expressed at low to moderate levels in all organisms because of their essential role in protein maintenance. The relationship between decreased HSP expression and hypoxia related neurological diseases has been confirmed in a variety of studies.³⁵ There is evidence showing that HSP70 overexpression can reduce ischemic injury and protect both neurons and glial cells, which may be attributed to the prevention of protein aggregation, refolding of partially denatured proteins, reduction of inflammatory responses, and inhibition of cell death pathways.³⁵ However, Vince *et al.*³⁶ recently noted that the benefits of HBO preconditioning might not be due to the inducement of HSP expression in circulating blood cells, but might involve an enhancement of stress response. In this study, HBO was performed for 1 hour at 2.8 ATA in healthy male volunteers, which consisted of 20-minute oxygen followed by 5-minute air, by two cycles. We speculate that hyperoxia exposure with this regimen seems not potent enough to induce the stress response.

Induction of reactive oxygen species and antioxidant expression

Exposure to HBO can generate oxidative stress,³⁷ which has been confirmed in numerous studies. The reactive oxygen species (ROS) are the main components in the oxidative stress. Studies have demonstrated that ROS of appropriate amount can act as signal molecules or messengers playing important roles in physiological and pathophysiological processes.³⁸ Mild oxidative stress (ROS) can subsequently activate antioxidants (increase in activities and/or expressions) to combat with ROS-induced damage to the DNA, proteins and lipids conferring protective effects. Although excessive oxidative stress can cause damage to tissues, previous findings have shown that preconditioning with mild hyperoxia can induce the expressions of some antioxidants (such as catalase, superoxide dismutase and glutathione peroxidase) producing an increased antioxidant response,³⁹⁻⁴² which may exert protective effect on subsequent lethal attack.

Hyperoxia preconditioning can induce the expression of heme oxygenase-1 (HO-1) contributing to its neuroprotection.³² Although HO-1 is not an antioxidant, its antioxidant effects arise from its capacity to increase antioxidants⁴³ and to degrade heme, as well as from the elaboration of biliverdin and bilirubin, which have potent antioxidant properties.⁴⁴ The carbon monoxide (CO), a product of HO-1, also has an antiapoptotic effect and can improve the endothelial function.⁴⁵ Therefore, hyperoxia preconditioning induced HO-1 expression represents an important mechanism of its neuroprotection.

Induction of hypoxia-inducible factor

Intermittent exposures to hyperoxia may produce a temporary 'hypoxic environment' between two hyperoxia exposures which may induce the expression and/or activity of a key oxygen sensor known as hypoxia-inducible factor (HIF).^{46,47} Under normoxic condition, the alpha subunits of HIF are hydroxylated at proline residues in the presence of HIF prolyl-hydroxylases, allowing their recognition and ubiquitination by the VHL E3 ubiquitin ligase, which labels them for rapid degradation by the proteasome.⁴⁸ Under hypoxic conditions, the activity of HIF prolyl-hydroxylase is inhibited because it utilizes oxygen as a cosubstrate. At this time, HIF-1 can upregulate the expression of several genes to promote survival under low-oxygen conditions.⁴⁹ The HIF-1 down-stream genes include vascular endothelial growth factor gene,⁵⁰ COX-2 gene,^{51,52} erythropoietin gene,⁴⁷ nitric oxide synthase gene⁵³ and matrix metalloproteinase gene.²⁷ The neuroprotective effect of HIF-1 and its down-stream genes has been confirmed in a series of studies.⁵⁴⁻⁵⁶

Moreover, hyperoxia preconditioning can suppress the activity of p38 MAPK^{28,57,58} but induce the expression of BDNF⁵⁷ which was also shown to induce the HIF-1 expression.⁵⁹ In addition, the neuroprotective effects of MAPK inhibition alone⁶⁰ and BDNF⁶¹ alone have been reported.

Of note, two facets of HIF-1 (prodeath or prosurvival) have been proposed⁶² in which mild increase in HIF-1 is neuroprotective via inducing its down-stream genes. A caveat is that not all consequences of HIF activation are neuroprotective. For example, the expressions of matrix metalloproteinase²⁷, nitric oxide synthase⁵³ and COX-2 (not published) are increased following HBO preconditioning before subsequent insult, and all have been found to be detrimental to hypoxic insult in the early stage.⁶³⁻⁶⁵ One of the explanations for the neuroprotective effect of increased expressions of these proteins might be due to the exhaustion of detrimental response before insult. However, more studies are required to confirm this hypothesis.

Apoptosis and autophagy

Apoptosis, also known as programmed cell death, is a normal component of the development and health of multicellular organisms.⁶⁶ Cells may die in response to a variety of stimuli in two ways: necrosis and apoptosis depending on the degree of stimulation. Apoptosis can execute in mitochondria dependent and independent pathways.⁶⁷ The relationship between hyperoxia preconditioning and mitochondria independent pathway is rarely studied. Herein, we described the evidence on the correlation between hyperoxia preconditioning and mitochondria dependent pathway.

Mitochondria are the center of energy production and also closely related to apoptosis. Recent data suggest that many mechanisms underlying the preconditioning converge on the mitochondria, positing mitochondria as master regulators of preconditioning-triggered endogenous neuroprotection.⁶⁸ Studies revealed hyperoxia preconditioning could decrease the apoptosis following cerebral insult, which was characterized by the decrease in apoptotic cells and reduction of caspase activities.^{30,31,57,69} Ostrowski *et al.*⁵⁷ speculated this effect might be attributed to the increase in BDNF level and/or suppression of p38 MAPK. In addition, the mitochondrion derived ROS, ATP-sensitive potassium channels, permeability transition pore, and uncoupling proteins are also involved in the relationship between hyperoxia preconditioning and apoptosis.⁶⁸ The exact mechanisms are required to be further investigated.

Autophagy is a complex cellular process that is involved in the degradation of a cell's own components through the lysosomal machinery.⁷⁰ It is a highly regulated process and plays a role in cell growth, development, and homeostasis, helping to maintain a balance between the synthesis, degradation, and subsequent recycling of cellular products.⁷⁰ Studies have confirmed that autophagy is implicated in a lot of diseases, especially the neurodegenerative diseases in which an improper clearance of proteins may either result from a compromise of the autophagy-lysosomal degradation pathway or induce alterations in this pathway.⁷¹

In a study of Sheng *et al.*⁷², results revealed ischemia preconditioning exerted a neuroprotective effect via activating autophagy and this effect could be mimicked by autophagy inducers. In the same year, Wang *et al.*⁷³ hypothesized that hyperoxia preconditioning could exert neuroprotective effect in an autophagy dependent manner, and this hypothesis was confirmed in a recent study in which the autophagy was enhanced in cerebral ischemia rats receiving hyperoxia preconditioning.⁷⁴ Following cerebral ischemia, a larger number of necrotic and apoptotic cells are produced. On the one hand, the products of these necrotic cells can elicit local inflammatory response, and on the other hand the degenerative intracellular components are required to be cleared and/or reused. Therefore, increased autophagy following hyperoxia preconditioning is helpful for the clearance and recycling of intracellular components. However, some studies reveal opposite results in which autophagic activities are increased in ischemic neurons, and strong neuroprotection can be achieved by post-ischemic inhibition of autophagy.⁷⁵ Thus, the exact role of autophagy in the hyperoxia preconditioning should be further studied.

Other mechanisms

The excitatory amino acid transporters (EAATs) are also closely related to the hypoxic insult.⁷⁶ EAATs can re-uptake glutamate into cells and also release glutamate into the extracellular space in a calcium-independent manner. Recent findings show that EAAT2 upregulation provides neuroprotection on ischemic insult, and inflammatory mediators such as tumor necrosis factor-alpha (TNF-alpha) and nuclear factor-kappa B (NF-kappa B) potentially increase the EAAT2-dependent uptake of extracellular glutamate.⁷⁷ Studies have demonstrated that TNF-alpha and NF-kappa B are involved in the neuroprotection of hyperoxia preconditioning, and the increase in EAATs following hyperoxia preconditioning is a critical event in the neuroprotection against cerebral ischemia.⁷⁸⁻⁸¹

Ribosomal protein S6 kinases (p70 S6 K) are a group of proteins involved in the protein synthesis, cell proliferation, cell cycle control, cell motility and neuronal cell differentiation.⁸² Qin *et al.*³² found hyperoxia preconditioning could activate p70 S6 K and reduce brain swelling after intracerebral hemorrhage.

In addition, microarray was also performed to explore the temporal profile of genomic responses and protein synthesis following hyperoxia preconditioning.⁸³ Results showed the genes/proteins relevant to neurotrophin and the inflammatory-immune system may be involved in HBO induced protection, but the specific role of each protein in this study requires to be determined in future studies.

Regimen for Hyperoxia Preconditioning

Currently, there is no consensus on the regimen for hyperoxia preconditioning. Hyperoxia preconditioning can be carried out under either normobaric or hyperbaric condition. When compared with HBO preconditioning, normobaric hyperoxia preconditioning dose not require specific and complicated facilities and thus can be performed at home. In addition, normobaric hyperoxia has the advantage in safety due to absence of decompression. However, no study has been conducted to compare the neuroprotection of normobaric hyperoxia preconditioning with that of hyperbaric hyperoxia preconditioning. Therefore, it is hard to confirm the superiority of one strategy to the other, although the therapeutic efficacy of hyperbaric hyperoxia is superior to that of normobaric hyperoxia in neurological diseases.⁸⁴

Usually, the hyperbaric hyperoxia preconditioning is carried out at 2-3 ATA. The duration of each exposure ranges from 60 to 90 minutes. In studies of Grimm *et al.*⁹ and Bigdeli,⁴¹ the preconditioning with 95% oxygen was performed for as long as 24 hours. This regimen is unacceptable due to the possibility of

pulmonary oxygen toxicity and impracticality. In clinical practice, intermittent oxygen inhalation has been introduced under hyperbaric hyperoxia condition even the total exposure time is only 90 minutes. In addition, the sessions for preconditioning vary in different studies and range from 1 to 6.⁹ Bigdeli *et al.*¹⁰ investigated the neuroprotective effect of prolonged and intermittent hyperoxia preconditioning. Their results showed that the neuroprotection of intermittent exposure was superior to that of prolonged exposure (24-hour exposure in this study is unacceptable). Another concern is the time from last hyperoxia exposure to subsequent insult. The interval of 24 hours is the most commonly applied in hyperoxia preconditioning. Hirata *et al.*⁸³ investigated the time window of hyperbaric hyperoxia preconditioning against ischemic injury. Their results showed the presence of neuroprotection at 6, 12 and 24 hours but not 72 hours after last preconditioning.

In addition, the organ-protective effect of hyperoxia in combination with steroids (dexamethasone) was also investigated in cardiac ischemia-reperfusion injury.⁸⁵ Whether this strategy is effective, applicable and/or feasible for neuroprotection should be further studied.

Issues in the Hyperoxia Preconditioning

Although hyperoxia preconditioning has been confirmed as a promising strategy for the prevention of some neurological diseases, there are some problems should be resolved before it is widely applied in clinical practice.

1. Almost all studies on hyperoxia preconditioning are conducted in healthy animals or volunteers. In clinical practice, this strategy is mainly applied in subjects with high risk for neurological diseases. Therefore, the applicability of above findings should be re-evaluated. In a recent study, preconditioning with HBO was found to exhibit cerebral protective effect in patients undergoing on-pump coronary artery bypass graft surgery.⁸⁶ Thus, application of hyperoxia preconditioning before surgery may be a direction in further clinical studies.

2. There is evidence that hyperoxia can mobilize the stem/progenitor cells in a nitric oxide dependent manner.⁸⁷ Actually, there are neural stem cells in adult brain (subventricular zone and dentate gyrus of the hippocampus). Insults to the brain such as cerebral ischemia can result in a physiological mobilization of endogenous neural stem cells.⁸⁸ Whether hyperoxia preconditioning has influence on the neural stem cells which then contributes to neuroprotection is required to be further elucidated.

3. What is the cost-effectiveness of hyperoxia preconditioning? This is an important issue in the application of almost all preventive strategies, and also a determinant of application of hyperoxia preconditioning although the oxygen acquisition is convenient and the cost for oxygen is relatively cheap.

4. Another issue is the regimen for hyperoxia exposure which has been addressed above. Before wide application of hyperoxia preconditioning, the optimal

regimen for preconditioning is better to be confirmed. Whether the regimen for preconditioning targeting distinct neurological diseases is different is still unknown. If so, the screening of optimal regimen will be tough work.

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