REVIEW

A review on the neuroprotective effects of hyperbaric oxygen therapy

Fahimeh Ahmadi, Ali Reza Khalatbary*
Molecular and Cell Biology Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

*Correspondence to: Ali Reza khalatbary, PhD, khalat90@yahoo.com.
orcid: 0000-0002-7686-2112 (Ali Reza khalatbary)

Abstract

Hyperbaric oxygen therapy, intermittent breathing of 100% oxygen at a pressure upper than sea level, has been shown to be some of the neuroprotective effects and used therapeutically in a wide range of neurological disorders. This review summarizes current knowledge about the neuroprotective effects of hyperbaric oxygen therapy with their molecular mechanisms in different models of neurological disorders.

Key words: apoptosis; clinical trial; hyperbaric oxygen; inflammation; *in vitro*; *in vivo*; neuroprotection; oxidative stress

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Introduction

Nervous system diseases are one of the leading causes of death and disability worldwide due to the limitation of effective treatment strategies. Although some promising strategies have been reported in the animal models of nerves system disorders, they often fail to work in clinical practice. Therefore, new treatment strategies need to be developed and exploited. Within the previous decades, various pharmaceutical compounds as well as various therapeutic methods with neuroprotective effects have been described, including high pressure oxygen therapy as a nondrug and noninvasive therapy. Hyperbaric oxygen (HBO) therapy (HBOT) is defined as the intermittent breathing of pure oxygen inside a hyperbaric chamber at a pressure above sea level. During HBOT, the amount of dissolved oxygen in the plasma as well as saturated hemoglobin with oxygen increases, leading to greater oxygen availability to the organs.[1,2] It is well documented that HBOT has neuroprotective effects against experimental spinal cord injury (SCI),[3] brain injury,[4,5] neurodegenerative disease,[6,7] peripheral nerve injury,[8,9] and neurotoxicity models of rodents.[10] On the other hand, clinical evidence to support the neuroprotective properties of HBOT is limited.[11] In regard to the neuroprotective effects of HBOT, accumulating evidence indicates an association between the beneficial effects to a variety of biological properties mainly anti-oxidative,[12] anti-inflammatory,[13] and anti-apoptotic properties,[14] in addition to improvement of oxygen supply and neural metabolism.[15,16] This paper presents an up-to-date review of the neuroprotective effects of HBOT with its molecular mechanisms in different models of neurological disorders in three parts.

In Vivo Studies

A lot of *in vivo* experimental studies have been conducted on the HBOT neuroprotection and its underlying molecular mechanisms, summarized in **Additional Tables 1–5**.

SCI

SCI is a complex process that is first caused by primary mechanical trauma or ischemia and then continues by secondary damage caused by various mechanisms.[17] SCI outcome is related to the amount of secondary damage caused by a series of biochemical, molecular, and cellular cascades including, apoptosis, inflammatory reaction, and lipid peroxidation.[18-21] In this regard, despite the report of Balentine[22] which indicates spinal cord gray matter necrosis and subsequent motor deficit following exposure to HBO (413.68 kPa on consecutive days) in rats, Higgins et al.[23] documented for the first time that HBOT during the early phases of SCI preserves the marginal spinal cord long tracts due to reduction of edema or reversal of focal hypoxia. HBOT shortly after spinal cord ischemia in rabbits (30 minutes after reperfusion) had protective effects through attenuation of the selective motor neuron death; however, delayed therapy (6 hours after reperfusion) with HBO did not change the prognosis.[24] Subsequent studies demonstrated that multiple HBOT (once daily for 1 week starting at 6 hours following injury) produced significantly more neurological improvements than the control group.[25,26] Biochemical analysis of HBOT on the oxidative status after SCI revealed that HBO prevents oxidative damage to the spinal cord.[27] Another study to determine other mechanisms of neuroprotective effects of HBOT on experimental SCI showed that HBOT significantly attenuated SCI-induced interleukin (IL)-1β and tumor necrosis factor-α (TNF-α) overproduction, and in turn significantly increased the number of both glial cell line-derived neurotrophic factor- and vascular endothelial growth factor (VEGF)-positive cells and spinal cord IL-10 production.[28] In regard to spinal cord tissue enzyme levels following HBOT, it was found that postoperative HBOT was useful in terms of biochemical parameters such as nitric oxide, glutathione peroxidase, superoxide dismutase (SOD), and nitric oxide synthase (NOS) activity rate in the damaged part of the spinal cord tissue following SCI.[29] HBOT decreases spinal cord edema, improves neuronal function, and stabilizes the blood-spinal cord barrier

through downregulation of matrix metalloproteinase (MMP)-2, IL-6, and MMP-9 and upregulation of VEGF.[30] Another study documented that HBOT through inducible NOS (iNOS) mRNA-iNOS-nitric oxide signaling pathway can promote the neuroprotection following SCI.3 The inflammatory process is one of the major causes of secondary SCI. In this regard, Yang et al.[31] documented that HBO intervention reduced secondary SCI via nuclear factor-κB (NF-κB) and high-mobility group protein B1 (HMGB1) downregulation in rats with acute SCI. In regard to the other neuroprotective mechanism of HBO on SCI, it was documented that hypoxia-inducible factor-1α (HIF-1α) reduction and VEGF elevation by HBO intervention may be inversely associated with spinal cord repair.[32] Another study documented that HBOT via Toll-like receptor (TLR)2/NF-κB signaling induced protective effects against rat SCI.[33] The researchers believe that HBOT reduces secondary SCI and promotes neurological outcome through TLR2/NF-κB signaling pathway. A research has shown that early HBOT (at the 1st hour after trauma) contributed to the biochemical and histopathological improvement of the rats after SCI.[34] To determine the mechanisms of HBOT in SCI, a study measured the expression levels of connexin 43 and VEGF in the damaged part of the spinal cord.[35] The results showed that VEGF significantly increased, while the level of connexin 43 significantly decreased after HBOT. Immunoreactive responses are like a double-edged sword in which the macrophages were considered as predominant inflammatory cells. In this regard, results of a study showed that HBOT by altering the macrophage M1 phenotype to the M2 phenotype modified the inflammatory environment, which promotes functional recovery and axonal extension.[36] Liang et al.[37] demonstrated that HBOT compromised NACHT domain leucine rich repeat and pyrin domain containing protein 3 (NALP-3) inflammasome, caspase 1 and adaptor molecule apoptosis-associated speck-like protein, in addition to mitigating IL-1β release in the damaged spinal tissue. HBOT has a protective effect on SCI by reducing neuronal cell apoptosis and *MMP-9/2* gene expression in rats, so that improved motor function scores and increased myelinated nerve fibers.[38] Studies emphasize the key role of endoplasmic reticulum stress in the induction of neuronal apoptosis following SCI. In this regard, it was documented that HBOT by inhibiting endoplasmic reticulum stress-induced apoptosis alleviated secondary SCI and thereby improved the neurological function.[39] Another study tested the hypothesis that HBOT via regulation of c-Jun N-terminal kinase (JNK) and glucose-regulated protein 78 expression ameliorates secondary SCI.[40] The results showed that HBOT increased glucose-regulated protein 78 level and decreased that of JNK which leads to tissue and motor recovery. In regard to the HBOT effects on inflammatory process after SCI, Kang et al.[41] documented that HBO intervention by regulation of NF-κB, TLR4, and HMGB1 signaling pathways reduces secondary SCI in rats. Autophagy, a lysosome mediated metabolic pathway, plays a key role in cell survival, differentiation, development, and homeostasis. It has been reported that regulation of autophagy improves neurological function after SCI.[42] In this regard, it was documented that enhancement of autophagy expression and acceleration of cell repair rate after SCI may be another mechanism of action of HBOT.[43] HBOT potentially by inhibiting receptor expression for monocyte chemoattractant protein 1 and advanced glycation end products recovers locomotor function.[44] Results of another study which was investigated the mechanisms of HBOT following SCI, suggested that reducing lipid oxidation and oxygen free radicals is one of the mechanisms.[45] Sun et al.[46] documented that HBO significantly improved the recovery of neuronal function and fractional anisotropy compared to SCI group on days 7, 14, and 21 after SCI. Recently, it was documented that HBOT improves neurological disorders by amelioration of apoptosis and suppressing dendritic/synaptic degeneration through upregulating the brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B signaling pathways in the anterior horn of spinal cord after SCI.[47] Also, another study revealed that HBO via stromal cell-derived factor-1/CXC chemokine receptor 4 axis activation and promotion of BDNF expression improves neurological function after SCI in rats.[48] HBO improves functional recovery through inhibiting iNOS, cyclooxygenase-2, glial fibrillary acidic protein, and neuron-glial antigen 2; meanwhile this process may be due to inhibition of NF-κB and Akt pathways.[49] Assessment of HBOT in rat model of SCI using diffusion tensor imaging showed that HBOT for 4 weeks is the more appropriate course.[50]

Brain injury

Studies have shown that brain damages after stroke or trauma are due to a variety of pathophysiological processes such as nitrative and oxidative stress, disruption of the blood-brain barrier (BBB), excitotoxicity, neural cell death, inflammatory reactions, and deficits in angiogenesis.[51-53] In this regard, Weinstein et al.[54] showed that HBOT conferred significant protection against death from untreated cerebral ischemia in anaesthetized gerbils, while histological examination showed that the extent of patchy bilateral ischemic neuronal damage was much less in surviving gerbils that received HBOT. After that, a study was conducted to determine the effects of HBOT on free radical generation and lipid peroxidation following global cerebral ischemia.[55] Results of this study showed that HBOT elevated the level of oxygen free radicals after ischemia in the brain, but, this elevation was not accompanied with increased lipid peroxidation or decreased neurophysiological recovery. In fact, despite the initial increase in free radical generation, the amount of peroxidation was similar to control group, while the cortical somatosensory evoked potential recovery was more than 50-fold in the HBO-treated animals relative to the control group. Another study documented that HBO reduces blood flow and brain vascular permeability after global cerebral ischemia in rabbits, however, recovery of the somatosensory evoked potential was the same as control and HBO groups.[56] While, HBOT in another study had no beneficial effects on neurologic outcome after acute focal cerebral ischemia.[57] It was reported that adult rats with middle cerebral artery occlusion which are exposed to HBO immediately or after a 60-minute delay showed improvement in motor impairment, as well as a reduced cerebral infarction compared to normal atmospheric pressure.[58] Assessment of the role of neutrophils and prophylactic HBO on cerebral injury revealed that HBOT before ischemia at 2.8 atmosphere absolute (ATA; 1 ATA = 101.325 kPa) for 45 minutes reduces myeloperoxidase

concentration, functional neurologic deficits, and cerebral infarct volume through inhibiting neutrophil sequestration.[59] Results of an investigation revealed that altered excitatory amino acids and brain energy metabolites which occurred during brain ischemia were regulated with HBOT at different times after ischemia.[60] Neurotrophin-3 plays a protective role against neuronal cell death in response to brain ischemia. In this regard, it was documented that HBOT decreases down-regulation of the post-ischemic neurotrophin-3 mRNA in the rat hippocampus.[61] HBOT has dual effect on cerebral infarction, and using HBO within 6 hours of ischemia-reperfusion injury can be beneficial but using HBO 12 hours or more after injury can be harmful, while tissue damage was not reduced by HBO during 4 hours of permanent focal cerebral ischemia.[62] Yin et al.[63] revealed that HBOT can lead to an inhibition of cyclooxygenase-2 over-expression in cerebral cortex after cerebral ischemia. Hyperbaric oxygenation reduces focal brain damage and reduces striatal dopamine secretion after occlusion of middle cerebral artery.[64] One of the molecular mechanisms of protection by HBO is the prevention of apoptosis which might preserve more tissue in the brain and improve neurological function. In this regard, Yin et al.[65] documented that HBOT (7 days after reperfusion) reduced brain infarction and improved neurologic scores by preventing apoptotic death (abolished DNA fragmentation and reduced terminal deoxynucleotidyl transferase dUTP nick end labeling-positive cell number) in rat ischemic cortex. It is well known that cerebral ischemia causes significant changes in the Na^+,K^+-ATPase and SOD activities. In this regard, it was documented that preservation of Na^+,K^+-ATPase and reinforcement of SOD activity are the possible mechanisms of HBOT in severe brain ischemia.[66] Assessment of the apoptotic cell number revealed that HBOT attenuated secondary brain damage in an experimental transient brain injury (TBI).[67] To elucidate the timing and mechanisms of HBO protection following cerebral ischemia, Veltkamp et al.[68,69] examined the early *in vivo* effects of HBO by repetitive magnetic resonance imaging and BBB permeability for sodium fluorescein 2 hours after transient focal ischemia. The results showed that HBO significantly decreased abnormal diffusion weighted imaging signal volume, lesion size on T2-weighted images, BBB permeability on T1-weighted images, and vasogenic edema assessed on T2-weighted images and histologic sections after 24 hours. Another study suggested that delayed, but multiple HBOT (2.5 ATA, 2 hours per dayfor 6 consecutive days) can improve neurological function and reduce cerebral infarction after transient focal ischemia.[70] Recent data emphasize the key role of apoptosis in the spread of lesion after TBI. In this regard, Bcl-xL, Bcl-2 and Bax proteins immunostaining in the brain tissue showed a significant increase in Bcl-2 and Bcl-xL anti-apoptotic proteins after HBOT, while staining for pro-apoptotic protein Bax did not significant.[71] A study was conducted to assess HBOT effects on intracranial pressure dynamics and survival in rat severe fluid percussion brain injury, concluding HBOT during the early phase of injury significantly diminished intracranial pressure elevation rate and reduced mortality rate.[72] In regard to BBB integrity preservation with HBOT after cerebral ischemia, Veltkamp et al.[73] documented that HBO decreases ischemic degradation of cerebral microvascular laminin-5 and blocks upregulation of postischemic plasma MMP. Calvert et al.[74] tested the hypothesis that HBO alternates the expression of HIF-1α in neonatal hypoxia-ischemia. The results showed that HBOT increased glucose transporter-1, glucose transporter-3, aldolase, and lactate dehydrogenase expression, while decreased p53 expression and HIF-1α-p53 interaction. Therefore, HIF-1α phenotype alternation is one of the underlying mechanisms of HBO neuroprotection following neonatal hypoxic-ischemic injury. Effectiveness of HBO is controversial in permanent ischemia models, so that in extensive focal ischemia HBOT is only effect in early recanalization.[75] HBOT can reduce neuronal apoptosis after TBI by reducing cytochrome c secretion and Bax dimers and over-regulation of Bcl-2 expression.[76] The effects of HBOT on inflammatory infiltration and expression of MMPs in rat dynamic cortical deformation have been evaluated.[77] HBOT showed that a significant reduction in the number of terminal deoxynucleotidyl transferase dUTP nick end labeling positive cells, neutrophilic inflammatory infiltration, and MMP-9 expression. The potential neuroprotective effects of HBOT in a focal cerebral ischemia model proved with significant neuroprotection (reduction of infarct volume) at 5 hours after ischemia that lasted for 168 hours.[78] A study revealed that early intra-ischemic HBOT could reduce hemorrhagic transformation (hemoglobin content) in a rat model of focal transient cerebral ischemia.[79] A 40-day series of 80 low-pressure HBOTs following TBI increases vascular density in the damaged hippocampus and improves cognitive function.[80] Zhou et al.[81] tested the effects of HBOT on mitochondrial function, as measured by cognitive improvement and cellular adenosine triphosphate after lateral fluid-percussion injury in rat. The results showed that HBO-treated animals had significantly higher levels of cerebral ATP and cognitive recovery and lower neuronal loss in the CA2/3 and hilar regions. In another study, cerebral partial pressure of oxygen was measured using electron paramagnetic resonance oximetry before and after occlusion of the middle cerebral artery and HBO exposure in rats.[82] The results of the study revealed that measurements of the partial pressure of oxygen showed no increase in ischemic or normal hemispheres minutes after HBO exposure, despite decreasing the infarct size. Another study suggested that hyperoxia protection is due to a negative regulation of the proapoptotic function of mitochondrial translocator protein such as mitochondrial membrane potential conservation after cerebral contusion.[83] Study on optimal dosing and timing of HBOT in a rat model of transient ischemia/reperfusion revealed that oxygen is a highly neuroprotective molecule when used early and in high doses.[84] Results of a study suggested that single HBOT has a time limitation of 12 hours after TBI; meanwhile multiple HBOTs have the ability to extend the delivery time window after TBI.[85] Sun et al.[86] found that HBO decreases infarct size and reduces post-thrombolytic intracerebral hemorrhage after thromboembolic occlusion of the middle cerebral artery in rats. Also, it was documented that hyperbaric oxygenation has neuroprotective effects in middle cerebral artery occlusion-induced brain injury through reducing hydroxyl free radical formation and glutamate release.[12] Zhao et al.[87] documented that HBOT increases claudin-5 and claudin-1 expression, and decreases permeability of the BBB

via the suppression of MMP-2 and MMP-9 after cerebral ischemia–reperfusion in rats, respectively. HBOT stimulates IL-10 overproduction, neurogenesis, and angiogenesis, while reduces gliosis following TBI in rat.[13] Also, HBOT reduced TBI-induced TNF-α expression and microglial activation during the acute phase of TBI resulting in a neuroprotective effect.[88] Data of another study showed that HBOT through promoting axonal sprouting and synapse remodeling can intensify neuroplastic responses, which contributes to the improvement of locomotor function following cortical ablation in rat.[89] Study on the effects of hyperbaric oxygenation on oxidative stress in acute transient focal cerebral ischemia in rats revealed significant reduction in infarct volume, activation of astrocyte, and increasing glutathione level.[90] Neonatal hypoxia-ischemia encephalopathy causes brain damage and neurodegeneration leading to cognitive and behavioral impairment. Liu et al.[91] suggested that HBOT is effective in promotion of histological and long-term functional recovery after neonatal hypoxia-ischemia brain damage due to caspase-3 inhibition and apoptosis inducing factor-mediated pathways. In regard to the effects of delayed HBOT on cerebral ischemia and its potential mechanisms, it was documented that delayed HBOT promotes neurogenesis and improves neurofunctional recovery in the late-chronic phase of stroke probably due to reactive oxygen species/HIF-1α/β-catenin pathway.[92] Despite the mentioned beneficial effects of HBOT in experimental models of stroke, Lu et al.[93] documented that HBOT increases brain damage area by activation of extracellular signal-regulated kinase (ERK) 1/2, which interrupts autophagy flux in a transient cerebral ischemic rat model. IL-10 plays an important role in the neuroprotection of HBOT against TBI, so that IL-10 deficiency aggravates the brain damage and abrogates the beneficial effects of HBOT on apoptosis, inflammation, and edema after injury.[94] A study was conducted to investigate the effect of the different hyperbaric oxygenation manipulations based on morphological, molecular-biological, and behavioral tests at 4 hours, 15 days and 75 days after TBI in rats.[95] The results showed that hyperbaric oxygenation inhibits cell apoptosis in the rat hippocampus and improves their physiological functions in the HBO-early group better than the HBO-delayed group. Another study demonstrated that HBO could enhance neuroprotection and improve prognosis through inhibiting cerebral edema, intensifying the metabolism of local neurons, reducing apoptosis, inhibiting the inflammatory reaction, and protecting BBB integrity in a blast-induced TBI model in rabbits.[96] Kraitsy et al.[97] showed that the long-term protective effects of HBOT are provided by the cortex remyelination, which is demonstrated by the recovery of sensorimotor function. Also, using diffusion-weighted imaging and DCE-magnetic resonance imaging revealed that HBO improves cytotoxic edema and impaired BBB and promotes the recovery of neurofunction after experimental TBI.[98] HBOT during the acute phase of TBI can attenuate TNF-α and transforming growth-interacting factor, and increase transforming growth factor β-1 which leads to decreased apoptosis in the affected cortex.[14] Liu et al.[99] found that daily HBOT significantly improved Morris water maze performance and attenuated edema in the ipsilateral hippocampus after TBI, suggesting that the therapeutic effect of HBO is at least partially mediated through reducing brain edema. The effects of HBO on cognitive dysfunction showed that HBOT, provided 5–7 days after craniocerebral trauma, improves cognitive function and neuroplasticity in a controlled cortical impact rat model.[100] Study of the relative neuroprotective effects HBOT and TLR4 knockout following temporary middle cerebral artery occlusion in mouse revealed that a single HBOT immediately after occlusion and after 24 hours reperfusion significantly reduces edema and improves perfusion, while, TLR4 knockout protects mice against ischemia but to a lesser extent than HBOT.[101] It was documented that HBOT due to inhibition of the TLR4/NF-κB signaling pathway protects the neurons after traumatic injury in rat, so that significantly inhibits the activation of the TLR4/NF-κB signaling pathway, reduces TNF-α, caspase-3, IL-1β and IL-6 expression, and reduces neural apoptosis and improves the neurological function.[102] HBOT increased expression of the heme oxygenase, nuclear factor erythroid 2-related factor 2 (Nrf2), and quinine oxidoreductase 1 in the brain tissue around the lesion and also improved neurological function after TBI.[103] A study revealed that HBO reduces IL-1β and IL-18 and suppresses protein expression of inflammasome components, along with high-mobility group box 1 reduction after TBI in the brain and serum.[104] In regard to repetitive mild TBI, it was found that HBOT significantly decreased the magnetic resonance imaging-identified abnormalities and tissue histopathology.[105] HBOT ameliorates TBI-induced depression-like behavior by reducing neuroinflammation if early intervention is possible, suggesting a possible mechanism by which depression-like behavior recovery might occur.[106] Results of a study showed that immediate and delayed HBOT for moderate TBI in mice have similar effects, so that displayed significant improvement in learning abilities, decreased neuronal loss and reactive astrocytes, and increased myelin basic protein.[107] Recently, it was found that HBO promotes neural stem cell proliferation and migration to the lesion area by activating VEGF/ERK signaling on day 7 after TBI.[108] It is well known that the nucleotide binding oligomerization domain like receptor family pyrin domain containing 3 (NLRP 3) inflammasome has been implicated in the secondary injury of TBI. In this regard, Qian et al.[109] documented that HBO improves motor score and reduces brain edema following TBI, along with IL 1β, IL 18, and NLRP 3 inflammasome components reduction. The results revealed that HBO decreases inflammation via modulation of microglial NLRP-3-inflammasome signaling. HBOT following hyperglycemic middle cerebral artery occlusion in rat reduces hemorrhagic transformation and infarction volume via ATP/NAD^+/Sirt1 pathway which may be a promising approach for diabetic patients with acute ischemic stroke.[110] Multiple HBOT significantly decrease the expression of c-jun, c-fos, and Bax, while increase the expression of Bcl-2, neurotrophin-3, glial cell line-derived neurotrophic factor, BDNF, and nerve growth factor.[111] Also, HBO exposure through increasing tight junction protein zonula occludens-1 and caveolin-1 improved BBB permeability following global cerebral ischemia/reperfusion injury in rat.[112] He et al.[113] found that HBOT attenuates neuronal apoptosis via Akt/GSK3β/β-catenin pathway after TBI.

Nerve injury

Muscle paralysis and neuropathic pain due to the destruction of motor and sensory neurons are among the most common symptoms of nerve injuries.[114,115] Meanwhile, neuroinflammation, oxidative stress, excitotoxicity, apoptosis, and neurotrophic support deficit are some of the mechanisms involved in neural degeneration after nerve injury.[116-118] In this regard, using the rat sciatic nerve model, the effect of HBO on peripheral nerve healing after destruction was evaluated.[119] Results of this study suggested that HBOT for 1 week following microsurgical repair promotes functional recovery in transected peripheral nerves. Also, another study concluded that HBO effectively saves fibers from ischemia.[120] Although, regard to rat peroneal nerve crush and transection injury there were no HBO-related changes in nerve/muscle force measurements and edema.[121,122] Whereas, a study on the regenerative effects of HBO on crushed sciatic nerve injury suggested that therapies consisting of 100% oxygen under pressure can improve the healing of peripheral nerve in rabbits.[123] HBOT (first at 0, 4, and 8 hours postoperatively and then every 8 hours) stimulates axonal outgrowth following a sciatic nerve crush lesion in rat, evaluated using the pinch-reflex test and with neurofilament staining.[124] Whereas, another study concluded that HBOT (twice daily for 3 consecutive days), had no influence on functional recovery after standard nerve crush injuries on sciatic nerves of rats using walking-track analysis.[125] After that, some investigators studied the effect of HBOT on axonal outgrowth in cellular and acellular nerve grafts of sciatic nerves in rat. The axonal outgrowth was significantly longer in animals treated with HBO after cellular nerve grafting,[126] in contrast to acellular nerve grafts with no beneficial effects on axonal outgrowth.[127] Another study confirmed that HBOT could not restore the gait or the strength of muscle after 90 days with nerve transection and repair or with nerve crush injury in rats.[128] Mrsić-Pelcić et al.[129] found that HBOT prevented ischemia-induced changes in the Na^+,K^+-ATPase activity after HBO administration in the optic nerves of global cerebral ischemia-exposed rats, while the level of the SOD activity in the ischemic animals was not changed. Evaluation of long-lasting effects of hyperbaric oxygenation on transected sciatic nerve and repaired with microsurgery showed functional recovery after 7 weeks.[130] Evaluation of the effects of HBOT on the histological pattern of damaged facial nerve in rabbits indicated an increase in the mean axon diameter 2 weeks after injury.[131] In spite of protective effects of HBOT in peripheral nerve injury, some evidence revealed that the ERK1/2 and p38 have been differently activated in the dorsal root ganglion by prolonged HBO exposure.[132] A study showed that HBOT reduces neuropathic pain and inhibits intraneuronal TNF-α production after chronic constrictive injury.[133] Analysis of the thermal hyperalgesia, mechanical allodynia, and neurochemical changes of neuropathic pain in rat sciatic nerve injury showed that repetitive HBOT greatly inhibited behavioral signs of neuropathic pain and nerve injury-induced induction of c-Fos and activation of astrocytes, and increased phosphorylation of N-methyl D-aspartate receptor subtype 2B receptor and the subsequent Ca^{2+}-dependent signals in rats.[134] Pre- and post-HBOT inhibits neuropathic pain following chronic constriction injury in rats through the regulation of neuronal and inducible NOS expression in the spinal cord, demonstrating that HBO has therapeutic effects on neuropathic pain.[8] The role of brain opioid receptors in the anti-allodynic properties of HBO following crush-induced neuropathic pain in rats was investigated in another study.[135] Data analysis of this study revealed that HBOT significantly decreased the nerve crush-induced allodynia, whereas, this anti-allodynic effect by the opioid antagonist naltrexone was reversed. Another study conducted to specify the effect of different times of HBOT application on transected-sciatic nerve regeneration using standard microsurgical techniques.[136] The results showed the best gait analysis and less fibrosis with HBOT started at postoperative first hour compared to postoperative first and second week. In regard to the neuroprotective mechanism of HBOT on chronic constriction-induced neuropathic pain, it was revealed the microglial mitophagy involvement.[137] Results of our laboratory revealed that pre- and post- HBOT had neuroprotective properties following sciatic nerve degeneration through decreasing lipid peroxidation, increasing SOD and catalase activities, attenuating caspase-3 and cyclooxygenase-2 expression, and increasing S100β expression.[9] Recently, it was found that iNOS and neuronal NOS levels were significantly decreased with HBOT following chronic construction injury in rats.[138]

Neurodegenerative disease

Neurodegenerative diseases are associated with progressive nerve cell damage and neuronal loss that impair motor or cognitive function.[139] On the other hand, oxidative stress and inflammatory response play an important role in the pathogenesis of neurodegenerative diseases.[140-142] Dave et al.[143] found that HBOT in an experimental motor neuron disease significantly ameliorates mitochondrial dysfunction in the spinal cord and motor cortex, meanwhile greatly delays the disease onset. Chen et al.[144] documented that HBO prevents cognitive impairments in D-galactose induced aging model in mice due to reducing oxidative stress and blocking NF-κB pathway. Attenuation of neuroinflammatory processes is another possible mechanism underlying the effect of HBO on Alzheimer's disease through decreasing microgliosis, astrogliosis, TNF-α, and IL-1β and increasing scavenger receptor A, arginase1, IL-4, and IL-10 expression.[145] Research on Parkinson's disease has shown that 11-week exposure to mild HBO inhibits the decrease of dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease.[146]

Neurotoxic injury

For the first time, the effect of HBOT on the peripheral nerve disorder produced by administration of clioquinol, an antifungal and antiprotozoal drug which is neurotoxic in large doses, to rabbits was studied.[147] The damage of myelin and axons, which was apparent after administration of clioquinol, decreased in grade with HBO. In another study, the effect of HBO on streptozotocin-induced diabetic neuropathy was investigated.[148] The findings indicated that HBOT will partially reverse induced neuropathy in chronic diabetes. In contrast, Aydin et al.[149] did not document any beneficial effects of HBOT on nerve regeneration in early diabetes. In regard to

the protective effects of HBOT following severe carbon monoxide neurotoxicity, it was found that HBO is not effective in preventing neurologic sequelae in mice following severe carbon monoxide neurotoxicity.[150]

In Vitro Studies

A few numbers of *in vitro* studies regarding HBO neuroprotection and its basic molecular mechanisms began to accumulate (**Additional Table 6**). In spite of the results suggested that activation of N-methyl-D-aspartate receptors and nitric oxide production are involved in the neurotoxicity produced by prolonged HBO exposure (6 ATA for 30, 60, and 90 minutes) in primary rat cortical cultures,[151] Günther et al.[152] found that HBO had neither favorable nor unfavorable effects on the early morphological and functional restitution of ischemically damaged primary corticoencephalic cell cultures of rats under Hypoxia and glucose-deprivation (*in vitro* ischemia). β-Catenin, a protein involved in Wnt signaling and cell adhesion, plays an important role in the development of nervous system. In this regard, it was documented that HBOT intensifies the neural stem cell proliferation and neurogenesis by β-catenin-induced activated Neurogenin 1 gene and suppresses astrocytogenesis by β-catenin-induced down-regulated bone morphogenetic protein 4 gene.[153] An *in vitro* study revealed that HBO via the induction of heat shock protein 32 protected cultured spinal neurons from oxidative and oxygen glucose deprivation injury, while HBO through reactive oxygen species/p38 mitogen-activated protein kinase/Nrf2 pathway induced the expression of heat shock protein 32.[154] Another study documented that *in vitro* HBO after cell injury significantly accelerated neural stem cell proliferation and the VEGF/phospho-ERK pathway.[108] Examination of the effect of HBOT on the neuroprotective factor secretion, proliferation, and BDNF-release in fibroblasts and mesenchymal stem cells showed a significant increased proliferation of fibroblasts and altered the protein expression pattern in mesenchymal stem cells after 5 days of HBOT.[155] Also, it was found that HBOT promotes differentiation of neural stem cells into oligodendrocytes and neurons and reduces the number of astrocytes via regulation of Wnt3/β-catenin and BMP-2 signaling pathways.[156]

Clinical Trials

Despite the growing body of preclinical evidence confirming HBOT neuroprotection, few clinical studies have been performed and therefore limited information is currently available, which are summarized in **Additional Table 7**. In regard to the neuroprotective effects of HBOT against spinal cord injuries, results of a clinical trial study indicated that 8 weeks of HBOT can significantly improve nerve function and consequently promote daily life activities in the patients with incomplete SCI.[157] Another randomized clinical trial studied the effect of HBO in 79 patients with acute SCI.[158] Results of this study showed that plasma HMGB1 and NF-κB expression down-regulated with HBOT in patients on days 3, 7, 10 and 30, and meanwhile F-wave chronodispersion decreased with HBOT on days 10 and 30. Also, American Spinal Injury Association and Frankel Grade motor/pain scores on day 30 were significantly improved in the treatment group.

In regard to brain injuries, results of a prospective randomized trial showed that HBOT did not increase the number of patients in the favorable outcome categories following severely brain injury.[172] A double-blind pilot study suggested that HBO improves outcome after acute ischemic stroke.[159] Rockswold et al.[160] for the first time demonstrated a prolonged effect of HBOT on cerebral blood flow and cerebral metabolism in severely brain injured patients, while, the increased cerebral metabolic rate of oxygen and decreased ventricular cerebrospinal fluid lactate levels after therapy indicated that HBO may improve aerobic metabolism in these patients. Another study documented that HBOT could improve obviously brain electric activity mapping, Glasgow coma and outcome scales in patients with severe brain injury, and decrease the morbidity and mortality.[161] A study was designed to investigate the efficacy, safety, and feasibility of HBO (60 minutes with 100% oxygen to 2.5 ATA) in 33 ischemic stroke patients.[173] Compared to medication treatment alone, HBOT was more effective in controlling epilepsy, improving clinical symptoms, and relieving hydrocephalus in patients with post-brain injury neural status.[162] Treatment of chronic brain injury with HBOT significantly improved motor skills, daily living, communication, and socialization.[163] Results of a study on the metabolism and cerebral circulation of patients in the subacute phase of head injury showed that HBOT significantly decreased both pulsatility index and jugular venous lactate after HBOT.[164] To assess the beneficial effects of HBOT on the prognosis of patients with subacute TBI , the clinical status of the patients were assessed before and 3 to 6 months after HBOT with the Glasgow outcome and Glasgow coma scales.[11] The Glasgow coma and outcome scales of the HBOT group were improved 6 months after HBOT, with minimal adverse side effects. Meanwhile, another study revealed that HBOT (2.4 ATA) following mild TBI had no effect on post-concussive symptoms.[174] Evaluation of the whether elevated dissolved oxygen by HBOT could activate neuroplasticity after stroke, revealed that HBOT significantly improves neurological outcome even in the late chronic stage.[165] A prospective, randomized phase II clinical trial revealed that combined hyperbaric hyperoxia/normobaric hyperoxia therapies after severe TBI significantly improved oxidative metabolism markers, decreased intracranial hypertension, and improved markers of cerebral toxicity, while the mortality significantly reduced.[166] Boussi-Gross et al.[167] tested the effect of HBOT on brain function and quality of life in patients with mild TBI. Results of this study revealed that HBOT induces neuroplasticity and improves quality of life with prolonged post-concussion syndrome. However, another studies demonstrated that HBO at either 1.5, 2.0 or 2.4 ATA equivalent had no effect on postconcussion symptoms after TBI.[175-178] A study conducted to evaluate the safety and potential long-term neurological consequences of HBOT on intracerebral hemorrhage in diabetic patients.[168] Results of this study showed that early HBOT is safe and effective in terms of long-term neurological outcome in diabetic patients suffering from intracerebral hemorrhage. Recently, a retrospective analysis was performed on 62 consecutive patients prescribed for HBOT after stroke.[169] Results of this study showed that some patients ($n = 24$) significantly benefitted from HBOT by

improving their clinical neurological status and quality of life.

In regard to nerve injuries, a clinical trial conducted in patients with idiopathic trigeminal neuralgia supported that one course of HBOT (10 consecutive days) is an effective approach for treating neuropathic pain in human with produced a long-lasting, rapid-onset, and dose-dependent analgesic effects.8

In regard to neurodegenerative disease, a phase I safety study and a phase II efficacy study of HBOT in patients with ALS did not recommended HBOT in ALS patients.[179,180] Some studies conducted on hyperbaric-oxygen therapy of multiple sclerosis. Results of a randomized, placebo-controlled, double-blind study suggested a positive effect of HBO on advanced multiple sclerosis.[170] In contrast, short-term results of a placebo-controlled, double-blind trial did not support the claims made for HBO in the management of multiple sclerosis,[181] similar to some other studies.[182-187]

In regard to neurotoxic injury, results of a study suggested that repetition of HBOT prevents the delayed neuropsychiatric sequelae of carbon monoxide poisoning when applied individually with monitoring of quantitative electroencephalography as an indicator of efficacy.[171]

Conclusion

In recent years, HBOT has attracted considerable attention because of its biological properties. Neuroprotection benefits of HBOT, as a therapeutic option, confirmed with a lot of preclinical *in vivo* and *in vitro* studies. These beneficial effects have been mainly attributed to anti-oxidative, anti-inflammatory, and anti-apoptotic properties, in addition to improvement of oxygen supply and neural metabolism and stimulating autophagy. The evidence presented in this review indicates the potential of HBOT in treatment and prevention of a variety of injuries to the nervous system. Meanwhile, because limited data is available to demonstrate the neuroprotective effects of HBOT in humans, newly designed clinical trials are needed on HBOT's neuroprotection and its possible mechanisms as well as the course and dose of HBOT.

Author contributions
FA and ARK designed and wrote the manuscript. Both authors read and approved the final manuscript.
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Additional files:
Additional Table 1: Summary of studies regarding the effects of HBOT against spinal cord injury.
Additional Table 2: Summary of studies regarding the effects of HBOT against brain injury.
Additional Table 3: Summary of studies of the effects of HBOT against nerve injury.
Additional Table 4: Summary of studies of the effects of HBOT against neurodegenerative diseases.
Additional Table 5: Summary of studies of the effects of HBOT against neurotoxic injury.
Additional Table 6: Summary of in vitro studies on neuroprotective effects of HBOT.
Additional Table 7: Summary of clinical trials on neuroprotective effects of HBOT.

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Additional Table 1: Summary of studies regarding the effects of HBOT against spinal cord injury

Author	Year	Model of injury	Therapy schedule	Finding	Possible mechanism
Higgins et al.[23]	1981	Transdural impact injury in cat	2 ATA for a period of 3 hours	Preservation of marginally injured neuronal elements of the spinal cord long tracts	Reversal of focal tissue hypoxia or reduction of tissue edema
Murakami et al.[24]	2001	Ischemia in rabbit	3 ATA for 1 h at 30 min after reperfusion	Attenuation of the selective motor neuron death and improvement of neurologic functions	Without providing possible mechanisms
Huang et al.[25,26]	2003	Contusion in rat	2.8 ATA for 1 h/day for 1 wk starting at 6 h following injury	Retained more sparing tissue and improved neurological outcome	Without providing possible mechanisms
Kahraman et al.[27]	2007	Clip compression in rat	2.8 atmospheres twice daily for a total of eight 90 min-sessions	Diminished TBARS, SOD and GSH-Px	Prevention of oxidative stress
Tai et al.[28]	2010	Clip compression in rat	2.5 ATA for 2 h immediately after SCI	Attenuating overproduction of IL-1β and TNF-α, stimulating production of GDNF, VEGF, and IL-10, attenuating hindlimb dysfunction	Upregulation of growth factors
Dayan et al.[29]	2012	Clip compression in rat	2.80 ATA for 60 min daily for 5 d	Decreasing SOD, NOS and NO, improving functional recovery	Without providing possible mechanisms
Yang et al.[30]	2013	Contusion in rat	2.5 ATA, twice daily at 12 h intervals	Reduced spinal cord edema, stabilized the blood–spinal cord barrier, and promoted recovery of neuronal function	Down regulation of IL-6, MMP-2, and MMP-9 and up regulation of expression of VEGF
Huang et al.[3]	2013	Contusion in rat	2 ATA, 30 min after SCI for 80 min once daily for consecutive 24 d	Reduced the mRNA and protein expression of iNOS and the serum NO content, improved motor evoked potential and locomotor recovery	Through the iNOS mRNA-iNOS-NO signaling pathway
Yang et al.[31]	2013	Contusion in rat	2.5 ATA, twice daily in the first 3 d at intervals of 8 h, and reduced to once daily thereafter	Down regulated HMGB1 and NF-κB	Anti-inflammatory activity
Zhou et al.[32]	2013	Contusion in rat	2 ATA for 60 min twice daily for the first 3 d and once daily for the following days	Repair of damage spinal cord, improved the hind limb functional recovery	Upregulation of VEGF and downregulation of HIF-1α
Tan et al.[33]	2014	Contusion in rat	2 ATA, 6 h after surgery for a 60 min once a day	Decreased TLR2 and NF-κB expression and histological scores as well as IL-1β and TNF-α levels	Inhibiting inflammatory responses
Yaman et al.[34]	2014	Clip compression in rat	2.4 ATA in two 90-min sessions for 5 d	Improved motor recovery, diminished nitrite levels	Without providing possible mechanisms
Liu et al.[35]	2014	Contusion in rat	2.0 ATA twice per day for 3 d and then daily for the following days consecutively after surgery	Improved hindlimb motor function, decreased histology scores	Changing VEGF and CX43 expression level
Geng et al.[36]	2015	Clip compression in rat	2.8 atm for 90 min every 12 h	Increased IL-4 and IL-13 levels, reduced TNF-α and IFN-γ levels, shifting the macrophage phenotype from M1 to M2	Macrophage polarization
Liang et al.[37]	2015	Contusion in rat	2 ATA for 60 min twice per day at 8 h intervals for the first 3 d and daily thereafter immediately after injury	Compromised NALP-3, ASC and caspase-1, mitigated IL-1β release	Inactivating NALP-3 inflammasome
Hou et al.[38]	2015	Contusion in rat	0.2 MPa at 0.01 MPa/min for 4 h after SCI, four times daily for 3 d	Improved motor function scores and increased myelinated nerve fibers	Reducing apoptosis and expression of MMP-9/2
Liu et al.[39]	2015	Contusion in rat	2.0 ATA 6 h after surgery for 60 min once a day	Decreased CHOP and caspase-12 and caspase-3, improved neurological function	Inhibiting ER stress induced apoptosis
Liu et al.[40]	2015	Contusion in rat	2.0 ATA 6 hours after surgery, once daily for 60 minutes	Increased GRP78 level, decreased JNK and suppressed caspase-3 activation, improved hind limb motor function	Inhibiting the ERS response
Kang et al.[41]	2015	Contusion in rat	2.5 ATA once daily, 24 h after the injury	Reduced HMGB1, TLR4, and NF-κB, improved locomotor function	Decreasing inflammatory process
Sun et al.[43]	2016	Contusion in rat	2.0 ATA for 90–100 min with inter-vales of 15 min, once per day	Upregulated Beclin-1 and LC3II, improved locomotor function	Enhancing autophagy expression
Wang et al.[44]	2016	Contusion in rat	2.0 ATA 60 min once daily	Inhibited RAGE and MCP-1, improved locomotor function	Relieving secondary inflammatory responses
Sun et al.[45]	2017	Contusion in rat	3 ATA for 60 min, began at 2 h after SCI, once a day for 5 d	Increased SOD activities and decreased MDA levels, improved locomotor function, less cystic degeneration	Increasing oxygen free radical scavenging and reducing lipid oxidation
Sun et al.[46]	2018	Contusion in rat	2.0 ATA immediately after surgery for 1 h	Improved neuronal function and FA	Without providing possible mechanisms
Ying et al.[47]	2019	Contusion in rat	2.0 ATA at 6 h after surgery for 90 min	Ameliorated neurological impairment, decreased TUNEL reaction, suppressed dendritic/synaptic degeneration	Upregulating the BDNF/TrkB signaling pathways
Meng et al.[48]	2019	Contusion in rat	2.0 ATA for twice a day at 12-h intervals for 3 consecutive days and thereafter once a day	Improved functional recovery	Activating SDF-1/CXCR4 axis and promoting BDNF expression
Zhou et al.[49]	2019	Contusion in rat	2 ATA for 60 min, three consecutive courses and each course lasted 10 d, once a day	Improved functional recovery, inhibited iNOS, COX-2, GFAP and NG2	Inhibiting inflammation and glial scar formation
Liu et al.[50]	2019	Contusion in rat	2.0 ATA for 60 min, 6 h after injury twice per day at 8 h intervals for the first 3 d and then daily for the consecutive days	Recovery of locomotor function	Without providing possible mechanisms

Note: 1 ATA = 101.325 kPa. ASC: Apoptosis-associated speck-like protein; ATA: atmosphere absolute; BDNF: brain-derived neurotrophic factor; CHOP: CCAAT-enhancer-binding protein homologous protein; COX-2: cyclooxygenase-2; CX43: connexin 43; CXCR4: CXC chemokine receptor 4; ERS: endoplasmic reticulum stress; FA: fractional anisotropy; GDNF: glial cell line-derived neurotrophic factor; GFAP: glial fibrillary acidic protein; GRP78: glucose-regulated protein 78; GSH-Px: glutathione peroxidase; HBOT: hyperbaric oxygen therapy; HIF-1α: hypoxia-inducible factor 1α; HMGB1: high mobility group protein B1; IFN-γ: interferon-γ; IL: interleukin; iNOS: inducible nitric oxide synthase; JNK: c-Jun N-terminal kinase; LC3II: Microtubule-associated proteins 1A/1B light chain 3B II; MCP 1: monocyte chemoattractant protein 1; MDA: malondialdehyde; MMP: matrix metalloproteinase; NALP-3: NACHT, LRR and PYD domains-containing protein 3; NF-κB: nuclear factor κB; NG2: neuron-glial antigen 2; NO: nitric oxide; NOS: nitric oxide synthase; RAGE: receptor for advanced glycation end products; SCI: spinal cord injury; SDF-1: stromal cell-derived factor-1; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; TLR: Toll-like receptor; TNF-α: tumor necrosis factor-α; TrkB: tropomyosin receptor kinase B; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; VEGF: vascular endothelial growth factor.

Additional Table 2: Summary of studies regarding the effects of HBOT against brain injury

Author	Year	Model of injury	Therapy schedule	Finding	Possible mechanism
Weinstein et al.[54]	1986	Cerebral ischemia in gerbil	1.5 ATA for 15 min	Decreased ischemic neuronal damage and mortality rate	Without providing possible mechanisms
Mink et al.[55]	1995	Global cerebral ischemia in rabbit	2.8 ATA for 75 min	Increased oxidized glutathione and the ratio of oxidized glutathione to reduced glutathione, promoted cortical somatosensory evoked potential recovery	Without providing possible mechanisms
Mink et al.[56]	1995	Global cerebral ischemia in rabbit	2.8 ATA for five cycles of oxygen and air, each for 20 and 5 min	Reduced brain vascular permeability and cerebral blood flow	Without providing possible mechanisms
Chang et al.[58]	2000	Cerebral ischemia in rat	3 atm, 2 × 90 min at a 24-h intervals	Reduced ischemic brain damage and behavioral dysfunctions	Without providing possible mechanisms
Atochin et al.[59]	2000	Temporary MACO	2.8 atm for 45 min before ischemia	Reduced MPO concentration, functional neurologic deficits, and cerebral infarct volume	Inhibiting neutrophil sequestration
Badr et al.[60]	2001	Temporary MACO	3 ATA for 1 h	Decreased glucose, pyruvate, and glutamate	Regulating brain energy metabolites and excitatory amino acids
Yang et al.[61]	2001	Transient forebrain ischemia in rat	2.5 ATA for 2 h	Increased cell survival	Reducing down-regulation of the NT-3 mRNA level
Badr et al.[62]	2001	Transient MACO	3 ATA for 1 h	Decreased infarcted area in the 3- and 6-h HBOT groups, increased infarcted area in the 12- and 23-h therapy groups	Without providing possible mechanisms
Yin et al.[63]	2002	Transient focal cerebral ischemia in rat	3 ATA for 1 h, at 6 h after reperfusion	Reduces infarct area	Inhibition of COX-2 over-expression
Yang et al.[64]	2002	Transient focal cerebral ischemia in rat	2.8 ATA during ischemia	Reduced edema and neuronal shrinkage	Reduction of dopamine
Yin et al.[65]	2003	Focal cerebral ischemia in rat	2.5 ATA for 2 h, at 6 h after reperfusion	Reduced brain infarction and improved neurologic scores	Preventing apoptotic death
Mrsić-Pelcić et al.[66]	2004	Global cerebral ischemia in rat	Not available	Enhanced SOD activity and preserved Na^+,K^+-ATPase activity	Without providing possible mechanisms
Palzur et al.[67]	2004	Brain contusion in rat	2.8 ATA for two consecutive sessions of 45 min each, 3 h after injury and thereafter twice every day for 3 consecutive days	Reduced the number of TUNEL positive cells and the volume of the lesion	Without providing possible mechanisms
Veltkamp et al.[68,69]	2005	Focal cerebral ischemia in rat	3.0 ATA for 1 h	Reduced volume of abnormal DWI signal and lesion size on T2w, increased BBB permeability and vasogenic edema	Without providing possible mechanisms
Yin and Zhang[70]	2005	Transient focal ischemia in rat	2.5 ATA for 2 h per day, repeated daily for 6 d	Decreased infarct ratio and ameliorated neurological deficits	Without providing possible mechanisms
Vlodavsky et al.[71]	2005	Cerebral contusion in rat	Not available	Decreased apoptosis and reduced TUNEL-positive cells	Increasing Bcl-2 and Bcl-xL
Rogatsky et al.[72]	2005	Severe traumatic brain injury in rat	1.5 ATA for 60 min beginning 2 h after FPBI	Diminished ICP elevation rate and decreased mortality level	Without providing possible mechanisms
Veltkamp et al.[73]	2006	Transient focal cerebral ischemia in rat	3.0 ATA for 1 h With a delay of 45 min after filament introduction	Preserved integrity of the BBB	Attenuating degradation of laminin-5 and blocked MMP-9 upregulation
Calvert et al.[74]	2006	Hypoxia-ischemia in rat	2.5 ATA for 2 h	Increased GLUT-1, GLUT-3, LDH, and Ald, decreased HIF-1α-p53 interaction and p53 expression	Alteration of the HIF-1α phenotype
Liu et al.[76]	2006	Traumatic brain injury in rat	Not available	Alleviated neuronal apoptosis	Reducing Cyt C and Bax and up-regulating Bcl-2
Vlodavsky et al.[77]	2006	Traumatic brain injury in rat	2.8 ATA, two sessions of 45 min each	Decreased neutrophilic inflammatory infiltration, MMP-9 expression, and TUNEL-positive cells	Without providing possible mechanisms
Henninger et al.[78]	2006	Embolic model of focal cerebral ischemia with partially spontaneous reperfusion	2.5 ATA for 60 min beginning 180 min after MCAO	Reduced infarct volume	Without providing possible mechanisms
Qin et al.[79]	2007	Focal transient cerebral ischemia	3 ATA for 1 h, 30 min after MACO	Reduces BBB disruption, hemorrhagic transformation, mortality, and infarct volume and swelling	Without providing possible mechanisms
Harch et al.[80]	2007	Chronic traumatic brain injury in rat	1.5 ATA, 7 d/wk	Improved cognitive function	Increasing hippocampus vascular density
Zhou et al.[81]	2007	Lateral fluid-percussion injury	1 h of hyperbaric oxygen plus 3 h of normobaric 100% oxygen	Increased cerebral ATP, improved cognitive recovery and reduced hippocampal neuronal cell loss	Without providing possible mechanisms
Hou et al.[82]	2007	Middle cerebral artery occlusion in rat	2.0 ATA for 60 min	pO(2) not show an increase in the ischemic or normal hemispheres despite decreasing the infarct size	Without providing possible mechanisms
Soustiel et al.[83]	2008	Cortical contusion in rat	Not available	Reduced TSPO expressing and TUNEL positive cells	Negative regulation of the proapoptotic function of mitochondrial TSPO
Yang et al.[12]	2010	Middle cerebral artery occlusion in rat	2.8 ATA for 1 h during ischemia	Alleviated brain injury	Reducing hydroxyl free radical formation and glutamate release
Zhao et al.[87]	2011	Cerebral ischemia-reperfusion in rat	0.25 MPa for 60 min and ventilated with pure oxygen for 10 min at intervals	Decreased permeability of the BBB	Reducing MMPs activity and augmenting claudins expression
Lin et al.[13]	2012	Traumatic brain injury in rat	2.0 ATA for 1 h/d for three consecutive days	Reduced motor and cognitive dysfunction, cerebral infarction and apoptosis	Inhibiting activated inflammation and gliosis , stimulating both angiogenesis and neurogenesis

Additional Table 2: Continued

Author	Year	Model of injury	Therapy schedule	Finding	Possible mechanism
Lim et al.[88]	2013	Traumatic brain injury in rat	2.0 ATA at 1 h or 8 h after TBI	Attenuated cerebral infarction, reduced microglial activation, TNF-α expression, and neuronal apoptosis	Attenuating microgliosis and proinflammatory cytokine expression
Brkic et al.[89]	2012	Cortical ablation in rat	2.5 ATA for 60 min, once a day for 10 d	Recovered motor functions, enhanced recovery of muscle strength, induced over-expression of GAP43 and SYP	Intensify neuroplastic responses by promoting axonal sprouting and synapse remodeling
Wang et al.[90]	2012	Acute transient focal cerebral ischemic rat	3 ATA for 1 h, starting at 3 h post brain ischemia	Reduced infarct volume and activated astrocyte, increased glutathione level	Decreasing oxidative stress
Liu et al.[91]	2013	Neonatal hypoxia-ischemia in rat	2.5 ATA for 90 min, 1 h after hypoxia exposure	Improved neurobehavioral functions especially for cognitive performances, reduced lesion size, decreased expression of caspase-3 positive cells and nuclear AIF translocation	Suppression of apoptosis
Hu et al.[92]	2014	Middle cerebral artery occlusion in rat	2.5 ATA starting at 7 d after MCAO for 3 sessions, each session was 1.5 h daily for consecutive 7 d followed with 5 d break	Promoted neurogenesis and improved neurofunctional recovery, increased ROS and HIF-1α, and up-regulated neurogenin-1, doublecortin and synapsin-1	Mediated by ROS/HIF-1α/β-catenin pathway
Chen et al.[94]	2014	Traumatic brain injury in mice	2.0 ATA for 1 h	Reduced lesion volume and cerebral edema, improved neurological status, attenuated apoptosis and inflammation, improved BBB	enhancing serumal and cerebral IL-10 protein levels
Zhang et al.[96]	2014	Blast-induced traumatic brain injury model in rabbit	2.0 ATA once, 12 h after injury	Promoted metabolism of local neurons, inhibited brain edema, protected BBB integrity, decreased cell apoptosis, and inhibited inflammatory response	Without providing possible mechanisms
Kraitsy et al.[97]	2014	Traumatic brain injury in rat	Repeated 2.2 atm for 1 h at days 1–21 following trauma induction	Regressed neurological impairment, increased myelin basic protein isoforms, PLP expression and myelin	Pronounced remyelination
Wee et al.[14]	2015	Traumatic brain injury in rat	2.0 ATA for 1 h immediately after TBI	Reduced TNF-α, neuronal damage, and neuronal apoptosis, attenuated TGIF and increased TGF-β1	Decreasing proinflammatory cytokine and TGIF, and increasing TGF-β1 leading to decreased neuronal apoptosis
Liu et al.[99]	2015	Traumatic brain injury in rat	2 ATA for 60 min, 6 h after injury once per day for 2 wk	Improved post-TBI MWM performance	Reducing edema
Pushkov et al.[101]	2016	Temporary middle cerebral artery occlusion in mouse	2.5 atmospheres pressure for 60 min	Reduced edema and improved perfusion better than TLR4 knockout	Without providing possible mechanisms
Meng et al.[102]	2016	Traumatic brain injury in rat	0.12 MPa for 60 min, 2 h after TBI, twice with a 10 h interval	Reduced caspase-3, TNF-α, IL-6 and IL-1β, reduced apoptosis, improved neurological function	Inhibition of the TLR4/NF-κB signaling pathway
Meng et al.[103]	2016	Traumatic brain injury in rat	0.12 MPa for 60 min, two therapies were a 10-h period	Increased Nrf2, HO-1, and NQO-1, reduced the number of apoptotic and injured nerve cells, improved neurological function scores	Up-regulation of the Nrf2 signaling pathway
Geng et al.[104]	2016	Traumatic brain injury in mice	Not available	Improved motor score and reduced brain edema, suppressed protein expression of inflammasome components, reduced IL-1β, IL-18 and HMGB1	Inhibiting the activation of inflammasome signaling
Huang et al.[105]	2016	Repetitive mild traumatic brain injury in rat	1 h/d for 3 d at 2 ATA consecutively, starting at 1 d after initial injury	Improved cumulative tissue damage	Without providing possible mechanisms
Lim et al.[106]	2017	Traumatic brain injury in rat	2.0 ATA for 60 min immediately after TBI for 3 d	Attenuated TBI-induced depression-like behavior, reduced neuronal apoptosis, marker OX42 activation, and TNF-α expression	Attenuating neuroinflammation
Baratz-Goldstein et al.[107]	2017	Traumatic brain injury in mice	HBOT for 4 consecutive days, at 3 h and 7 d post-injury	Improved learning abilities, decreased neuronal loss and reactive astrocytes, increased myelin basic protein	Without providing possible mechanisms
Yang et al.[108]	2017	Traumatic brain injury in rat	3 atmospheres for 1 h, once daily for 7 consecutive days	Improved neurological function, promoted NSC proliferation and migration, increased VEGF, VEGFR2, Raf-1, MEK1/2, and ERK 1/2 protein	Activating VEGF/ERK signaling
Qian et al.[109]	2017	Traumatic brain injury in mice	2.0 ATA for 1 h, once daily for 7 consecutive days.	Improved motor score and reduced brain edema, reduced IL-1β and IL-18, suppressed NLRP-3-inflammasome components	Modulating microglial NLRP-3-inflammasome signaling
Hu et al.[110]	2017	Middle cerebral artery in rat	2 ATA for 1 h immediately after ischemia	Increased ATP, and NAD+, and Sirt1, attenuated hemorrhagic transformation and brain infarction, improved neurological function	Activation of ATP/NAD+/Sirt1 pathway
Xing et al.[111]	2018	Traumatic brain injury in rat	3 atmospheres ATA for 1 h in 12 h interval for the following 3 d and a total of six therapies	Reduced c-fos, c-jun, Bax and weakened the activation of Caspase-3, alleviated the decrease of Bcl-2, promoted the expression of NGF, BDNF, GDNF and NT-3	Without providing possible mechanisms
Li et al.[112]	2018	Global cerebral ischemia-reperfusion in rat	2.5 atm for 60 min	Improved BBB permeability	Increasing caveolin-1 and tight junction protein ZO-1
He et al.[113]	2019	Traumatic brain injury in mice	2.8 ATA for 90 min	Attenuated neuronal apoptosis	Akt/GSK3β/β-catenin pathway

Note:1 ATA (atm) = 101.325 kPa. AIF: Apoptosis Inducing Factor; Akt: protein kinase B; Ald: aldolase; ATA: atmosphere absolute; atm: atmospheric pressure; ATP: adenosine triphosphate; BBB: blood-brain barrier; BDNF: brain-derived neurotrophic factor; COX-2: cyclooxygenase-2; Cyt C: cytochrome C; DWI; diffusion weighted imaging; ERK: extracellular signal-regulated kinase; FPBI: percussion brain injury; GAP43: growth Associated Protein 43; GDNF: glial cell line-derived neurotrophic factor; GLUT: glucose transporter; GSK3β: glycogen synthase kinase 3β; HBOT: hyperbaric oxygen therapy; HIF-1α: hypoxia-inducible factor 1α; HMGB1: high mobility group protein B1; HO-1: heme oxygenase 1; ICP: intracranial pressure; IL: interleukin; LDH: intracranial pressure; MACO: middle cerebral artery occlusion; MEK1/2: mitogen-activated protein kinase kinase 1/2; MMP: matrix metalloproteinase; MPO: myeloperoxidase; MWM: Morris water maze; NALP-3: NACHT, LRR and PYD domains-containing protein 3; NF-κB: nuclear factor-κB; NGF: nerve growth factor; NQO-1: quinine oxidoreductase 1; Nrf2: nuclear factor erythroid 2-related factor 2; NSC: neural stem cell; NT-3: neurotrophin-3; pO(2): partial pressure of oxygen; ROS: reactive oxygen species; SOD: superoxide dismutase; SYP: synaptophysin; TBI: traumatic brain injury; T2w: T2-weighted; TGF-β1: transforming growth factor-β1; TGIF: transforming growth interacting factor; TLR: Toll-like receptor; TNF-α: tumor necrosis factor-α; TSPO: translocator protein; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor 2; ZO-1: zonula occludens-1.

Additional Table 3: Summary of studies of the effects of HBOT against nerve injury

Author	Year	Model of injury	Therapy schedule	Finding	Possible mechanism
Zamboni et al.[119]	1995	Transected-devascularized sciatic nerve in rat	2.5 ATA, twice daily for 1 wk	Improved sciatic function index	Without providing possible mechanisms
Kihara et al.[120]	1995	Ischemic sciatic nerve injury in rat	2.5 atm for 2 h/d for 7 d beginning within 30 min of ischemia	Rescued fibers from ischemic degeneration	Without providing possible mechanisms
Bradshaw et al.[123]	1996	Crushed sciatic nerve in rabbit	202, 242, and 303 kPa initiated 4 d post injury	Improved nerve morphology	Without providing possible mechanisms
Haapaniemi et al.[124]	1998	Crushed sciatic nerve in rat	A series of 45-min exposures at 3 ATA at 0, 4, and 8 h postoperatively and then every 8 h	Stimulated axonal outgrowth	Without providing possible mechanisms
Haapaniemi et al.[126]	2001	Sciatic nerve graft in rat	3.2 ATA for 45 min repeated at 4 and 8 h postoperatively and then every 8 h until evaluation	Longer axonal outgrowth	Without providing possible mechanisms
Mrsić-Pelcić et al.[129]	2004	Global cerebral ischemia	Not available	Prevented ischemia-induced changes in the Na^+,K^+-ATPase activity	Without providing possible mechanisms
Eguiluz-Ordoñez et al.[130]	2006	Sciatic nerve transection in rat	Not available	Increased axons and blood vessel number	Without providing possible mechanisms
Vilela et al.[131]	2008	Facial nerve crush injury in rabbit	Not available	Promoted the mean axonal diameter	Without providing possible mechanisms
Li et al.[133]	2011	Chronic constrictive injury in rat	For 1 hat 2.4 atm once a day	Alleviated CCI-induced neuropathic pain	Reducing TNF-α production
Han et al.[8]	2013	Chronic constriction injury in rat sciatic nerve	Pre-HBO or post-HBO 12 h before or after CCI at 0.25 MPa at a rate of 0.0125 MPa/min for 60 min	Increased mechanical withdrawal threshold, extended thermal withdrawal latency, decreased nNOS and iNOS	Regulation of spinal NOS expression
Gibbons et al.[135]	2013	Sciatic nerve crush injury in rat	3.5 ATA for 60 min	Reduced allodynia	Through opioid receptors
Ince et al.[136]	2016	Sciatic nerve transection in rat	Not available	Best gait analysis and less fibrosis at postoperative first hour	Without providing possible mechanisms
Han et al.[137]	2017	Chronic constriction injury in rat	0.25 MPa for 60 min, five times at a frequency of once per day	Ameliorated pain-related behaviors, decreased mitochondrial membrane potential indexes, upregulated NIX and BNIP3 expression	Upregulating microglial mitophagy
Shams et al.[9]	2017	Sciatic nerve transection in rat	2.0 ATA, 60 min/d for 5 consecutive days beginning on 1 d before and immediately after nerve transaction	Decreased MDA, increased SOD and CAT, attenuated caspase-3 and COX-2, increased S100β	Antioxidative, anti-inflammatory, and anti-apoptotic activity
Ding et al.[138]	2018	Chronic construction injury in rat	2.5 ATA for 60 min one day after CCI for 5 consecutive days	Improved hyperalgesia	Decreasing iNOS and nNOS

Note: 1 ATA (atm) = 101.325 kPa. ATA: Atmosphere absolute; atm: atmospheric pressure; ATP: adenosine triphosphate; BNIP3: Bcl2 interacting protein 3; CAT: catalase; CCI: chronic constrictive injury; COX-2: cyclooxygenase-2; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; iNOS: inducible nitric oxide synthase; MDA: cyclooxygenase-2; NIX: Bcl2 interacting protein 3-like; nNOS: neuronal nitric oxide synthase; NOS: nitric oxide synthase; NR2B: N-methyl D-aspartate receptor subtype 2B; S100β: S100 calcium-binding protein B; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-α.

Additional Table 4: Summary of studies of the effects of HBOT against neurodegenerative diseases

Author	Year	Model of injury	Therapy schedule	Finding	Possible mechanism
Dave et al.[143]	2003	Wobbler mice	2 ATA for 1 h/d for 30 d	Delayed the onset of disease, improved the rate of respiration for complex IV in mitochondria	Without providing possible mechanisms
Chen et al.[144]	2017	D-galactose induced aging model in mice	0.25 MPa for 60 min	Improved behavioral performance	Reducing oxidative stress and blocking nuclear factor-κB pathway
Shapira et al.[145]	2018	3xTg-induced Alzheimer's disease in mice	Not available	Reduced astrogliosis, microgliosis, IL-1β, and TNF-α, increased scavenger receptor A, arginase 1, IL-4 , and IL-10, reduced hypoxia, amyloid burden, and tau phosphorylation, ameliorated behavioral deficits	Attenuating neuroinflammation
Kusuda et al.[146]	2018	MPTP-induced Parkinson's disease in mice	1317 hPa with 45% oxygen for 3 h, three times a week	Decreased dopaminergic neuron loss	Without providing possible mechanisms

Note: 1 ATA = 101.325 kPa. ATA: Atmosphere absolute; HBOT: hyperbaric oxygen therapy; IL: interleukin; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TNF-α: tumor necrosis factor-α.

Additional Table 5: Summary of studies of the effects of HBOT against neurotoxic injury

Author	Year	Model of injury	Therapy schedule	Finding	Possible mechanism
Mukoyama et al.[147]	1975	Clioquinol-induced peripheral nerve damage	Not available	Decreased damage of myelin and axons	Without providing possible mechanisms
Low et al.[148]	1988	Streptozotocin-induced diabetic neuropathy in rat	2 atm for 2 h, 5 d/wk for 4 wk	Increased albumin blood-nerve barrier index, normalized caudal nerve action potential	Without providing possible mechanisms

Note: 1 atm = 101.325 kPa. atm: Atmospheric pressure; HBOT: hyperbaric oxygen therapy.

Additional Table 6: Summary of *in vitro* studies on neuroprotective effects of HBOT

Author	Year	Model of induction	Cell type	Finding	Possible mechanism
Zhang et al.[153]	2011	HBO-induced neurogenesis	Neural stem cells	Promoted neural stem cells proliferation	β-Catenin signaling pathway
Huang et al.[154]	2016	HBO exposure	Spinal neurons	Induced HSP32 expression	ROS/p38 MAPK/Nrf2 pathway
Yang et al.[108]	2017	Cell injury controller II system	Neural stem cell	Accelerated NSC proliferation and the levels of proteins related to cell cycle	Activating VEGF/ERK signaling
Chen et al.[156]	2019	HBO exposure	Neural stem cells	Promoted differentiation of NSCs into neurons and oligodendrocytes and reduced the number of astrocytes	Regulation of Wnt3/β-catenin and BMP2 signaling pathways

Note: ERK: Extracellular signal-regulated kinase; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; HSP32: heat shock protein 32; Nrf2: nuclear factor erythroid 2–related factor 2; NSC: neural stem cell; p38 MAPK: p38 mitogen-activated protein kinase; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor.

Additional Table 7: Summary of clinical trials on neuroprotective effects of HBOT

Author	Year	Model of injury	Therapy schedule	Finding
Feng et al.[157]	2017	Incomplete spinal cord injury	2.0 ATA once a day and 6 days per week for a total of 8 weeks	Higher American spinal injury association and functional independence measure scores, lower depression and anxiety
Sun et al.[158]	2019	Acute spinal cord injury	Not available	Down-regulated HMGB1 and NF-κB expression, decreased F-wave chronodispersion, improved American Spinal Injury Association and Frankel grade motor/pain scores
Nighoghossian et al.[159]	1995	Middle cerebral artery occlusion	Daily to 40 min at 1.5 ATA for a total of 10 dives	Detected an outcome trend favoring HBOT
Rockswold et al.[160]	2001	Severely brain injury	1.5 ATA for 60 min every 24 h	Prolonged effect on cerebral blood flow and cerebral metabolism, increased cerebral metabolic rate of oxygen and decreased ventricular cerebrospinal fluid lactate levels
Ren et al.[161]	2001	Severe brain injury	Not available	Improved Glasgow coma scale, brain electric activity mapping and Glasgow outcome scale, reduced mortality and morbidity
Shi et al.[162]	2003	Postbrain injury neural status	2 to 4 courses of HBO	HBOT was superior to medication treatment alone in the recovery of clinical symptoms, control of epilepsy, and resolution of hydrocephalus
Golden et al.[163]	2006	Chronic brain injury	Not available	Improved daily living, socialization, communication, and motor skills
Nakamura et al.[164]	2008	Head injury in the subacute phase	2.7 ATA for 60 min every 24 h	Decreased both pulsatility index and jugular venous lactate
Lin et al.[11]	2008	Traumatic brain injury	Not available	Improved Glasgow coma scale and Glasgow outcome scale 6 mon after HBOT
Efrati et al.[165]	2013	Stroke	Two months of 40 sessions (5 d/wk), 90 min each at 2 ATA	Improved neurological functions and life quality
Rockswold et al.[166]	2013	Severe traumatic brain injury	1.5 ATA for 60 min followed by normobaric hyperoxia, 3 h of 100% fraction of inspired oxygen at 1.0 ATA	Improved markers of oxidative metabolism, reduced intracranial hypertension, improved in markers of cerebral toxicity, reduced mortality and improved clinical outcome
Boussi-Grosset al.[167]	2013	Mild traumatic brain injury	1.5 ATA for 60 min at 40 therapy sessions (5 d/wk)	Induced neuroplasticity and improved quality of life
Xu et al.[168]	2018	Intracerebral hemorrhage	2.5 ATA for 60 min	Early HBOT was safe and effective with regards to the long-term neurological outcome
Golan et al.[169]	2020	Ischemic stroke	60 daily sessions consisting of 90 min of exposure at 0.2 MPa	Improvement of clinical neurologic status and quality of life in some patients
Fischer et al.[170]	1983	Multiple sclerosis	2 ATA for 90 min once daily for a total of 20 exposures	A positive, though transient, effect with minor side effects
Murata et al.[171]	2005	Carbon monoxide poisoning	Repetitive HBOT five times a week	Delayed neuropsychiatric sequelae of carbon monoxide poisoning

Note: 1 ATA = 101.325 kPa. ATA: atmosphere absolute; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; HMGB1: high mobility group protein B1; NF-κB: nuclear factor-κB.