



Hyperbaric oxygen preconditioning improves postoperative cognitive dysfunction by reducing oxidant stress and inflammation

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Abstract

Postoperative cognitive dysfunction is a crucial public health issue that has been increasingly studied in efforts to reduce symptoms or prevent its occurrence. However, effective advances remain lacking. Hyperbaric oxygen preconditioning has proved to protect vital organs, such as the heart, liver, and brain. Recently, it has been introduced and widely studied in the prevention of postoperative cognitive dysfunction, with promising results. However, the neuroprotective mechanisms underlying this phenomenon remain controversial. This review summarizes and highlights the definition and application of hyperbaric oxygen preconditioning, the perniciousness and pathogenetic mechanism underlying postoperative cognitive dysfunction, and the effects that hyperbaric oxygen preconditioning has on postoperative cognitive dysfunction. Finally, we conclude that hyperbaric oxygen preconditioning is an effective and feasible method to prevent, alleviate, and improve postoperative cognitive dysfunction, and that its mechanism of action is very complex, involving the stimulation of endogenous antioxidant and anti-inflammation defense systems.

Key Words: nerve regeneration; brain injury; hyperbaric oxygenation; preconditioning; antioxidants; anti-inflammation; reactive oxygen species; oxidant stress; inflammation; protection; post-operation; cognitive dysfunction; neural regeneration

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Introduction

Postoperative cognitive dysfunction (POCD) is a complication of surgery that is widely considered an important clinical problem, particularly in elderly patients (Shoair et al., 2015). However, the pathophysiology underlying POCD is fairly complex, involving numerous mechanisms including oxidant stress, inflammation, and apoptosis (Eckenhoff et al., 2004; Dong et al., 2009; Thom, 2009; Cao et al., 2012; Wilson et al., 2013). Over the past several decades, researchers have explored a wide array of methods for improving POCD, including hyperbaric oxygen preconditioning (HBOPC). HBOPC is one of the most economical, simple, safe, and effective strategies among all the possible choices (Zhu et al. 2016). Indeed, studies have successfully utilized HBOPC to improve cognitive dysfunction (Alex et al., 2005; Peng et al., 2010; Sun et al., 2014). The purpose of this narrative review is to summarize and discuss the literature concerning HBOPC and POCD, with an emphasis on the evidence for a role of HBOPC in treating patients undergoing POCD. The review is organized into the following sections: introduction of HBOPC, mechanisms underlying POCD, and the effect of HBOPC on POCD (Figure 1).

HBOPC

Definition of HBOPC

During HBO treatment, patients usually inhale pure oxygen (100%) at pressures greater than the atmospheric pressure in a steel vessel (Löndahl, 2012), which increases both the dissolved oxygen and the partial pressure of oxygen in blood plasma (Tibbles and Edelsberg, 1996). Consequently, a large amount of oxygen-dependent reactions and signaling pathways are enhanced (Babchin et al., 2011).

Application of HBOPC

Normobaric oxygen and various levels of HBO have been widely utilized therapeutic agents, and Valenzuela pioneered the application of pure oxygen (as high as 2 MPa) in clinical research (Edwards, 2010). The use of HBO as an adjuvant treatment for a number of medical conditions has been widely supported by the experience of experts in hyperbaric medicine and the scientific literature in areas such as traumatic brain injury (Hu et al., 2016; Zhou et al., 2016a, b) complex refractory wounds (Morykwas and Argenta, 1996), cerebral infarction (Tian, 2015), and radiation-tissue injury (Kindwall and Hunt, 1995; Kindwall and Wheland, 1999). Along with the development of medicines, disease prevention has increasingly become recognized as important. Pre-

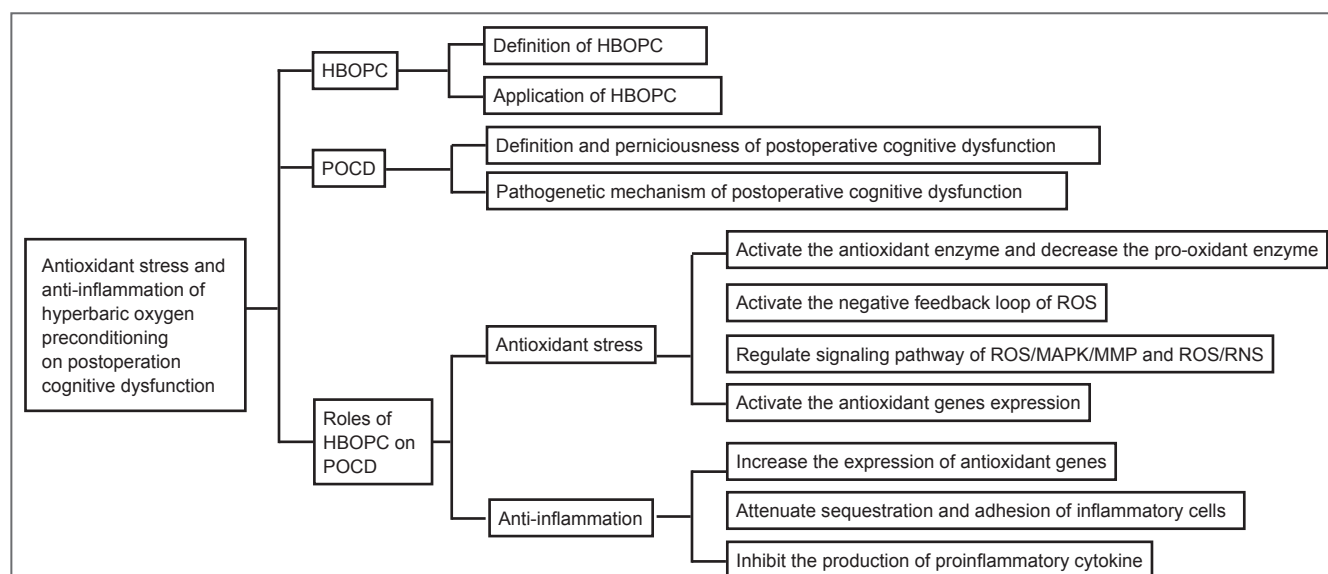


Figure 1 Summary of article structure.

POCD: Postoperative cognitive dysfunction; HBOPC: hyperbaric oxygen preconditioning; MMP: matrix metalloproteinase; ROS: reactive oxygen species; MAPK: mitogen-activated protein kinase; RNS: reactive nitrogen species.

conditioning is a type of primary prevention that activates endogenous protective mechanisms, which can reduce the risk of morphologic and functional sequelae. The preconditioning state is typically defined by the response to a sublethal stimulus that extends beyond its presence in the system. This response significantly lessens the level of signal cascades for stress-activated and stress-reactive proteins, which subsequently shows a protective effect for cells. Recently, HBO has become recognized as an effective preconditioning method for reducing mental and cellular stresses, especially in regimented sessions of moderate HBO (Nie et al., 2006; Li et al., 2008). In the clinic, however, HBOPC has had only minimal impact before surgery, and no role in the surgery or post-surgical care of patients (Allen et al., 2014). HBO protocols are performed at 2.0–2.5 atmosphere absolute (ATA) oxygen partial pressures, and usually only applied for one or a few days. The physical adaptations in response to alterations in atmospheric oxygen appear to extend not only to survival, but also a preconditioned state. Similar to ischemic and stress preconditioning, many different paradigms have been used to demonstrate that either rapid or delayed tolerance is affected by the HBO (Stetler et al., 2014). To achieve the best outcome using HBOPC, it requires a certain O₂ concentration and high pressure. When air (20% oxygen) rather than 100% O₂ was infused into the hyperbaric chamber, the tolerance was negated, demonstrating the need for high O₂ concentration in the hyperbaric preconditioned state (Wada et al., 2001). Additionally, Kocaoğullar et al. (2004) compared normobaric oxygen with HBO treatment of rats with cerebral vasospasm after subarachnoid hemorrhage and found that normobaric oxygen was less effective in ameliorating neurological deficits associated with the central nervous system. Many experiments have shown that HBOPC can protect against subsequent multi-organ injury to the brain, heart, or liver (Alex et al., 2005; Yu et al., 2005;

Qin et al., 2008). Previous studies suggest that preconditioning with pressures of 2 ATA 3–5 sessions/every other day was effective in inducing tolerance against global ischemia in gerbils (Wad et al., 1996; Wada et al., 2001). Cheng et al. (2011) reported that 2.5 ATA preconditioning, 1 hour daily for 5 days, protected against subsequent global ischemic injury in rats (Cheng et al., 2011). Similarly, pretreatment with HBO has been found both to improve the degree and accelerate the rate of neurologic recovery. Additionally, long-term HBOPC paradigms have been shown to be more effective at establishing tolerance than are acute paradigms (Xiong et al., 2000; Dong et al., 2002; Nie et al., 2006; Liu et al., 2012). Animal studies of ischemia/reperfusion (I/R) injury in the myocardium have indicated that HBO preconditioning can lead to ischemia tolerance, resulting in protection against myocardial ischemia (Kim et al., 2001). In addition to these experimental studies, clinical studies have demonstrated that preconditioning patients who have coronary artery disease with HBO before on-pump cardiopulmonary bypass or coronary artery graft bypass were in a position improved myocardial function, and reduced myocardial injury, the duration of staying in the intensive care unit, blood loss, postoperative complications, and cost (Yogarathnam et al., 2010; Li et al., 2011). Karu et al. (2010) indicated that exposure to hyperoxia for a limited time before ischemia induced a mild oxidative stress and resulted in an (ischemic) preconditioning-like effect in the myocardium, which protected the heart from subsequent injury. Yu et al. (2005) performed an experimental study in rats and reported preconditioning with single-dose HBO (90 minutes) protects the rat liver against subsequent I/R injury. Ren et al. (2008) similarly reported that HBO preconditioning increased the number of new cells and the density of microcirculation in the regenerating liver. Therefore, HBO preconditioning is an encouraging and feasible therapeutic strategy for protecting organs from the subsequent lethal stimulus. The effect and

mechanism of HBOPC on POCD will be described below.

POCD

Definition and perniciousness of POCD

Every year, numerous people undergo surgery hoping that the operation will lighten symptoms, heal diseases, and improve quality of life (Berger et al., 2015). Although there is much interest in, and controversy about, the mechanism and treatment of POCD, there is little doubt that cognitive decline after surgery (especially in the elderly population) is a critical clinical issue that shows a high morbidity. POCD is defined as an impairment in mental processes of perception, memory, and information processing that occurs in the postoperative period (Hanning, 2005), and which is diagnosed by specific tests after exclusion of other neurological complications. Both cardiac surgery and non-cardiac surgery are associated with the cognitive dysfunction after hospital discharge from 30% to 50% of patients (Newman et al., 2001; McDonagh et al., 2010; Selnes et al., 2012). One study reported the incidence of cognitive decline to be 53% at discharge, 36% at 6 weeks after discharge, 24% at 6 months after discharge, and 42% at 5 years after coronary-artery bypass grafting (Newman et al., 2001). Shoaib et al. (2015) showed that 15.9% of older adult patients developed POCD within 3 months after elective major non-cardiac surgery. Other studies have found that POCD is associated with poor short-term and long-term outcomes, including an increased risk of disability, increased expenditure on hospitalization, inability to cope independently, reduced quality of life, and possible permanent dementia (Hovens et al., 2014; Shoaib et al., 2015). Patients with POCD are at an increased risk of death in the first year after surgery and the elderly (aged 60 years or older) are at a significant risk for long-term cognitive problems (Moller et al., 1998; Monk et al., 2008; Avidan et al., 2009; Steinmetz et al., 2009).

Pathogenic mechanism of POCD

There is strong standpoint that cognitive decline experienced by elderly patients is directly mediated by neuro-inflammation and the enhancement of amyloid-beta oligomerization after surgery and general anesthesia (Bedford, 1955; Eckenhoff et al., 2004; Müller et al., 2004; Newman et al., 2007; Dong et al., 2009; Cao et al., 2012). At the same time, some results suggest that surgery results in neuro-inflammation and cognitive impairment, and that anesthesia might not be an essential influential factor for these effects (Zhang et al., 2015; Zhou et al., 2015). Despite these controversies, existing evidence has confirmed that neuro-inflammatory response to operative stress is an independent risk factor associated with the development of POCD (Wan et al., 2007; Barrientos et al., 2012; Hovens et al., 2014; Lu et al., 2015; Ma et al., 2015; Zheng et al., 2015). Amyloid beta, the peptide associated with Alzheimer's disease, was also detected in the serum of POCD patients. Another important player is acetylcholine, which has significant roles in memory, learning, and attention (Hsieh et al., 2008). The most likely mechanism underlying POCD is a central cholinergic deficiency caused by the deregulation

of cholinergic anti-inflammatory pathways, which results in increased inflammation (Inouye, 2006; Androsova et al., 2015). Many scholars have highlighted the importance of the cholinergic reflex in resolving the inflammatory pathogenesis of several diseases, including sepsis (Borovikova et al., 2000), rheumatoid arthritis (van Maanen et al., 2009), and colitis (Ghia et al., 2007). Researchers have reported that pro-inflammatory cytokines, including interleukin (IL)-1 and tumor necrosis factor- α (TNF- α), play key roles in mediating surgery-induced neuro-inflammation and subsequent cognitive decline (Cibelli et al., 2010; Terrando et al., 2010). Results reveal that surgery, not propofol-based anesthesia, induces neuro-inflammation and the impairment of learning and memory. Pyrrolidine dithiocarbamate attenuates these effects by inhibiting nuclear factor-kappa B activation and downstream matrix metalloproteinase 9 activity (Zhao et al., 2013; Zhang et al., 2014). Other studies have demonstrated that peripheral surgery affects the blood-brain barrier through the release of TNF- α . This promotes macrophage migrating into the hippocampus (Rudolph et al., 2008; Terrando et al., 2011; Vacas et al., 2013). Activation of $\alpha 7$ nicotinic acetylcholine receptors trigger an endogenous inflammation-resolving pathway that has been proven to be useful in blocking TNF- α -induced nuclear factor-kappa B activation and cognitive decline after surgery (Terrando et al., 2011). Jiang et al. (2015) suggested that IL-6 has a crucial role in POCD, and that IL-6R antagonists may serve as novel agents for its prevention or treatment. Chen et al. (2015) also demonstrated that dexmedetomidine reduces the incidence of POCD by suppressing inflammation in aged patients.

Roles of HBOPC on POCD

Cognitive decline after surgery includes deterioration in cognition, disturbance in attention, and reduced awareness of the environment. In light of recent clinical developments, HBO preconditioning has been shown to protect against focal and global cerebral ischemia as well as traumatic brain injury (Cheng et al., 2011; Yan et al., 2011; Lin et al., 2012). Furthermore, HBO preconditioning can promote both cerebral-protective and cardiac-protective effects, as determined by biochemical markers of neuronal and myocardial injury and clinical consequences in patients experiencing on-pump coronary artery bypass-graft surgery (Yogaraj et al., 2010; Li et al., 2011). Additionally, Alex et al. (2005) indicated that while pretreatment with 2.4-ATA HBO can reduce neuropsychometric dysfunction and modulate the inflammatory response that occurs after cardiopulmonary bypass. In basic studies, Sun et al. (2014) indicated that HBO preconditioning can significantly lessen cognitive impairment, and that it can be considered responsible for decreases in pro-inflammatory (either systemic or central) cytokines and caspase-3 activity. Similarly, Peng et al. (2010) indicated that continuous HBOPC could lead to an apparent improvement in impairments of associative learning and spatial memory. The study also showed that HBOPC has an effective anxiolytic effect and provided experimental evidence that supports the idea that HBOPC is useful for treating some affective disorders, including post-traumatic stress disorder. All

these results showed that HBO preconditioning is a safe and feasible procedure that can attenuate cognitive impairments after surgery. Additionally, they show that it is associated with anti-oxidants stress, anti-inflammation, and anti-apoptosis, as well as increased regional cerebral blood flow distribution and improvement of blood-brain barrier integrity (Li et al., 2007; Micarelli et al., 2013; Tian et al., 2013; Sun et al., 2014). Among these phenomena, the anti-oxidative stress and anti-inflammatory action of HBOPC are considered two crucial mechanisms with respect to easing POCD.

Antioxidant stress

(1) Anti-oxidative stress is achieved through activation of antioxidant enzymes and the decrease of pro-oxidant enzymes. HBO can elevate the partial pressure of oxygen and enhance the cellular tolerance against harmful stimuli by inducing the expression of cell protective proteins (Thom, 2009). Several studies have shown that the endogenous antioxidant-defense system becomes active in parallel with the development of HBOPC-induced neuroprotection (Nie et al., 2006; Thom, 2009; Huang et al., 2014). Numerous studies have shown that repeated preconditioning with HBO, but not normal conditions, can protect the spinal cord against I/R damage (Nie et al., 2006; Lu et al., 2012; Huang et al., 2014). These results have been attributed to the protective effect of up-regulated HO-1, and the activity of catalase and superoxide dismutase (SOD), which are triggered by HBO preconditioning (Li et al., 2007). Further investigations have shown that when dimethylthiourea, a potent free radical scavenger, was administered before each session of HBO treatment, the HBO-induced catalase and SOD activities were abolished. Similarly, when the catalase inhibitor 3-amino-1,2,4-triazole or dimethylthiourea was administered before spinal cord ischemia, the ischemic tolerance induced by HBOPC was attenuated (Nie et al., 2006; Huang et al., 2014). HBOPC was shown to decrease mortality rate, improve neurological recovery, lessen neuronal injury, reduce the level of malondialdehyde, and increase antioxidant activity of catalase and SOD (Li et al., 2008). Repeated HBO exposure supplies protection against oxygen toxicity in the central nervous system and this may be attributed to the decreased enzymatic activity of the antioxidant system and reduced levels of peroxynitrite, primarily in the hippocampus (Arieli et al., 2014). In related work, Peng et al. (2010) suggested that HBOPC is beneficial for the improvement of anxiety-like behavior and cognitive impairments arising from a single prolonged exposure to stress, and that this effect might be associated with inhibition of neuronal apoptosis *via* upregulation of thioredoxin reductase in stressed rats. These results confirmed that HBO preconditioning can induce upregulation of antioxidant-enzyme activity, leading to the generation of tolerance against I/R injury in the brain (Li et al., 2008). Expression of antioxidant enzymes, including Cu/Zn-superoxide dismutase, catalase, and glutathione peroxidase, have been shown to be enhanced by HBOPC (Kim et al., 2001; Li et al., 2008). Additionally, levels of pro-oxidant enzymes such as inducible nitric oxide synthase and gp91-phox have

been shown to significantly decrease after HBOPC (Zhang and Gould, 2014). However, few animal experiments reported that in the hippocampus of preconditioned rats, the activities of glutathione reductase and glucose-6-phosphate dehydrogenase were substantially decreased, while the activity of glutathione peroxidase was greatly increased (Arieli et al., 2014).

(2) Anti-oxidative stress is also achieved through the reactive oxygen species negative feedback loop. Transiently increased reactive oxygen species (ROS) levels activate a negative feedback loop, which leads to downregulation of oxidant enzymes and upregulation of antioxidant enzymes, thereby limiting subsequent higher levels of reactive species of oxygen and nitrogen production (Zhang and Gould, 2014). Furthermore, these results also indicate that ROS-related enzymes, including inducible nitric oxide synthase and nicotinamide adenine dinucleotide phosphate oxidase, rather than the ROS itself, can be crucial therapeutic targets for inhibiting oxidative stress.

(3) Anti-oxidative stress can also result from regulation of the ROS/mitogen-activated protein kinase (MAPK)/matrix metalloproteinase (MMP) and ROS/reactive nitrogen species (RNS) signaling pathways. HBO repairs ischemic wounds by decreasing the phosphorylation of extracellular signal-regulated kinases 1/2, c-Jun N-terminal kinase, and c-Jun, which suggests that mitogen-activated protein kinase is downregulated. All these results demonstrate that HBO acts *via* the ROS/MAPK/MMP signaling pathway to decrease neurodegeneration and ameliorate healing of ischemic wounds (Zhang and Gould, 2014). For example, the level of oxidative stress in ischemic wound tissue will be highly enhanced when the effect of HBO is completely blocked (Zhang and Gould, 2014). The oxidized N-linoleoyl tyrosine marker is sufficiently sensitive to detect oxidative stress imposed on cells and cell-free systems and to react selectively with the various ROS/RNS that are induced as a result. Thus, it is very useful for characterizing oxidative stress in general, and possibly also in oxidative stress-associated diseases (Szuchman et al., 2006). In one ingenious and delicate experiment, the oxidized N-linoleoyl tyrosine marker and the protein products of advanced oxidation were analyzed to demonstrate that preconditioning with multiple short HBO exposures followed by a long exposure will lead to a decrease in oxidative adducts, reaching even lower levels than that which initially existed in the control group. Endogenous antioxidant defense mechanisms induced by HBOPC play an important role in the formation of tolerance against long HBO exposure (Palzur et al., 2011).

(4) Antioxidant gene expression is another factor that increases anti-oxidative stress. Ferrer et al. (2007) showed that HBO can also act to activate antioxidant genes in human tissue. Endothelial cells are sensitive to high pressure oxygen exposure, which easily triggers the expression of many Nrf2-regulated antioxidant genes and molecular chaperones (Godman et al., 2010a, b). Additionally, the expression of antioxidant genes also occurs in other cells and tissues activated by HBO (Padgaonkar et al., 1997; Dennog et al., 1999; Rothfuss et al.,

2001; Verma et al., 2015).

All these observations serve to illustrate central role that anti-oxidative stress has as a mechanism underlying HBO treatment. The findings strongly suggest that HBO preconditioning is a potentially promising treatment for preventing the development of cognitive impairment after surgery.

Anti-inflammation

Despite advances in surgical techniques, the incidence of neuropsychometric dysfunction after surgery is high. Previous studies have demonstrated that the systemic and central inflammatory response plays a critical role in the development of postoperative cognitive impairment (Cibelli et al., 2010; Fidalgo et al., 2011; Barrientos et al., 2012; He et al., 2012; Hovens et al., 2014; Sun et al., 2014), and HBO treatment can improve POCD by attenuating inflammatory responses (Alex et al., 2005; Daniel et al., 2011; Lin et al., 2012a, b).

(1) Inflammatory responses can be reduced by increased expression of antioxidant genes. ROS plays a significant role in transduction cascades and pathways (Allen and Balin, 1989; Maulik, 2002; Ushio-Fukai and Alexander, 2004; Calabrese et al., 2007). HBO-related anti-inflammatory action can be partially induced through increased expression of antioxidant genes and other cellular defense genes *via* non-cytotoxic oxidative stimuli (Godman et al., 2010a, b; Matsunami et al., 2010, 2011; He et al., 2011; Simsek et al., 2011).

(2) Attenuation of inflammatory cells sequestration and adhesion can also reduce inflammatory responses. Tissue inflammation can occur when circulating neutrophils adhere to vascular endothelium through interactions with $\beta 2$ -integrins. However, neutrophil $\beta 2$ -integrin function is inhibited by exposure to HBO (Thom et al., 2008; Thom, 2009). In some cases, when animals or humans are exposed to HBO (2.8–3.0 ATA), the ability of circulating neutrophils to adhere to target tissues is temporarily inhibited, and inflammation is subsequently reduced (Thom, 1993; Zamboni et al., 1993; Thom et al., 1997; Labrousche et al., 1999; Kalns et al., 2002). In ameliorating I/R injuries, HBO is notably superior to $\beta 2$ -integrin monoclonal antibodies because it does not compromise the immune system (Mileski et al., 1990; Buras et al., 2006). At the same time, HBO exposure also leads to the impaired synthesis of cyclic guanosine monophosphate (Chen et al., 1996), which consequently reduces the activity of the neutrophil specific adhesion molecule CD18 (Malik and Lo, 1996). In the meantime, intercellular adhesion molecule 1, which is a marker of acute and chronic inflammation, acts as the receptor of leukocyte function associated antigen-1 (CD11a/CD18). This antigen is expressed on various inflammatory cells, including neutrophils, monocytes, and lymphocytes. For example, some studies have indicated that levels of intercellular adhesion molecule 1 are downregulated by HBO (Buras et al., 2000). By downregulating the accumulation of these cellular adhesion molecules, neutrophil sequestration and adhesion is attenuated, which reduced inflammation (Zamboni et al., 1993).

(3) Inflammation is also reduced through the inhibition

of pro-inflammatory cytokine production. The production of pro-inflammatory cytokines by monocyte-macrophages is inhibited after exposure to HBO. Pro-inflammatory cytokine-regulating adhesion molecules and enhancement of heme oxygenase-1 and heat shock proteins (*e.g.*, heat shock protein 70) (Rothfuss et al., 2001) are all mechanisms considered to play important roles in the anti-inflammatory effects of HBO. Compared with cells isolated from HBO-exposed rats (Lahat et al., 1995), those isolated from rats that were not previously exposed to HBO released more TNF- α . Additionally, in endotoxic rats, HBO treatment inhibits the endotoxin lipopolysaccharide-induced pro-inflammatory cytokines in monocytes and macrophages (Benson et al., 2003). Niu et al. (2007) reported that pyrogenic fever is prevented and suppressed by HBO *via* decreased overproduction of circulating TNF- α and hypothalamic prostaglandin E2. Similarly, several studies have demonstrated that the rise of TNF- α (Huang et al., 2006) and IL-6 (Niu et al., 2009) induced by lipopolysaccharide administration also can be significantly decreased by HBO pretreatment. Further, HBO decreases the release of IL-1 β and TNF- α in monocytes and macrophages derived from human blood (Benson et al., 2003). HBO exposure is also indicated to lessen cytokine induction (Yamashita and Yamashita, 2000; Kang et al., 2014). Additionally, HBO pretreatment inhibits activated inflammation and gliosis, and stimulates angiogenesis, neurogenesis, and production of IL-10. This consequently improves outcomes of traumatic brain injury (Lin et al., 2012). Pretreatment with HBO is beneficial for recovery after brain surgery, and can enhance expression of osteopontin, which reduces the expression of IL-1 β /nuclear factor- κ -gene binding and expansive protein kinase B (Akt) (Hu et al., 2015).

Discussion

As presented here, there is substantial evidence for a central involvement of oxidant stress and inflammatory response in POCD. In addition, numerous basic and clinical studies have demonstrated that HBOPC has a protective effect on POCD by reducing the detrimental inflammation and balancing the oxygen free radicals. The mechanism underlying preconditioning is not yet fully understood. Many researchers have suggested that HBOPC can alleviate cognitive impairment after surgery (Sun et al., 2014) and subsequently decrease the density of apoptotic cells and further recovery of nerve function (Wang et al., 2009; Lu et al., 2013). The mechanism underlying the protection might involve the reduction of systemic and hippocampal pro-inflammatory cytokines (Cheng et al., 2011) and upregulation of heat-shock protein 32 (Nie et al., 2006). Based on the experimental evidence, the prospect for using HBOPC to reduce cognitive impairment after surgery is bright. However, the number of relevant clinical studies remains low at present. Therefore, further studies are critical for understanding the fundamental mechanisms of this phenomenon and to explore the optimal parameters for pretreatment.

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