

● PERSPECTIVE

## Hyperbaric oxygen therapy as a new treatment approach for Alzheimer's disease

**Hyperbaric oxygen therapy as a new treatment approach for Alzheimer's disease (AD):** Alongside the increase in life expectancy, the prevalence of age-related disorders, such as neurodegenerative diseases, is on the rise. For example, AD, the most common form of dementia in the elderly, accounts for 60–80% of all dementia cases. However, there is presently no cure for this disease and no effective treatment that would slow disease progression despite billions of dollars invested in drug development. As AD is a complex disease, the development of effective and specific drugs is difficult. Thus, examining alternative treatments that target several disease-related pathways in parallel is of the utmost importance. Hyperbaric oxygen treatment (HBOT) is the medical administration of 100% oxygen at environmental pressure greater than 1 atmosphere absolute (ATA). HBOT has been shown to improve neurological functions and life quality following neurological incidents such as stroke and traumatic brain injury, and to improve performance of healthy subjects in multitasking. The current perspective describes a recent study demonstrating that HBOT can ameliorate AD-related pathologies in an AD mouse model, and provides unique insights into HBOT's mechanisms of action. Old triple-transgenic model (3xTg)-AD mice were exposed to 14 days of HBOT and showed reduced hypoxia and neuroinflammation, reduction in beta-amyloid (A $\beta$ ) plaques and phosphorylated tau, and improvement in behavioral tasks. This and additional studies have shown that cerebral ischemia is a common denominator in many of the pathological pathways and suggests that oxygen is an important tool in the arsenal for our fight against AD. Given that HBOT is used in the clinic to treat various neurological conditions, we suggest that this approach presents a new platform for the treatment of AD.

**Dementia and AD:** Dementia, a disorder characterized by chronic deterioration of cognitive function, affects 47.5 million people worldwide. AD is the most common form of dementia in the elderly, accounting for most of the cases. Although several drugs have been approved for AD patients, they have limited effects on disease progression and fail in the recovery of cognitive capacity once the disease has progressed. Therefore, there is a real need for new and early interventions.

AD is characterized by extracellular senile plaques, formed by deposits of beta-amyloid (A $\beta$ ) and intracellular neurofibrillary tangles formed by the accumulation of abnormally phosphorylated tau protein, which ultimately lead to loss of synapses and degeneration of neurons. Hypoxia-lack of oxygen in the tissue has a major role in AD pathogenesis. The association between hypoxia and dementia emerged from epidemiological studies, showing increased incidence of dementia in ischemic stroke patients. Recent evidence suggests that AD patients present reduced cerebral perfusion, which can be detected in early stages of the disease, and declines further with disease progression (Binnewijzend et al., 2013). Furthermore, cerebral hypoperfusion can lead to hypoxia, which has been shown to promote AD pathogenesis through acceleration of A $\beta$  accumulation, increasing the hyperphosphorylation of tau, activating microglia and astroglia, inducing proinflammatory cytokine secretion, increasing the generation of reactive oxygen species (ROS) and facilitating loss of neurons (Zhang and Le, 2010).

While reduced levels of oxygen lead to pathological complications, higher oxygen levels can improve or boost brain function. Studies have shown that in elderly (Kim et al., 2013) healthy subjects, oxygen supplementation improves the subjects' performance in cognitive tasks and changes the electroencephalographic (EEG) pattern of brain activity, indicating that oxygen is a rate-limiting factor in normal and disease-associated cognitive function.

**HBOT:** HBOT—the medical administration of 100% oxygen at environmental pressure greater than 1 ATA—has been used in the clinic for a wide range of medical conditions. One of HBOT's main

mechanisms of action is more effective elevation of the partial pressure of oxygen in the blood and tissues as compared to simple oxygen supplementation (Calvert et al., 2007). Indeed, HBOT improved the performance of healthy subjects in both motor and cognitive single tasks or in multitasking (cognitive and motor) compared to subjects under normobaric conditions (Vadas et al., 2017).

This raises many questions regarding the cellular and molecular, as well as system-level effects of HBOT on brain performance, and whether it can be used to reverse or reduce pathologies in neurological disorders. At the cellular level, HBOT can improve mitochondrial redox, preserve mitochondrial integrity, hinder mitochondrion-associated apoptotic pathways, alleviate oxidative stress and increase levels of neurotrophins and nitric oxide through enhancement of mitochondrial function in both neurons and glial cells (Huang and Obenaus, 2011). Similarly, many studies have demonstrated a neuroprotective effect of HBOT in both experimental ischemic brain injury and experimental traumatic brain injury. Moreover, HBOT has been shown to significantly improve neurological functions and life quality in stroke patients, even at chronic late stages, after the stroke has already occurred (Efrati et al., 2013).

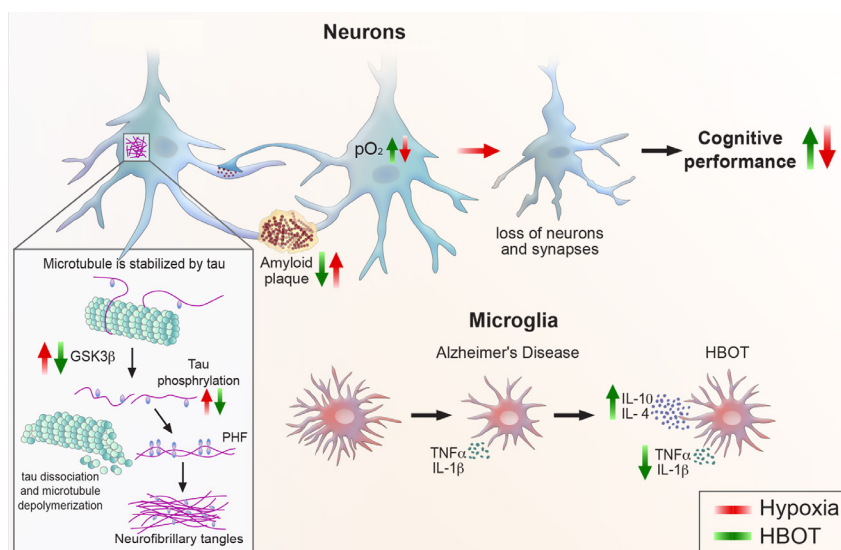
To further understand the underlying molecular mechanisms and changes following HBOT in the context of AD, we recently examined the effects of HBOT on AD pathologies in the 3xTg-AD mouse model (Shapira et al., 2018). We exposed 17-month-old 3xTg mice to HBOT (administration of 100% oxygen at 2 ATA; HBO group) or normobaric air (21% oxygen at 1 ATA; control group) for 60 minutes daily for 14 consecutive days. Following this treatment, mice were subjected to a battery of behavioral tasks (Y-maze, open-field test and object recognition test). In all of the behavioral tests, 3xTg mice showed impaired performance compared to non-transgenic controls, and HBOT significantly improved or restored 3xTg-treated mouse behavior. The impaired performance of 3xTg mice in behavioral tasks was accompanied by a strong presence of hypoxia in the hippocampal formation, and this was significantly reduced by HBOT (Figure 1).

The improved performance in behavioral tasks following HBOT was also associated with marked changes in the pathological hallmarks of AD. HBOT reduced the amyloid burden in 3xTg mice by decreasing the number and size of A $\beta$  plaques. Furthermore, HBOT attenuated abnormal amyloid precursor protein (APP) processing, which leads to the excessive generation of A $\beta$ 42 and formation of A $\beta$  plaques. Specifically, HBOT reduced the levels of  $\beta$ -secretase 1 (BACE1) and presenilin 1 (a component of  $\gamma$ -secretase), which promote the amyloidogenic APP processing. This observation is in accordance with evidence of hypoxia inducing A $\beta$  generation by facilitating  $\beta$ - and  $\gamma$ -secretase cleavage of APP (Li et al., 2009).

Apart from amyloid plaques, we showed that HBOT reduces the phosphorylation of tau without changing the total level of tau protein. The reduction in tau phosphorylation was associated with an elevated ratio of phosphorylated glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) at site Ser9 to total GSK3 $\beta$  protein, mainly due to a decrease in the total levels of GSK3 $\beta$  (Figure 1). Elevated GSK3 $\beta$  levels have been associated with increased tau phosphorylation due to hypoxia (reviewed in Zhang and Le, 2010).

Hypoxia has been shown to activate microglia and astroglia and to induce proinflammatory cytokine secretion. The 3xTg-AD mice show high levels of cytokines and neuroinflammation. Interestingly, HBOT reduced microgliosis, astrogliosis, and the secretion of proinflammatory cytokines, such as interleukin (IL)-1 $\beta$  and tumor necrosis factor alpha (TNF $\alpha$ ), and increased the production of anti-inflammatory cytokines, such as IL-4 and IL-10 in 3xTg mice (Figure 1). Moreover, HBOT induced a morphological change in microglia near plaques to a more ramified state, and increased microglial expression of scavenger receptor A and arginase 1, which are known to mediate A $\beta$  clearance (Frenkel et al., 2013). These results suggest that HBOT attenuates neuroinflammation and represses inflammatory mediators (Figure 1). This modulation of the immune system by HBOT is consistent with previous studies investigating this treatment's effect on other neurological conditions, such as traumatic brain injury, stroke and brain ischemia.

Hypoxia is a major cause for generation of ROS, peroxidation of cellular membrane lipids, cleavage of DNA, protein oxidation, and mitochondrial dysfunction (reviewed in Zhang and Le, 2010). It was previously shown that elevation of oxygen in the brain of AD rat



**Figure 1 Hypoxia and hyperbaric oxygen therapy (HBOT) effect on neurons and microglia.**

Hypoxia (red), the lack of oxygen in the tissue, contributes to the accumulation of amyloid plaques, phosphorylation of tau and loss of synapses and neurons that ultimately leads to cognitive decline. HBOT (green) reduces hypoxia (elevates the partial pressure of oxygen (pO<sub>2</sub>)), amyloid burden and tau phosphorylation, decreases the total levels of GSK3β, and improves cognitive performance. Furthermore, HBOT induces a morphological change in microglia near plaques to a more ramified state, reduces the secretion of proinflammatory cytokines (interleukin (IL)-1β, tumor necrosis factor alpha (TNF-α)) and increases the secretion of anti-inflammatory cytokines (IL-4, IL-10). GSK3β: Glycogen synthase kinase 3β.

models by HBOT increased the activity of antioxidant enzymes and led to the suppression of oxidative damage and decreased neuronal degeneration, thus contributing to the protective effect of HBOT in AD (Tian et al., 2012; Zhao et al., 2017).

Taken together, our results suggest that in the context of AD, oxygen is a rate-limiting factor for tissue recovery and cognitive function, similar to other neurological conditions.

**Implications for treatment of AD patients:** The growing understanding of the importance of oxygen in brain functionality under normal and diseased conditions marks it as a key player in AD treatment. As such, HBOT emerges as a well-tolerated, safe and effective platform to enhance brain oxygenation. Due to its neuroprotective effects, HBOT is used to treat various neurological conditions associated with hypoxia (such as stroke, ischemia and traumatic brain injury). Our recent findings lay the first stone for the use of HBOT in the treatment of AD as well. Unfortunately, when AD is clinically diagnosed, the patients already have significant brain atrophy, which means significant tissue loss that cannot be recovered. Moreover, AD patients present different pathological patterns and severities, making them a heterogeneous population. Therefore, one of the most important challenges in the application of HBOT to the clinical setting is to identify the subpopulation of patients which will benefit the most from the treatment. The classical candidate for HBOT would be a patient in the early stages of AD, before it is fully developed. Hence, early biomarkers for AD should be sought (blood, cerebral spinal fluid, imaging, and cognitive indications) and measured routinely. When deterioration in these measures is detected before significant functional decline, HBOT should be applied. Early diagnosis of AD will enable treatment when irreversible damage is still minimal, thereby maximizing the effect of HBOT.

In summary, we discussed the effects of HBOT on the pathology of the 3xTg mouse model of AD. Application of HBOT in the clinic calls for further optimization to achieve similar effects in human patients. Specifically, the optimal or ideal treatment should be determined with respect to oxygen pressure, time of treatment, and sustainability of the treatment. We expect that similar to other neurological disorders, HBOT will show promising results in the treatment of AD.

*This work was supported in part by the Israeli Ministry of Science, Technology and Space to UA (Grant number 3-12069).*

**Ronit Shapira, Shai Efrati, Uri Ashery\***

Department of Neurobiology, the George S. Wise Faculty of Life Sciences, Tel Aviv University, Israel (Shapira R, Ashery U) Sackler School of Medicine, Tel Aviv University, Israel; Sagol Center for Hyperbaric Medicine & Research, Assaf Harofeh Medical Center, Israel (Efrati S)

Sagol School of Neuroscience, Tel Aviv University, Israel (Ashery U)

\*Correspondence to: Uri Ashery, Professor, [uriashery@gmail.com](mailto:uriashery@gmail.com).

orcid: 0000-0001-6338-7888 (Uri Ashery)

Accepted: 2018-04-09

doi: 10.4103/1673-5374.232475

**Copyright license agreement:** The Copyright License Agreement has been signed by all authors before publication.

**Plagiarism check:** Checked twice by iThenticate.

**Peer review:** Externally peer reviewed.

**Open access statement:** This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**Open peer reviewer:** Laia Farràs-Permanyer, Universitat de Barcelona, Spain.

## References

- Binnewijzend MA, Kuijter JP, Benedictus MR, van der Flier WM, Wink AM, Wattjes MP, van Berckel BN, Scheltens P, Barkhof F (2013) Cerebral blood flow measured with 3D pseudocontinuous arterial spin-labeling MR imaging in Alzheimer disease and mild cognitive impairment: a marker for disease severity. *Radiology* 267:221-230.
- Calvert JW, Cahill J, Zhang JH (2007) Hyperbaric oxygen and cerebral physiology. *Neurol Res* 29:132-141.
- Efrati S, Fishlev G, Bechor Y, Volkov O, Bergan J, Kliakhandler K, Kamiager I, Gal N, Friedman M, Ben-Jacob E, Golan H (2013) Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial. *PLoS One* 8:e53716.
- Frenkel D, Wilkinson K, Zhao L, Hickman SE, Means TK, Puckett L, Farfara D, Kingery ND, Weiner HL, El Khoury J (2013) Scara1 deficiency impairs clearance of soluble amyloid-beta by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. *Nat Commun* 4:2030.
- Huang L, Obenaus A (2011) Hyperbaric oxygen therapy for traumatic brain injury. *Med Gas Res* 1:21.
- Kim HJ, Park HK, Lim DW, Choi MH, Kim HJ, Lee IH, Kim HS, Choi JS, Tack GR, Chung SC (2013) Effects of oxygen concentration and flow rate on cognitive ability and physiological responses in the elderly. *Neural Regen Res* 8:264-269.
- Li L, Zhang X, Yang D, Luo G, Chen S, Le W (2009) Hypoxia increases Abeta generation by altering beta- and gamma-cleavage of APP. *Neurobiol Aging* 30:1091-1098.
- Shapira R, Solomon B, Efrati S, Frenkel D, Ashery U (2018) Hyperbaric oxygen therapy ameliorates pathophysiology of 3xTg-AD mouse model by attenuating neuroinflammation. *Neurobiol Aging* 62:105-119.
- Tian X, Wang J, Dai J, Yang L, Zhang L, Shen S, Huang P (2012) Hyperbaric oxygen and Ginkgo Biloba extract inhibit Abeta25-35-induced toxicity and oxidative stress in vivo: a potential role in Alzheimer's disease. *Int J Neurosci* 122:563-569.
- Vadas D, Kalichman L, Hadanny A, Efrati S (2017) Hyperbaric oxygen environment can enhance brain activity and multitasking performance. *Front Integr Neurosci* 11:25.
- Zhang X, Le W (2010) Pathological role of hypoxia in Alzheimer's disease. *Exp Neurol* 223:299-303.
- Zhao B, Pan Y, Wang Z, Xu H, Song X (2017) Hyperbaric oxygen pretreatment improves cognition and reduces hippocampal damage via p38 mitogen-activated protein kinase in a rat model. *Yonsei Med J* 58:131-138.