Hyperbaric oxygen therapy and cerebral ischemia: neuroprotective mechanisms

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Introduction: *Numerous studies have demonstrated a protective effect of hyperbaric oxygen therapy in experimental ischemic brain injury, and many physiological and molecular mechanisms of hyperbaric oxygen therapy-related neuroprotection have been identified.*
Methods: *Review of articles pertaining to hyperbaric oxygen therapy and cerebral ischemia in the National Library of Medicine and National Institutes of Health database, emphasizing mechanisms of hyperbaric oxygen therapy-related neuroprotection.*
Results: *Hyperbaric oxygen therapy has been shown to ameliorate brain injury in a variety of animal models including focal cerebral ischemia, global cerebral ischemia, neonatal hypoxia–ischemia and subarachnoid hemorrhage. Small human trials of hyperbaric oxygen therapy in focal ischemia have not shown benefit, although one trial of hyperbaric oxygen therapy before cardiopulmonary bypass demonstrated improved neuropsychological and inflammatory outcomes with hyperbaric oxygen therapy. Hyperbaric oxygen therapy is associated with improved cerebral oxygenation, reduced blood–brain barrier breakdown, decreased inflammation, reduced cerebral edema, decreased intracranial pressure, reduced oxidative burden, reduced metabolic derangement, decreased apoptotic cell death and increased neural regeneration.*
Conclusion: *On a molecular level, hyperbaric oxygen therapy leads to activation of ion channels, inhibition of hypoxia inducible factor-1α, up-regulation of Bcl-2, inhibition of MMP-9, decreased cyclooxygenase-2 activity, decreased myeloperoxidase activity, up-regulation of superoxide dismutase and inhibition of Nogo-A (an endogenous growth-inhibitory factor). Ongoing research will continue to describe the mechanisms of hyperbaric oxygen therapy-related neuroprotection, and possibly expand hyperbaric oxygen therapy use clinically.* [Neurol Res 2009; **31**: 114–121]

Keywords: Hyperbaric oxygen; cerebral ischemia; neuroprotection

INTRODUCTION

Hyperbaric oxygen therapy has been identified as a potential therapy for ischemic injury to the central nervous system[1,2]. Many studies have reported improved neurological outcomes with hyperbaric oxygen therapy in experimental animal models of ischemic brain injury including focal ischemia, global ischemia, neonatal hypoxia–ischemia and subarachnoid hemorrhage[3–6]. Human clinical studies have generated mixed results to date, although hyperbaric oxygen therapy may be beneficial in chronic cerebral vascular disease[7] or in the setting of cardiopulmonary bypass[8]. A small number of studies have tested hyperbaric oxygen therapy in acute focal ischemia, but these studies have not shown benefit to date[9].

In this review, we consider publications about hyperbaric oxygen therapy and cerebral ischemia, with an emphasis on the mechanisms of hyperbaric oxygen therapy-related neuroprotection. Relevant literature was located in the National Library of Medicine and National Institutes of Health Database (http://www.pubmed.gov) between 1970 and 2007 using keywords 'hyperbaric oxygen' and 'cerebral ischemia', related topic links on http://www.pubmed.gov, and from bibliographies of articles reviewed. In the last 15 years, there have been no fewer than 65 animal and human studies of hyperbaric oxygen therapy in cerebral ischemic injury.

Hyperbaric oxygen therapy is defined as a fraction of inspired oxygen (FiO_2) of 1 (100% oxygen) at greater than 1 atmosphere absolute (ATA)[2]. Recent animal studies have used pressures ranging 1.5–3.5 ATA[10–14], and duration of treatment ranging from 1 to 3 hours[12,13]. Frequently investigators use a range of 2.6–3.0 ATA. Individual studies may use single[11] or multiple[14] treatment sessions. For safety and comfort of treatment subjects, gradual compression and decompression (5–15 minutes) is usually used before and after treatment[12]. Hyperbaric oxygen is administered by a specialized chamber that is designed to maintain supra-atmospheric pressures. *Figure 1A* shows an example of a small animal hyperbaric oxygen chamber. The horizontal platform permits placement of a rodent cage

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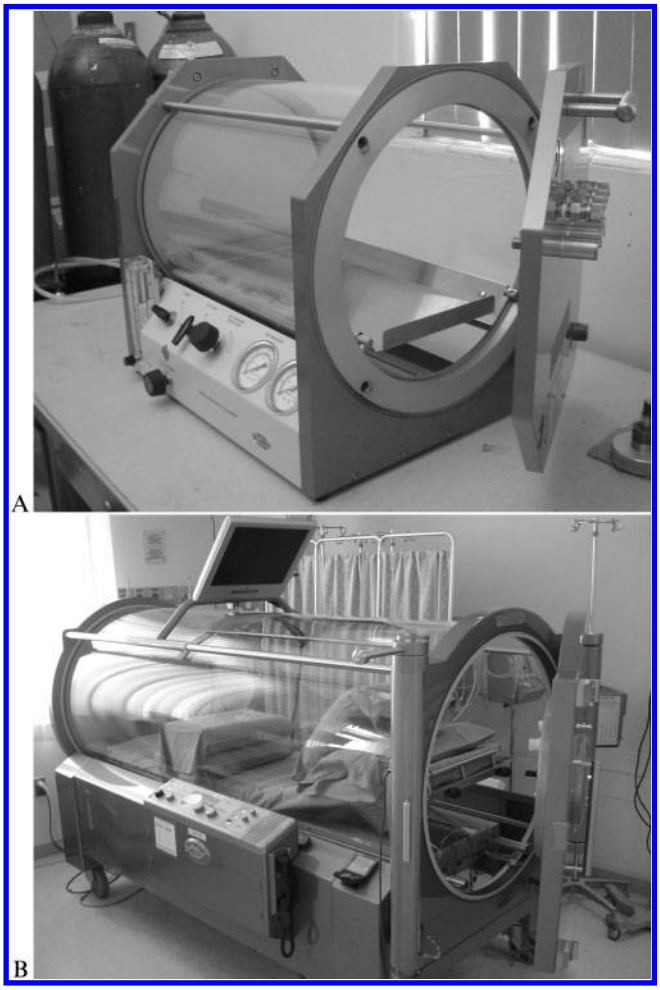

Figure 1: (**A**) A typical bench-top small-animal hyperbaric oxygen chamber; (**B**) a human hyperbaric oxygen chamber. The patient lies supine during therapy, and is able to watch the television monitor on top of the unit for entertainment

within the chamber. *Figure 1B* shows an analogous hyperbaric oxygen chamber for human patients. The patient is supine during treatment, and is permitted to use a television, radio or reading materials during the hyperbaric treatment session.

Hyperbaric oxygen therapy is indicated for a variety of conditions including infection (gangrene, osteomyelitis and others), ischemia of surgically implanted tissue, poor wound healing, radiation injury, thermal burns, gas embolism and carbon monoxide poisioning[15]. At our institution, hyperbaric oxygen therapy is most frequently used in the care of patients with non-healing wounds or chronically infected tissues.

PHYSIOLOGICAL EFFECTS OF HYPERBARIC OXYGEN THERAPY IN THE CENTRAL NERVOUS SYSTEM

Exposure to hyperbaric oxygen leads to increased oxygen tension in the brain, modulation of cerebral blood flow and modulation of intracranial pressure. The arterial partial pressure of oxygen (P_aO_2) with hyperbaric oxygen therapy may rise as high as 2000 mmHg from a normal baseline of 80–100 mmHg[16]. Because of the overwhelming increase in oxygen availability with hyperbaric conditions, oxygen partial pressure in most body compartments rises dramatically, even without a robust vascular supply. For example, brain tissue partial pressure of oxygen ($P_{Br}O_2$) may increase from a baseline from 20–40 mmHg to 420 mmHg with 2.5 ATA hyperbaric oxygen[17]. In some circumstances, hyperbaric oxygen therapy may support normal tissue metabolism even in the absence of an adequate supply of oxygen delivered by hemoglobin[2] (normally the quantity of dissolved of oxygen while breathing room air is insufficient to support life in the absence of hemoglobin[18], but hyperbaric oxygen therapy can potentially sustain life in a state of extreme anemia). The increase in tissue oxygen tension under hyperbaric conditions is transient and only persists as long as hyperbaric conditions are maintained[11].

Hyperbaric oxygen therapy has variable effects on cerebral blood flow. In healthy human and animal subjects, hyperbaric conditions cause a mild decrease in cerebral blood flow of up to 20%[17]. This change in cerebral blood flow may have an anatomical variance depending on region of interest[17]. Measurement of cerebral blood flow in experimental models of ischemia have yielded variable results. One study of permanent middle cerebral artery ischemia reported that hyperbaric oxygen therapy (3 ATA × 120 minutes) did not alter blood flow in the ischemic penumbra[19]. In experimental SAH, hyperbaric oxygen therapy was reported to increase cerebral blood flow[4]. In transient global cerebral ischemia, hyperbaric oxygen therapy (2.8 ATA × 125 minutes) caused decreased cerebral blood flow[20]. In human patients, the changes in cerebral blood flow reported with hyperbaric oxygen therapy are also variable. In intensive care unit patients with a variety of types of brain injury, hyperbaric oxygen therapy (1.5 ATA × 1 hour) was associated with elevated cerebral blood flow in patients with reduced pre-treatment cerebral blood flow, but reduced cerebral blood flow in patients with elevated pre-treatment cerebral blood flow[21]. Mechanisms of the effect of hyperbaric oxygen therapy on cerebral blood flow are not well understood.

Hyperbaric conditions generally appear to reduce intracranial pressure[17]. This has been demonstrated in experimental traumatic brain injury (hyperbaric oxygen therapy, 1.5 ATA × 1 hour), experimental subarachnoid hemorrhage (hyperbaric oxygen therapy, 2.8 ATA × 2 hours) and in human patients with severe brain injury[4,21–23]. The mechanisms responsible for decreased intracranial pressure with hyperbaric oxygen therapy are not well understood.

HYPERBARIC OXYGEN THERAPY AND CEREBRAL ISCHEMIA IN ANIMAL STUDIES

Hyperbaric oxygen therapy ameliorates brain injury in experimental studies when administered as pre-ischemic therapy[14,24–29] or post-ischemic therapy[11–13,30–33]. Investigators have demonstrated the protective effect of hyperbaric oxygen therapy in experimental animal

models such as middle cerebral artery occlusion[11], neonatal hypoxia–ischemia[32,34], global forebrain ischemia[35], subarachnoid hemorrhage[4,5] and cardiac arrest[36]. Early exposure to hyperbaric oxygen is associated with improved outcomes in experimental middle cerebral artery occlusion[37]. Hyperbaric oxygen therapy has been shown to be a superior neuroprotectant compared to normobaric oxygen therapy[31] or hyperbaric air therapy[38]. Beneficial effects of hyperbaric oxygen therapy in focal ischemia in animal studies include decreased infarction size[11], decreased edema[12], decreased blood–brain barrier breakdown[31], decreased apoptotic cell death[30,39], improved cerebral glucose utilization[33] and improved neurobehavioral scores[12].

Outcomes from hyperbaric oxygen therapy after experimental focal ischemia depend partly on the model of focal ischemia. Hyperbaric oxygen therapy after *transient* focal ischemia is frequently beneficial[11–13], whereas hyperbaric oxygen therapy after *permanent* focal ischemia is frequently not protective[30, 40–42]. Why this distinction exists between *transient* and *permanent* focal ischemia is not clear presently, although the time course of initiation of hyperbaric oxygen therapy relative to the onset of ischemia may be critically important. Studies with rapid initiation of hyperbaric oxygen therapy after the onset of *permanent* focal ischemia have shown increased benefit[19].

Common therapeutic parameters for hyperbaric oxygen therapy in animal studies include absolute pressures between 2 and 3.5 ATA and duration of treatment between 1 and 3 hours[11–13,43]. Focal ischemic stroke in humans frequently comes to attention after a delay of several hours, and much of the experimental focal ischemia research has emphasized the allowable post-ischemic delay in administration hyperbaric oxygen therapy. Hyperbaric oxygen therapy is most effective in the setting of focal ischemia if administered within the first six hours after reperfusion[41,44]. Interestingly, post-ischemic exposure to hyperbaric oxygen may actually be harmful[41,44], although there is not universal agreement on this point[45]. Two studies have reported better outcomes with hyperbaric oxygen therapy (3 ATA × 1 hour) within 6 hours of reperfusion after middle cerebral artery occlusion but worse outcomes if hyperbaric oxygen therapy is administered after 6 hours of reperfusion[41,44]. One study has reported that hyperbaric oxygen therapy (2.5 ATA × 2 hours × 6 treatments) is beneficial after middle cerebral artery occlusion if delayed as long as 24 hours after reperfusion[45]. In this latter study, multiple doses of hyperbaric oxygen therapy (six treatments) may have expanded the therapeutic window for treatment. This finding may be critically important for successfully translating hyperbaric oxygen therapy into clinical practice because human patients frequently come to medical attention many hours after the onset of ischemic stroke.

Hyperbaric oxygen therapy preconditioning has been effective in a variety of models of cerebral ischemia. Hyperbaric oxygen therapy (3.5 ATA × 1 hour × 5 treatments) before experimental global cerebral ischemia is protective if given within 24 but not 72 hours before ischemia[14]. In neonatal rats, hyperbaric oxygen therapy preconditioning (2.5 ATA × 150 minutes × 1 treatment) is effective before hypoxia–ischemia[24]. Hyperbaric oxygen therapy preconditioning before experimental middle cerebralartery occlusion ischemia (2.5 ATA × 1 hour × 3–5 treatments) is protective[28]. Further study is needed to refine ideal treatment protocols for pre-treatment and to identify patients who might benefit from preconditioning.

HYPERBARIC OXYGEN THERAPY AND CEREBRAL ISCHEMIA IN HUMANS

Translation of hyperbaric oxygen therapy from experimental models to clinical practice has resulted in limited success. There have been several randomized, controlled clinical trials of hyperbaric oxygen therapy after focal cerebral infarction[9,46,47] and other ischemic pathology[7,8]. A study by Rusyniak *et al.* tested hyperbaric oxygen therapy (2.5 ATA × 1 hour) after focal ischemia[9]. In this randomized, prospective, controlled, double-blinded trial, patients were given hyperbaric oxygen therapy shortly after admission to the hospital after a diagnosis of acute ischemic stroke. Patients were then studied for 90 days. There was no apparent benefit of hyperbaric oxygen therapy at 24 hours on neurological testing, and surprisingly the hyperbaric oxygen therapy group fared worse on examination after 90 days. This study was well designed though had several limitations. First, the study was relatively small in size (n=17 for hyperbaric oxygen therapy, n=16 for sham treatment). Second, only a small percentage (~15%) of patients received hyperbaric oxygen therapy within the first 6 hours of the onset of symptoms. Animal studies have suggested that early hyperbaric oxygen therapy is most effective[41, 44], although there is a possibility that multiple doses may expand the treatment window[45]. Third, the study enrolled patients who did not receive thrombolysis. Animal studies have demonstrated that hyperbaric oxygen therapy is more effective in transient ischemia than in permanent ischemia, and perhaps hyperbaric oxygen therapy would be beneficial in the post-thrombolytic patient population. However, this study generally agrees with other human trials which have failed to show benefit of hyperbaric oxygen therapy, and perhaps there are other unrecognized factors that preclude successful translation of hyperbaric oxygen therapy into clinical use for ischemic stroke[48,49]. Additional research is needed, possibly with an emphasis on earlier (within 6 hours) administration of hyperbaric oxygen therapy.

Although human studies in focal ischemia have not shown benefit of hyperbaric oxygen therapy, other studies have demonstrated that hyperbaric oxygen therapy may be beneficial in other patterns of brain ischemia. In chronic symptomatic cerebrovascular disesease, daily hyperbaric oxygen therapy may be associated with improved motor and cognitive function[7]. Hyperbaric oxygen pre-treatment (2.4 ATA × 1 hour × 3 treatment) before coronary bypass artery

grafting (CABG) is associated with improved neuropsychological performance and decreased serum markers of inflammation and stress such as E-selectin, CD18 and HSP-70[7]. CABG surgery places a patient at risk for focal ischemia or post-operative cognitive decline[50–53], and therefore is an attractive target for hyperbaric oxygen therapy pre-treatment studies.

HYPERBARIC OXYGEN THERAPY SIDE EFFECTS

Transient exposure to hyperbaric pressures in healthy human subjects is not associated with long-term physiological changes or brain changes on magnetic resonance imaging[54]. However, extreme hyperbaric conditions (4.95 ATA × 1 hour) may be associated with central nervous system oxygen toxicity[55]. Lipid peroxidation and altered enzymatic anti-oxidative processes have been shown to occur at 4 ATA[56]. Elevated pressures (5.0 ATA) may also increase the susceptibility to seizures[57]. Mechanistically, some of these side effects may relate to alterations in nitric oxide metabolism at high pressure. Several studies have reported that hyperbaric oxygen therapy of 5 ATA is associated with up-regulation of nitric oxide synthase[57] and direct inactivation of nitric oxide[58].

Hyperbaric oxygen therapy at lower pressures (for example, 2 ATA × 1 hour) is associated with few side effects. Lipid peroxidation is not increased by hyperbaric oxygen therapy at standard conditions. Hyperbaric oxygen therapy (2 ATA × 1 hour) after experimental middle cerebral artery occlusion[59] or global cerebral ischemia[60] (2.8 ATA × 125 minutes) was not associated with increased lipid peroxidation. Hyperbaric oxygen therapy (2.8 ATA × 2 hours) after subarachnoid hemorrhage may actually be associated with decreased lipid peroxidation and oxidative stress[5]. In subarachnoid hemorrhage, decreased lipid peroxidation may relate mechanistically to decreased NADPH oxidase[5]. Significant lipid-peroxidation appears to occur with hyperbaric oxygen therapy at 4 ATA or higher[3], and guidelines for hyperbaric oxygen therapy recommend maximum hyperbaric oxygen therapy exposure of no greater than 3 ATA[15].

One major concern regarding the application of hyperbaric oxygen therapy to neonatal patients relates to the potential for hyperbaric oxygen therapy to cause retinopathy of prematurity[61]. Oxygen toxicity has long been thought to be a cause of retinopathy of prematurity, although recent work has begun to call this assumption into question[62]. A recent multicenter study of supplemental oxygen therapy in premature infants found that oxygen exposure did appear to worsen retinopathy of prematurity in premature infants who already had a diagnosis of retinopathy of prematurity, and that oxygen therapy may actually help a subgroup of infants with retinopathy of prematurity[62]. Other work suggests that the development of retinopathy of prematurity may relate more to rapid cycling of relative hypoxia and hyperoxia[63]. Although there is still strong concern for retinopathy of prematurity with hyperbaric oxygen therapy in neonates, preliminary work in animal models of hyperbaric oxygen therapy for neonatal hypoxia–ischemia have demonstrated significant potential benefit from hyperbaric oxygen therapy[34] without development of retinopathy of prematurity[61].

MECHANISMS OF HYPERBARIC OXYGEN THERAPY

Experimental studies of hyperbaric oxygen therapy in cerebral ischemia have shown that hyperbaric oxygen therapy is associated decreased brain infarction[11], decreased edema[12] and improved neurobehavioral outcomes[12]. These effects have been linked to multiple molecular mechanisms, outlined in *Figure 2*.

Increased oxygen tension in hypoxic tissue

In acute ischemic injury, hyperbaric oxygen may help sustain acutely hypoxic tissue. This may be especially true in penumbral or watershed areas after an infarction[19]. By increasing oxygen delivery to ischemic areas of the brain, hyperbaric oxygen therapy may improve local tissue metabolism[64]. However, because of the highly transient nature of the elevated oxygen tension[11], it seems likely that increased oxygen tension is not the only mechanism that explains the benefit of hyperbaric oxygen therapy. In a cardiac arrest model of global cerebral ischemia, post-ischemic hyperbaric oxygen therapy (2.7 ATA × 1 hour) was shown to lead to a correction of an elevated oxygen extraction ratio and improved neurological outcomes[36].

Absolute versus relative oxygen tension

One important question about the mechanism of hyperbaric oxygen therapy is whether *absolute* oxygen tension is more or less important than *relative* oxygen tension and similarly, whether the mechanisms of hyperbaric oxygen therapy and hypoxic preconditioning are distinct. Hypoxic preconditioning is neuroprotective prior to cerebral ischemia, possibly because of molecular changes induced by relative periods of hypo- and normoxia[65]. Studies comparing hyperbaric preconditioning and hypoxic preconditioning have detected significant mechanistic distinctions between the two[24]. In experimental neonatal hypoxia–ischemia, hyperbaric oxygen preconditioning suppresses mitochondrial aconitase activity, whereas hypoxic preconditioning does not (mitochondrial aconitase activity is generally regarded as a measure of oxidative stress because it is suppressed by superoxides). Additionally, manganese–superoxide dismutase (Mn–SOD) mRNA decreases with hypoxic preconditioning but not hyperbaric oxygen preconditioning in neonatal hypoxia–ischemia[24]. These observations suggest that mechanisms of hypoxic preconditioning and hyperbaric oxygen preconditioning are distinct, although much work remains in fully describing this distinction.

Reduction of excitotoxic stress

Ischemic brain injury is associated with excitotoxic stress and physiological derangement that may further exacerbate brain injury. Hyperbaric oxygen therapy is

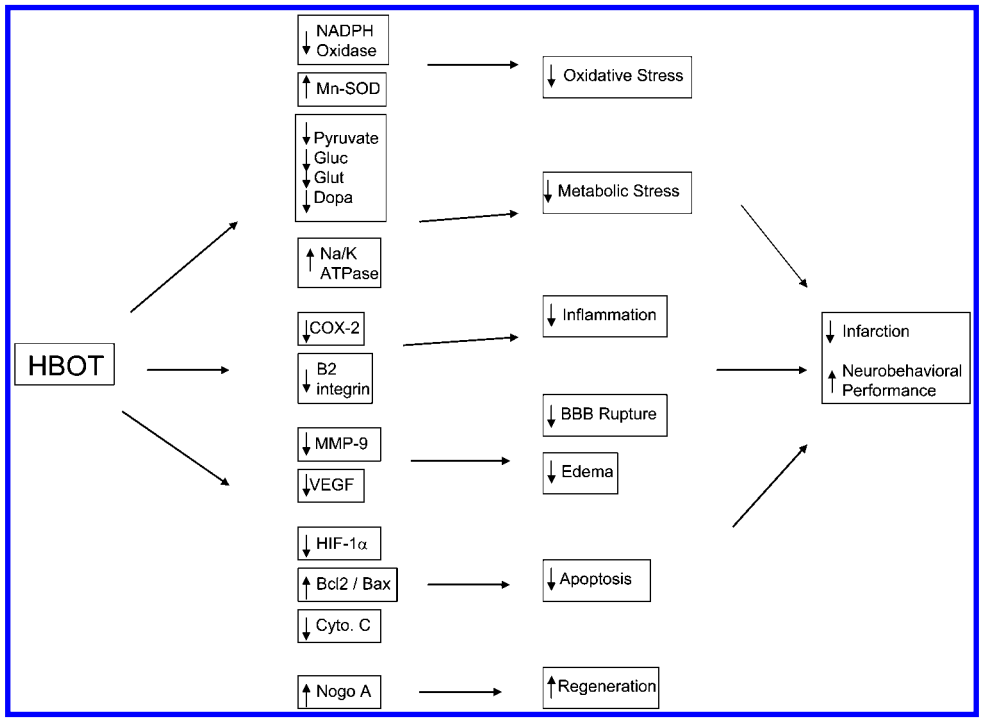

Figure 2: Mechanisms of hyperbaric oxygen therapy-related neuroprotection

associated with a normalization of extracellular homeostasis and relative protection from excitotoxic stress. Studies of hyperbaric oxygen therapy in focal ischemia have shown that hyperbaric oxygen therapy (3 ATA × 1 hour) is associated with a reduction of excitotoxic metabolites such as glucose, pyruvate, lactate and glutamate[66]. Likewise, hyperbaric oxygen therapy (2.8 ATA × 1 hour) is associated with a reduction of striatal dopamine[67]. In neonatal hypoxia–ischemia, hyperbaric oxygen therapy (2.5 ATA × 2 hours) has been shown to aid in preservation of ATP and other high energy phosphate compounds[68].

Activation of ion channels

Hyperbaric oxygen therapy after global cerebral hemorrhage and subarachanoid hemorrhage is associated with normalization of Na/K-ATPase activity[69,70]. This may occur as a result of improved energy balance within the ischemic brain, although work in an experimental lung injury model has shown that hyperbaric oxygen therapy may actually up-regulate Na/K-ATPase expression[71]. Hyperbaric oxygen therapy may also activate mitochondrial ATP-sensitive potassium channels (mitoK_{ATP}). Activation of mitoK_{ATP} may be neuroprotective by suppressing Bax translocation and cytochrome C release from mitochondria, and thereby inhibiting apoptosis[33]. MitoK_{ATP} activation also tends to hyperpolarize the cell, which helps to preserve the energy balance of the cell and limit excitotoxic stress[72]. The net result from activation of these ion channels is an inhibition of depolarization and an inhibition of apoptosis.

Stabilization of the blood–brain barrier

Hyperbaric oxygen therapy is associated with stabilization of the blood–brain barrier in ischemic pathology[31,73,74]. In studies of laminin-5, a marker of blood–brain barrier breakdown, hyperbaric oxygen therapy (3 ATA × 1 hour), is associated with decreased levels of laminmin-5 compared to normobaric oxygen after focal ischemia[31]. Decreased free laminin-5 suggests preservation of the vascular basal lamina. Hyperbaric oxygen therapy is also associated with reduced matrix metalloproteinase-9[31]. Hyperbaric oxygen therapy may inhibit the up-regulation of matrix metalloproteinase-9 after ischemia, which would likely result in less degradation of the vascular basal lamina and lower laminin-5 levels[31]. Other studies have shown that hyperbaric oxygen therapy is associated with decreased levels of vascular endothelial growth factor[6], and decreased vascular endothelial growth factor is associated with preservation of the blood–brain barrier.

Reduction of oxidative stress

Ischemic brain injury is associated with the elaboration of free radicals and reactive oxygen species[75]. Studies of oxidative stress and hyperbaric oxygen therapy have shown that hyperbaric oxygen therapy is associated with decreased lipid peroxidation in Carbon Monoxide-mediated brain injury[76] and in subarachnoid hemorrhage[5]. In middle cerebral artery occlusion, hyperbaric oxygen therapy is not associated with increased lipid peroxidation[59]. Mechanistically, decreased oxidative burden with hyperbaric oxygen therapy may relate to decreased NADPH oxidase activity[5].

Defenses against oxidative stress includes factors such as SOD, glutathione peroxidase, catalase and glutathione[75,77]. Hyperbaric oxygen therapy is associated with maintenance of these intracellular defenses. In global cerebral ischemia, hyperbaric oxygen therapy (2 ATA × 1 hour × 7 treatments) after global cerebral ischemia in rats was associated with enhanced superoxide dismutase activity[69]. Hyperbaric oxygen therapy (2.5 ATA × 150 minutes) before neonatal hypoxia–ischemia in rats leads to elevation Mn–SOD[24]. These changes help protect against free radical damage.

Modulation of inflammation

Inflammation after ischemic stroke contributes to post-ischemic pathology[78], and hyperbaric oxygen therapy (2.8 ATA × 45 minutes) is associated with reduced inflammation after experimental middle cerebral artery occlusion[29]. Hyperbaric oxygen therapy is associated with decreased neutrophil infiltration[29] and reduced myeloperoxidase activity in middle cerebral artery occlusion[25]. In carbon monoxide-induced ischemia, hyperbaric oxygen therapy (3 ATA × 45 minutes) is associated with decreased leukocyte adherence to microvasculature[76]. Hyperbaric oxygen therapy may also disrupt a specific $\beta 2$ integrin interaction that is important for inflammatory cells[76]. In experimental middle cerebral artery occlusion, hyperbaric oxygen therapy (3 ATA × 1 hour) is associated with reduced cyclooxygenase-2 mRNA and protein levels (an inducible enzyme responsible for elaboration of inflammatory prostanoids, prostaglandins, prostacyclins and thromboxane)[79]. In inflammatory pathology of the gastric intestine system such as Crohn's disease, hyperbaric oxygen therapy is associated with decreased inflammatory mediators such as TNF-α, IL-1 and IL-6[80].

Inhibition of apoptosis

Pharmacological inhibition of apoptosis has been an attractive target for stroke research because apoptosis is a common pathway for cell death in many types of ischemic brain injury[81]. Numerous studies have reported an anti-apoptotic effect of hyperbaric oxygen therapy[12,30,33,39]. Hyperbaric oxygen therapy is associated with reduced PARP cleavage, reduced cleaved caspase 3 and reduced in DNA fragmentation characteristic of apoptotic death[3,12,30,33,39]. In global cerebral ischemia and focal ischemia, hyperbaric oxygen therapy appears to increase the Bcl-2/Bax ratio in favor of anti-apoptotic outcomes[12,26,27]. Hyperbaric oxygen therapy-induced activation of mitoK_{ATP} may also promote an anti-apoptotic increase in the Bcl-2/Bax ratio and an inhibition of cytochrome C release[33]. Hypoxia inducible factor 1α (HIF-1α) is associated with apoptotic cell death after cerebral ischemia[82], and hyperbaric oxygen therapy has been associated with an inhibition of HIF-1α[6,12,32,83]. Hyperbaric oxygen therapy is also associated with lower levels of the target gene products of HIF-1α including BNip3 and vascular endothelial growth factor[6].

Regeneration of the central nervous system

In peripheral nerves, hyperbaric oxygen therapy stimulates regeneration after injury[84,85]. Studies of repetitive doses of hyperbaric oxygen therapy after cerebral ischemia have shown that hyperbaric oxygen therapy may cause gliosis[37], and hyperbaric oxygen therapy may potentially stimulate central nervous system regeneration. Central nervous system regeneration after injury or ischemia is inhibited by endogenous factors such as Nogo-A[86,87]. Nogo-A is up-regulated after cerebral ischemia, and this inhibits regeneration[87]. Hyperbaric oxygen therapy is associated with decreased levels of Nogo-A, which may be a mechanism by which hyperbaric oxygen therapy promotes central nervous system regeneration[87].

CONCLUSION

Hyperbaric oxygen therapy has been shown to be neuroprotective in multiple models of ischemic brain injury in animal studies. Hyperbaric oxygen therapy is associated with improved cerebral oxygenation, reduced blood–brain barrier breakdown, decreased inflammation, reduced cerebral edema, decreased intracranial pressure, reduced oxidative burden, reduced metabolic derangement, decreased apoptotic cell death and increased neural regeneration. These beneficial effects of hyperbaric oxygen therapy have been linked to multiple molecular mechanisms including activation of ion channels, inhibition of HIF-1α, up-regulation of Bcl-2, inhibition of matrix metalloproteinase-9, decreased cyclooxygenase-2 activity, decreased myeloperoxidase activity, up-regulation of SOD and inhibition of Nogo-A. Hyperbaric oxygen therapy has been used successfully for neuroprotection prior to cardiac surgery, although trials of hyperbaric oxygen therapy in focal cerebral ischemia have not shown benefit. Future research will continue to identify mechanisms of hyperbaric oxygen therapy-related neuroprotection and to expand hyperbaric oxygen therapy in humans with cerebral ischemia.

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