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Traumatic brain injury (TBI) and stroke are the major causes of brain damage and chronic neurological impairments. There is no agreed-upon effective metabolic intervention for TBI and stroke patients with chronic neurological dysfunction. Clinical studies published this year present convincing evidence that hyperbaric oxygen therapy (HBOT) might be the coveted neurotherapeutic method for brain repair. Here we discuss the multi-faceted role of HBOT in neurotherapeutics, in light of recent persuasive evidence for HBOT efficacy in brain repair and the new understanding of brain energy management and response to damage. We discuss optimal timing of treatment, dosage, suitable candidates and promising future directions.

The challenge

Traumatic brain injury (TBI), stroke and age-related metabolic brain disorders are the major causes of brain damage and chronic neurological impairments. Today, there is no agreed-upon effective metabolic treatment/intervention in the routine clinical practice for TBI and stroke patients with chronic neurological dysfunction. Intensive therapy and rehabilitation programs are valuable for improving quality of life right after brain injury, but often provide only partial relief and leave the patients chronically disabled. With the aging of the population, the severity of the problem posed by stroke, TBI (mainly due to home accidents) and metabolic disorders (which can lead to dementia and Alzheimer's disease) is expected to increase. Experts agree that novel neurotherapeutic methods to repair and protect the brain from damage caused by these insults are needed more than ever before.

New hope

Clinical studies published this year present convincing evidence that hyperbaric oxygen therapy (HBOT) might be the coveted neurotherapeutic method for brain repair [1,2]. HBOT is a treatment

in which oxygen-enriched air (up to 100%) is administrated to patients in a chamber where the pressure is elevated above one atmosphere absolute (1ATA), which is the ambient atmospheric pressure). It is becoming widely acknowledged that the combined action of hyperoxia and hyperbaric pressure leads to significant improvement in tissue oxygenation while targeting both oxygen- and pressure-sensitive genes [3–6], resulting in improved mitochondrial metabolism with anti-apoptotic and anti-inflammatory effects [7–12].

Here, we reflect on the multifaceted role of HBOT in neurotherapeutics, in light of recent persuasive evidence for HBOT efficacy in brain repair and of new understanding of brain energy management and response to damage. We discuss the optimal timing of treatment, optimal dose–response curve (oxygen–pressure levels), suitable candidates and promising future directions.

A generation of debate

The idea that HBOT can provide a valuable tool for brain repair was first proposed almost half a century ago and has been considered anecdotal ever since. Interest was renewed in the mid-90s [8,13], but the results were either ignored or seriously questioned by the medical

community. Huang and Obenaus, in their 2011 review, presented an objective summary of the clinical trials and associated debate till 2011, and a thoughtful description of the animal trials and their implications [8]. They reasoned that the HBOT-induced neuroprotection in animal model is due to the observed improved tissue oxidation, improved mitochondrial redox, preservation of mitochondria integrity, hindering of mitochondria-associated apoptotic pathways as well as anti-inflammatory effects [8]. Until 2011, all human HBOT studies involved severe TBI patients. While mortality was decreased in those studies, there was no significant change in the quality of life. This, combined with knowledge from a wealth of animal studies, indicated that the time of treatment and dose–response curve should be reassessed. Most importantly, it led to the understanding that HBOT should be practiced on mild-to-moderate TBI patients who are more apt to achieve clinically meaningful recovery.

Persuasive new evidence

Convincing evidence that HBOT can revitalize chronically impaired brain functions and significantly improve the quality of life of mild TBI (mTBI) patients with prolonged post-concussion syndrome at late chronic stage, even years after injury, are presented in a new randomized prospective trial published this year [2]. A crossover approach was adopted in order to overcome the HBOT inherent sham control constraint (discussed further below). The participants, who had suffered mTBI 1–5 years prior to the trial, were randomly divided into two groups: trial and control. The trial group patients received 2 months of HBOT, while the control group went without treatment in those 2 months. The latter were given the same treatment as the trial group 2 months later. The advantage of the crossover approach is the opportunity for a triple comparison: between treatments of two groups, between treatment and no treatment periods of the same group and between treatment and no treatment in different groups. It also overcomes the problem posed by the impossibility of making people believe they are exposed to high pressure when they are actually not.

The treatment consisted of 40 daily sessions lasting 1 h at pressure of 1.5ATA and breathing 100% oxygen. The patients' cognitive functions and quality of life were assessed by detailed computerized evaluations and compared, for all patients, with single photon emission computed tomography (SPECT) scans. HBOT sessions led to similar significant improvements in tests of cognitive function and quality of life in both groups. No significant improvements occurred by the end of the non-treatment period in the control group. Analysis of brain imaging showed significantly increased neuronal activity after a 2-month period of HBOT compared with the control period. What makes the results particularly persuasive is the remarkable agreement between the cognitive function restoration and the changes in brain functionality as detected by the SPECT scans. The diffuse nature of the mTBI injury renders the pathological damage hard to detect by common neuroimaging methods such as computed tomography and MRI.

Pre- and post-treatment SPECT imaging showed that HBOT led to restoration of neuronal activity in stunned areas.

A second randomized prospective trial published earlier this year used a similar crossover approach and presented equally persuasive evidence that HBOT can also revitalize chronically impaired brain function and significantly improve the quality of life of post-stroke patients, even years after the event [1]. The participants in this study suffered a stroke 6–36 months prior to the trial. They were also randomly divided into treated and control group, went through brain function and quality evaluations. These stroke patients were also treated with 40 HBOT daily sessions. However, while the mTBI patients were treated at a lower pressure of 1.5ATA since they all had an intact macrovascular bed, the stroke patients were given 90 min sessions at 2.0ATA and 100% oxygen. The results of SPECT imaging were well correlated with clinical improvements and revealed restored activity mostly in stunned areas in the surroundings of necrotic foci.

HBOT can activate cerebral plasticity & revitalize chronically impaired brain functions

The new trials provide convincing evidence that HBOT can induce cerebral plasticity leading to repair of chronically impaired brain functions and improved quality of life in post-stroke patients and mTBI patients with prolonged post-concussion syndrome, even years after the brain insult [1,2]. The term 'cerebral plasticity' is used here as an umbrella term that encompasses both neuroplasticity as commonly used in neuroscience and beyond-synaptic changes such as myelination, regeneration of axonal white matter, angiogenesis and changes in the glial fabric. The observed restoration of neuronal activity in the metabolically dysfunctional stunned areas indicate HBOT as a potent means of delivering to the brain sufficient oxygen needed for activation of neuroplasticity and restoration of impaired functions. These are entailed via assortment of intricate mechanisms, some of which are mentioned below.

Underlying repair mechanisms

Brain insults may result in a variety of brain injuries, including impairment of microvascular integrity and cerebral perfusion. These lead to reduced metabolism and neuronal activity, which in turn lead to loss of synapses and tampered neuronal connectivity [2,8,9]. The stunned areas mentioned earlier are characterized by anaerobic metabolism and ATP depletion culminating in stagnation and shortage of energy for the healing processes, and they may persist like this, dysfunctional but alive, for years after injury [2,8,9]. The decreased oxygen level not only causes reduction in neuronal activity but also prevents the generation of new synaptic connections and angiogenesis. HBOT can initiate vascular repair and improve cerebral vascular flow, induce regeneration of axonal white matter, stimulate axonal growth, promote blood–brain barrier integrity and reduce inflammatory reactions as well as brain edema [7–12].

At the cellular level, HBOT can improve cellular metabolism, reduce apoptosis, alleviate oxidative stress and increase

levels of neurotrophins and nitric oxide through enhancement of mitochondrial function in both neurons and glial cells, and may even promote neurogenesis of endogenous neural stem cells [7–12,14]. Regarding mitochondria, it is important to note that stroke and TBI engender depolarization of the mitochondrial membrane and induction of mitochondrial permeability transition pore, which reduces the efficiency of energy production and elevate the level of reactive oxygen species [15]. HBOT can inhibit mitochondrial permeability transition pore and thus has the potential to reverse this abnormality [8]. However, it must be applied carefully to ascertain that the increased tissue oxygen does not cause cellular toxicity due to overly high reactive oxygen species levels.

Time of treatment

Many innate repair mechanisms, each with a different characteristic time, are activated following the onset of acute brain injury, and some may be negatively affected by premature application of HBOT. HBOT procedure can begin either at the degenerative or at the regenerative stage. At the degenerative stage, it must be administered with great care to avoid toxicity. On the other hand, elevated oxygen levels during the regenerative stage would supply the energy needs for the innate brain repair processes. While it is not possible to mark a clear line between the regenerative and the degenerative phases [16], it is quite clear that more than 1 month after the acute event, in a stable patient, the degenerative process has ended. The differences in initiation times and protocols of HBOT may explain contradictory results in previous studies, where HBOT timing was not taken into consideration [1,2,17–21].

Dose–response curve & treatment duration

The minimal effective dosages of the active ingredients in HBOT (pressure and oxygen concentration) are still unknown, and future studies are needed to test this issue by evaluating the optimal, case-specific dose–response curves. For example, in the previously described trials, 2.0ATA was used for post-stroke patients and 1.5ATA was used for mTBI [1,2]. There are many case reports illustrating significant effects with even small increases in air pressure, including effects on the brain [22].

The dose–response curve is related to the inherent difficulties in handling the sham control, and is a source of misinterpretation of clinical studies: the minimal elevated pressure a patient can sense is 1.3 atmosphere, which can induce more than 50% elevation in tissue oxygenation. Since such oxygenation can have significant physiological effects [1,2], treatment with room air at 1.3ATA is not an ‘ineffectual treatment’ as is required from a proper sham control. At the same time, over oxygenation in response to pressure above 2.0ATA can have an inhibitory effect or even focal toxicity. It is conceivable that HBOT above two atmospheres can be less effective than 1.3ATA, explaining the ‘unexpected’ improvements in control groups when 1.3ATA was used for sham control.

The duration of treatment is also an unresolved issue. It is quite clear that weeks-to-months would be necessary for brain tissue regeneration and angiogenesis, but the upper time limit from which no further improvement is expected is still unknown. More studies are needed to determine the minimal effective dosage and the duration for a specific brain injury. Non-invasive in-chamber measurements are currently being developed, specifically EEG and diffusion tensor imaging, and may shed some light on this important question. Clearly, there is an urgent need for additional, larger-scale, multi-center clinical studies to further confirm the findings and determine the most effective and personalized treatment protocols. To guarantee effective and well-designed clinical studies, wide-scale biomedical research is required. Such research will also provide validation of the clinical findings, crucial aid in interpretation of the results and important clues to additional applications of HBOT.

Optimal candidates for HBOT

Since hyperbaric oxygen therapy is the only treatment proven to significantly benefit post-stroke and mTBI patients without limiting side effects, it is reasonable to allow the millions of these patients to benefit from it right away and not wait for rigorous studies. The classical candidate for HBOT is a patient with unrecovered brain injury where tissue hypoxia is the limiting factor for the regeneration possesses. In this patient, HBOT may induce neuroplasticity in the stunned regions where there is a brain anatomy/physiology (e.g., SPECT/computed tomography) mismatch [1,2]. The anatomical/physiological imaging should serve as part of the basic evaluation of every HBOT candidate, just like transcutaneous oximetry at the ulcer bed serves as a basic evaluation for patients suffering from peripheral non-healing wounds [23,24].

Looking ahead

Based on the aforementioned rationale, one can surmise that HBOT could also be effective in early stages of vascular dementia, Alzheimer’s disease and other conditions where the clinical presentation could not be fully explained by anatomical imaging. However, this will require novel basic biomedical research to understand the HBOT effect on the recently discovered mitochondria-associated cellular response to hypoxia [7–12], which is a common denominator of stroke, TBI, dementia and aging [25,26].

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