Hyperbaric Oxygen Treatment - Cognitive Effects

Subjects: Others

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Hyperbaric oxygen treatment (HBOT)—the medical use of oxygen at environmental pressure greater than one atmosphere absolute—is a very effective therapy for several approved clinical situations, such as carbon monoxide intoxication, incurable diabetes or radiation-injury wounds, and smoke inhalation. In recent years, it has also been used to improve cognition, neuro-wellness, and quality of life following brain trauma and stroke. This opens new avenues for the elderly, including the treatment of neurological and neurodegenerative diseases and improvement of cognition and brain metabolism in cases of mild cognitive impairment.

Keywords: hyperbaric oxygen treatment (HBOT) ; cognition ; brain disorders ; neuroprotection ; neuroinflammation ; Alzheimer’s disease

1. Hyperbaric Oxygen Treatment (HBOT): The Concept

HBOT—the medical administration of 100% oxygen at environmental pressure greater than one atmosphere absolute (ATA)—is used clinically for a wide range of medical conditions. One of HBOT’s main mechanisms of action is elevation of the partial pressure of oxygen in the blood and tissues as compared to simple oxygen supplementation [1][2]. This allows five to ten times more oxygen to enter the blood plasma and to reach tissues suffering from low oxygen supply (following, e.g., brain injury, stroke, or vascular dysfunction). Therefore, it is not surprising that HBOT has been used for over 50 years for wounds (non-healing diabetic foot ulcers), air embolisms or decompression sickness, burned tissue repair, carbon monoxide intoxication, peripheral arterial occlusive disease, smoke inhalation, radiation injury, and promoting recovery from serious illness [3][4][5][6][7][8][9][10]. Nevertheless, today, there are only 13 FDA-approved HBOTs [11]; however, in parallel, there are a growing number of “off-label” uses, which have not been cleared by the FDA, such as treatment for stroke patients or patients suffering from Alzheimer’s disease (AD) [12][13], and even treatment of COVID-19 patients, which have shown very promising results [14][15][16][17][18][19]. Further clinical trials that are currently in progress, and additional basic scientific studies aimed at understanding HBOT’s mechanisms of action, will most probably expand the use of HBOT to other areas.

2. Cognitive Improvement

Although the use of HBOT in cases of brain-related disorders is pending FDA approval, there are numerous studies showing improved cognitive assessment following treatment for several brain injuries [20], neurodegenerative disorders [13][20][21][22][23][24][25], and even for healthy individuals [26][27]. For example, HBOT for stroke patients at late chronic stages has shown significant improvements in all memory measures, even at the late chronic phase after stroke [28][29]. In patients with mild traumatic brain injury (TBI), HBOT improved hippocampal cerebral blood flow (CBF) [30] and facilitated recovery during the rehabilitation phase [31]. Mechanistically, HBOT has been suggested to reduce oxidative stress, inflammation, and neural apoptosis, thereby improving functional recovery from stroke [32]. Additionally, it was shown to stimulate the expression of trophic factor and neurogenesis, and the mobilization of bone marrow stem cells to the ischemic area, which can enhance cell repair [33].

Recent human studies have shown that HBOT can improve cognitive functions in patients with mild cognitive impairment (MCI), Alzheimer’s Disease (AD), and Vascular Dementia (VD) [13][20][21][22][23][24][25]. Nevertheless, the current belief is that HBOT cannot revert severe cases with major neuron loss and therefore should be considered mainly at early disease stages, when only minimal cognitive deficiency is detected.

Importantly, the improvement in cognition and executive functions, as well as in physical abilities and quality of life continued for up to three months after the last treatment in stroke patients [34], one month in AD patients and up to three months in amnestic MCI patients [21]. These encouraging results suggests the occurrence of long-term changes, lasting the order of months.

Several recent studies examined the effects of HBOT on healthy young [35] and old [27][36] adults. In these studies, HBOT resulted in an improved learning curve and higher resilience to interference of episodic memory in the healthy young adults [35], and induced cognitive enhancements in healthy aging adults, which were associated with regional improvement in CBF [27][36].

Altogether, it is clear that the HBO environment improves cognitive performance, and that this can be attributed directly to the elevated oxygen levels, suggesting that oxygen is a rate-limiting factor for brain activity [37]. However, repeated exposure to HBOT for longer periods of time is needed to achieve long-lasting effects that lead to changes in vascular, neuronal, and cellular activity.

3. Mechanistic Explanation for the Effects of HBOT on Cognition

A series of studies using animal models for brain injuries and brain diseases showed an improvement in the animals' cognitive performance and provided a mechanistic understanding of some of HBOT's effects. Not surprisingly, these effects are not mediated by a single pathway, but were found to be mediated by several pathways, including inhibition of apoptosis, improvement of mitochondrial function, stem cell proliferation, enhancement of antioxidant defense activity, reduction in neuroinflammation, and neuroprotection.

Mitochondria consume roughly 85 to 90% of the oxygen that we breathe and are the major source of ATP production. It is therefore likely that the main molecular target of HBOT is the mitochondrion. Humanin, a neuroprotective mitochondrion-derived peptide, was shown to be elevated in VD patients following HBOT [23], suggesting a major role for mitochondrial activity in HBOT's mechanisms of action. Recent studies have suggested facilitation of mitochondrial transfer from astrocytes to neuronal cells, making the latter more resilient to neuroinflammation [38][39]. In a rat model for AD, HBOT reduced mitochondria-mediated apoptosis signaling by increasing Bcl-2, which is anti-apoptotic, and decreasing Bcl-2-associated X protein (Bax), which is pro-apoptotic [40].

An additional avenue for cognitive improvement might be stem cell proliferation. It has been documented on various occasions following HBOT, and evidence for neuronal cell proliferation has emerged in the last two decades [41][42][43]. HBOT promoted neurogenesis of endogenous neuronal stem cells for hypoxic ischemic and TBI rats, as measured by different markers (5-bromo-2'-deoxyuridine (BrdU), doublecortin, nestin) in the hippocampus area [44][45][46]. Another study, aimed at HBOT and recovery from TBI, found that HBOT increases neuronal stem cell proliferation and migration to the lesion area, as well as the levels of vascular endothelial growth factor (VEGF) and its receptor VEGFR-2, Raf-1, Mitogen-activated protein kinase (MEK1/2), and phospho-extracellular signal-regulated kinase (ERK) 1/2 protein [47]. Accordingly, it was suggested that HBOT promotes neuronal stem cell proliferation and possibly angiogenesis through VEGF/ERK signaling [47]. A recent study showed that HBOT improves blood flow in an AD mouse model by mitigating the blood vessel constriction that occurs in these AD mice under the regular course of the disease. This was associated with an improved performance of the AD mice [36]. Moreover, in elderly patients with significant memory loss at baseline, HBOT increased CBF and improved cognitive performance [36].

Another important effect of HBOT in several brain dysfunctions is reduced neuroinflammation. TBI is usually associated with increased inflammation, apoptosis and gliosis, neuronal cell death, and cognitive and motor dysfunction. In a TBI rat model, HBOT was shown to reduce neuroinflammation and increase levels of the anti-inflammatory cytokine interleukin (IL)-10; these changes were associated with improvements in cognitive deficit [48]. In an AD mouse model, HBOT reversed hypoxia and ameliorated brain pathology, and improved the animals' behavioral performance [49][50]. This improvement was also associated with a reduction in proinflammatory cytokines such as IL-1b, IL-6, and tumor necrosis factor alpha (TNFa), and an increase in anti-inflammatory cytokines such as IL-4 and IL-10, leading to reduced neuroinflammation.

HBOT was also shown to improve neuroprotective, antioxidant, and antiapoptotic processes. HBO preconditioning induced tolerance to cerebral ischemia [51], through an increase in SIRT1, a class III histone deacetylase, which has been suggested to be involved in neuroprotection [52]. Changes in SIRT1 level were also associated with elevation in B-cell lymphoma 2 (Bcl-2) expression and a decrease in cleaved caspase 3 level, suggesting that some of the effects might be mediated via inhibition of apoptosis [52]. Moreover, expression of SIRT1 in the brain was associated with increased expression of the nuclear factor erythroid 2-related factor 2 (Nrf-2), heme oxygenase 1 (HO-1), and superoxide dismutase 1 (SOD1), whereas the level of malondialdehyde (MDA) decreased, supporting the notion that HBOT enhances the antioxidant defense pathway, thereby assisting in neuroprotection [53]. In a mouse model for mild TBI, HBOT improved learning abilities and prevented astrocyte activation and neuronal loss, suggesting a neuroprotective effect [54]. Additional involvement in apoptotic pathways was demonstrated in an AD rat model that showed improved cognitive and memory abilities following HBOT, which were associated with NF-κB pathway activation and reduced hippocampal neuron loss [55].

4. Summary

HBOT improves several aspects of brain activity including an improvement in cerebral blood flow, brain metabolism, and brain microstructure, and this leads to improvement in cognitive functions and physical functions, sleep, and gait leading to an overall improved performance. As HBOT use in the clinic is considered to be safe and well-tolerated, it should be considered and recommended as an alternative therapeutic approach for different brain related disorders. Nevertheless, it is also clear that although the effects of HBOT last, in some studies, for several months, when treating patients with progressive neurodegenerative diseases such as AD, maintenance HBO treatments will probably be needed.

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