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Cellular Mechanisms of Spatial Memory Recovery via Hyperbaric Oxygen Therapy in Experimental TBI: A Review

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ABSTRACT

Traumatic Brain Injury (TBI) impairs spatial memory, affects individuals' quality of life, and increases disability and mortality rates. Hyperbaric Oxygen Therapy (HBOT), which delivers nearly 100% oxygen in a pressurised environment, has a potential intervention to ameliorate these cognitive deficits. This narrative review presents evidence from animal studies demonstrating the efficacy of HBOT in enhancing spatial memory in rats with TBI. Specifically, we present evidence that HBOT increases levels of Brain-Derived Neurotrophic Factor (BDNF) and activates the Hypoxia-Inducible Factor 1-alpha (HIF-1α) pathway. These molecular changes foster neuroplasticity and reduce oxidative stress, thereby promoting the repair and growth of dendritic spines and decreasing Reactive Oxygen Species (ROS) levels to prevent neuronal death. By elucidating these mechanisms, this review shows how HBOT contributes to spatial memory recovery in TBI, suggesting a promising therapeutic avenue that need further clinical exploration to refine treatment protocols and evaluate its applicability in human TBI recovery.

1. Introduction

Traumatic brain injury (TBI) is a prevalent global health concern that disrupts the brain's structure and functionality due to external forces, leading to significant morbidity and mortality.[1] With an estimated 64,000 new cases annually and a substantial portion resulting in hospitalizations, TBI poses a considerable challenge to healthcare systems worldwide.[2] Among the debilitating consequences of TBI, spatial memory impairment stands out, severely affecting an individual's ability to navigate and interact with their environment.[3] Current therapeutic strategies, including pharmacological treatments and non-invasive therapies like virtual reality, have shown limited efficacy in addressing the cognitive deficits arising from TBI, highlighting a critical gap in treatment modalities.[4]

Given the limitations of current TBI treatments, Hyperbaric Oxygen Therapy (HBOT)—administering 100% oxygen in a pressurized chamber—represents a promising alternative to address cognitive impairments.[5,6] Sakas et al. found disparities in performance between TBI mice and those that received HBOT during a five-day study. The results indicated that the TBI group had a larger average latency to the hidden platform than the TBI group that received HBOT, indicating poor spatial memory. Consequently, the findings indicate that HBOT may enhance spatial memory following TBI.[7] Despite preliminary findings that suggested HBOT's potential to enhance spatial memory in TBI patients, a comprehensive understanding of its underlying cellular mechanisms remains elusive. This review aims to synthesize current animal studies to shed light on how HBOT facilitates spatial memory recovery in TBI rats. We will examine its role in elevating Brain-Derived Neurotrophic Factor (BDNF) levels, activating Hypoxia-Inducible Factor 1-alpha (HIF-1α), and reducing oxidative stress. By delving into these cellular processes, we endeavor to bridge the knowledge gap and provide insights that may inform future clinical research and treatment

protocols. This review will first explore the pathophysiology of TBI, followed by an examination of spatial memory impairment, and finally discuss how HBOT addresses these issues through specific cellular mechanisms.

2. Methods

This review employed a narrative review approach to summarize the cellular mechanisms by which HBOT supports spatial memory recovery in animal models of TBI. The articles discussed in this review were selected based on their relevance to the research focus, which includes hyperbaric oxygen therapy (HBOT), traumatic brain injury (TBI), and spatial memory outcomes in animal models. the selection emphasized studies that provided mechanistic insights into cellular pathways affected. The literature included diverse experimental designs, animal strains, and intervention protocols to allow a comprehensive and integrative discussion of the potential therapeutic mechanisms involved in spatial memory recovery following TBI. The literature search was performed in PubMed, and SCOPUS using the keywords: brain, head, hippocampal, hippocampus, injury, damage, trauma, hyperbaric, spatial memory, neuroplasticity, oxidative stress. The search covered publications from January 2004 to December 2024.

3. Traumatic Brain Injury

Pathophysiology

TBI is characterized by damage to the brain caused by an external mechanical force, leading to temporary or permanent impairment of cognitive, physical, and psychosocial functions.[8] This condition is a significant global health concern, categorized based on the mechanism (open or closed head injury), the nature of the injury (diffuse, focal, or vascular), and severity (mild, moderate, or severe).[9] The primary injury, occurring at the moment of impact, includes contusions, axonal injury, and blood vessel damage. This is closely followed by secondary injury mechanisms, which may evolve over hours to days, exacerbating the damage through processes such as excitotoxicity, oxidative stress, and inflammation, ultimately leading to neuronal death and cognitive deficits including spatial memory impairment.[10,11]

Spatial Memory

This refers to the ability to navigate and orient oneself. This type of memory relies on the capacity to create, maintain, and utilize cognitive representations of the surrounding environment[12]. Spatial memory, formerly known as reference memory, involves movement to update the body location and orientation relative to external or environmental references.[3] The blast injury animal model examined the effects of single and repeated traumatic brain injuries on spatial memory. A decrease in the frequency of entrances into novel arms was seen in rats sustaining both single and recurrent injuries, which is related with spatial memory deterioration.[13] Studies in humans have yielded similar findings. There is a high prevalence of memory impairments in individuals with traumatic brain injuries, demonstrating difficulties in identity-location relation tasks and correlating with spatial memory decline.[14]

Neuroplasticity

Neuroplasticity is a set of mechanisms and principles that enables the brain to change its structure and form new neural pathways in response to external stimuli and experiences. It is classified into two main categories: functional plasticity and structural plasticity.[15] Functional plasticity pertains to the formation and alteration of synaptic strength between neurons, which underlies learning and memory, on the other hand, structural plasticity refers to changes in the physical structure of the brain, such as brain tissue reorganization and the development of new connections between neurons.[16] Neuroplasticity is crucial as they form the basis for developing therapeutic strategies to support brain rehabilitation.[15]

TBI results an excitotoxicity, which subsequently induces cellular hypoxia and impairs spatial memory. Excitotoxicity can occur in traumatic brain injuries due to increased extracellular excitatory neurotransmitter glutamate, leading to a significant decrease in glutamate reuptake.[17] Glutamate interacts to N-methyl-D-aspartate (NMDA) receptors, causing cell membrane depolarization and the subsequent entry of Na^+, K^+, and Ca^{2+}. Elevated intracellular calcium concentrations activate enzymes such as phospholipase and calpain, which disrupt membrane integrity and the cytoskeleton, eventually leading to neuronal damage and death, which causes spatial memory impairment.[18,19] Neuronal hypoxia also occurs due to ischaemia involving the regulation of the transcription factor HIF-1α. When oxygen levels decrease within the cell, prolyl hydroxylase domain (PHD) enzymes do not hydroxylate HIF-1α protein, preventing von hippel-lindau factor (VHL) recognition of newly synthesized HIF-1α.[20] Consequently, HIF-1α protein accumulates in the cytoplasm. Therefore, HIF-1α shifts to the nucleus with HIF-1α and subsequently heterodimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT), leading to the activation of target genes to promote vascular endothelial growth factors (VEGF), iron metabolism, erythropoietin regulation to address neuronal hypoxia conditions, and brain-derived neurotrophic factor (BDNF) gene activation.[20,21] BDNF is a gene involved in BDNF protein synthesis as a neurotropic factor that contributes to angiogenesis, antioxidant reducing infarct area, and mitochondrial biogenesis. BDNF also plays a role in neuroplasticity.[22]

4. Experimental TBI Model

TBI animal models induced by impact are generally classified into three types: the weight-drop (WD) model, the fluid percussion (FP) model, and the controlled cortical impact (CCI) model.[23] In the WD model, injury is induced by a free-falling weight dropped through a vertical tube designed to strike the skull, thereby generating trauma. The severity of the injury can be modulated by adjusting the height and mass of the falling weight. While this model is relatively quick and easy to perform, it has several limitations, including unintended skull fractures, the risk of secondary impact injuries, and reduced accuracy in localizing the impact site.[23] In contrast, both the FP and CCI models require a craniotomy performed between the bregma and lambda. The FP model utilizes a pendulum striking a piston attached to a fluid reservoir, producing a fluid pressure wave that is transmitted to the exposed but intact dura, whereas the CCI model employs an electromagnetic impactor device to drive a rigid impactor tip, delivering a controlled mechanical force to the rodent's head.[24]

Four out of five studies employed Sprague Dawley rats. The selection of the Sprague Dawley strain in experimental research is commonly based on their relatively large brain size, which facilitates surgical procedures. Additionally, Sprague Dawley rats tend to adapt more quickly to training sessions prior to physiological function testing.[25] Long–Evans rats, a hybrid strain resulting from the crossbreeding of albino Wistar females with wild *Rattus norvegicus* males, are characterized by their distinctive appearance—white bodies with a black "hood" covering the head, neck, and shoulders. This strain is widely used in behavioral studies.[26]

5. Hyperbaric Oxygen Therapy

Mechanisms of Action

As stated by the *Undersea and Hyperbaric Medical Society*, hyperbaric oxygen therapy (HBOT) involves administering near 100% oxygen concentration along with other breathing gases in a specially pressurized chamber with atmospheric pressure exceeding 1 ATA intermittently.[5,6] Under hyperbaric conditions, oxygen can penetrate ischemic areas and reduce lesions caused by traumatic brain injuries.[6] HBOT can be administered to both humans and animals.[27] While the principles and mechanisms involved in therapy delivery for humans and animals are largely similar, they are carried out in specialized chambers.[27,28]

HBOT can inhibit these conditions to prevent neuronal death and spatial memory decline. HBOT increases tissue oxygen levels, known as hyperoxia, through intermittent hyperbaric oxygen therapy.[6] Intermittent HBOT boosts the body's antioxidant defenses by leveraging the hyperoxia-hypoxia paradox (HHP), a mechanism where alternating oxygen levels trigger an adaptive response.[29] HBOT aids mitochondrial function by reducing ROS production and increasing antioxidants.[17,29] Hyperbaric oxygen therapy involves gas and pressure. Administering higher oxygen content in a pressurized chamber leads to an increase in oxygen molecules in the alveoli. Consequently, oxygen molecules diffuse from areas of high concentration (alveoli) to areas of lower concentration (arteries).[28] Through diffusion, this increased oxygen concentration occurs in tissues (hyperoxia) and arterial blood flow (hyperoxemia), enhancing overall tissue oxygenation. Hyperoxia and hyperoxemia are unaffected by hemoglobin levels and can thus alleviate hypoxia in tissue.[30] Dissolved oxygen in arterial blood flows throughout the body, inaccessible to hemoglobin, making hyperbaric oxygen therapy applicable to conditions caused by oxygen transport disruptions. HBOT plays a role in increasing Plasma-based oxygenation, thereby elevating tissue oxygen partial pressure.[31] To understand how HBOT emerges as a promising treatment, it is crucial to delve into the cellular mechanisms it influences such as Hyperoxia-hypoxia paradox phenomenon and Reactive Oxygen Species.

Hyperoxia-Hypoxia Paradox Phenomenon

HBOT has been identified as a pivotal intervention for mitigating cognitive impairments subsequent to TBI (Table 2).[7,32–35] Intermittent hyperbaric oxygen therapy consists of providing oxygen from 21% physiological levels to around 100% oxygen and returning to physiology oxygen levels numerous times during sessions of therapy lasting 60-90 minutes. This fluctuation is perceived by the body as a hypoxia signal. Such signals and fluctuations activate transcription factors, forming the basis of the positive effects of HBOT known as the hyperoxia-hypoxia paradox (HHP). When cells are in a state of hyperoxia, more oxygen is dissolved, leading to increased ROS levels.[29] This causes cells to respond adaptively by producing more antioxidant proteins (scavengers) to offset the increase in ROS, avoiding DNA damage and intracellular signaling disturbance. Upon recovery to normoxia, oxygen and ROS levels stabilize, but scavenger activity remains increased for an extended period. With repeated hyperoxia exposures, the ROS and scavenger ratio diminish as scavenger half-life exceeds that of ROS. Consequently, fewer ROS are produced, leading to reduced degradation of HIF-1α and more active HIF-1α entering the nucleus for gene transcription. Intermittent hyperoxia condition within cells occurs due to repeated exposure to HBOT.[31]

Reactive Oxygen Species

Hyperbaric oxygen therapy restores a balance between oxidative stress and mitochondrial function. Oxygen intake through the lungs efficiently elevates dissolved oxygen levels in plasma, enhancing tissue oxygenation. Hyperoxia causes the citric acid cycle to become more active inside tissue cells, particularly

mitochondria. NADH, a product of the citric acid cycle, may directly react with oxygen, generating ROS within mitochondria.[36] Excessive ROS generation activates HIF-1α, which combines with HIF-2α for stabilizing HIF-1α in its active state. (Another method HBOT stabilizes HIF-1α is through circumstances similar to hypoxia during intermittent intervals).[29] HIF-1α suppresses mitochondrial biogenesis. Increased NADH consumption by mitochondria elevates NAD+ levels, activating Sirtuin 1. It boosts mitochondrial biogenesis through PGC-1α acetylation and produces an antioxidant response through FOXO3a deacetylation. High ROS levels can also stimulate the creation of scavenger proteins as an adaptive strategy. The half-life of scavenger proteins is longer than that of ROS, which explains HBOT's antioxidant properties. HBOT activates Nrf2 and its downstream targets, such as SOD and GCLC and reduces pro-oxidant enzyme production, such as iNOS.[36] ROS can be removed by antioxidant enzymes. Antioxidants convert ROS into innocuous molecules (e.g., water or oxygen). Antioxidants operate as scavenger proteins, lowering ROS levels and providing electrons to neutralize unstable ROS. Although HBOT is known to enhance ROS generation, intermittent HBOT raises antioxidant levels and activity, thus lowering ROS levels.[17]

HBOT also increases BDNF in rats with hypoxia. Research on rats induced with transient middle cerebral artery occlusion (MCAO) and subsequently given hyperbaric oxygen therapy reported that HBOT boosted the production of neurotrophic factors such as BDNF in the affected motor cortex and significantly increased BDNF levels in the serum.[37] BDNF is a protein that regulates the growth and pruning of dendritic spines in rat hippocampal neuron cultures. BDNF binds to Tropomyosin receptor kinase B (TrkB) at the post synapse and promote signaling pathway. This process involved in synapse formation, neurogenesis, angiogenesis, and the induction of long-term potentiation (LTP) which plays a role in in vivo memory formation.[38] In the nucleus, BDNF genes are transcribed into mRNA for pre-pro BDNF protein synthesis. Pre-pro BDNF undergoes cleavage into pro BDNF. Pro BDNF can undergo intracellular and extracellular cleavage to become mature BDNF (mBDNF).[39] mBDNF or BDNF binds to TrkB and causes dendritic spine head enlargement as structural plasticity inducing LTP. BDNF/TrkB complex induces actin polymerization by stimulating Rac1 and Cdc42 protein activities in dendritic spines. Additionally, NMDAR activation increases protein synthesis via Calcium/calmodulin-dependent protein kinase II (CaMKII).[40] CaMKII stimulates the proteins Cdc42, RhoA, and Rac1. These activation pathways lead to Arp2/3 and cofilin phosphorylation, which subsequently govern actin polymerization, forming the basis for dendritic spine volume increase.[41] Thus, hyperbaric oxygen therapy promotes neuroplasticity in TBI.

Table 1. Summary spatial memory recovery via hyperbaric oxygen therapy in experimental TBI

Author	TBI Model	Strain	HBOT Pressure (ATA)	Time of Intervention	Session Duration	Frequency per Day	Total Days	n	Time of Assessment	Spatial Memory Outcome
Harch[34]	Focal cortical weight-drop impact	Long–Evans	1.5	51 days after injury	90 minutes	2×/day, 4-hour intervals	7 days	64	Day 101 post-injury	Improved in HBOT group; declined in sham and TBI-only groups
Liu[32]	Feeney's weight-drop method	Sprague Dawley	2.0	6 h after injury	90 minutes	1×/day	14 days	32	Days 7 and 14 post-injury	Improvement in spatial memory in HBOT group
Liu[33]	Feeney's free-fall method	Sprague Dawley	3.0	7 h after injury	60 minutes	1×/day	14 days	33	Days 3, 7, and 14 post-HBOT	Memory declined after TBI; HBOT group improved at 1 and 2 weeks vs. TBI-only
Sakas[7]	Controlled cortical impact	Sprague Dawley	2.5	4 h after injury	90 minutes	2×/day, 12-hour intervals	4 days	28	Days 1–5 post-injury	Significant difference between pre- and post-treatment (TBI vs. TBI+HBOT)
Zhang[35]	Controlled cortical impact	Sprague Dawley	2.0	Not specified	60 minutes	4×/day, 30-min intervals	7 days	70	8 weeks post-injury	Improved from baseline, not statistically significant

6. Conclusion

Traumatic brain injury (TBI) induces two types of damage, primary injury and secondary injury, which play crucial roles in the pathophysiology of TBI. TBI leads to excitotoxicity, resulting in cell death and decreased spatial memory. Hyperbaric oxygen therapy triggers neuroplasticity via the hyperoxia-hypoxia paradox (HHP) phenomenon, which involves hypoxia-inducible factor 1-alpha (HIF-1α) and Brain-Derived Neurotrophic Factor (BDNF). Hyperbaric oxygen therapy promotes neuroplasticity with dendritic spine growth, which induces long-term Potentiation (LTP) supporting the recovery of spatial memory post-TBI. Additionally, hyperbaric oxygen therapy plays a role in antioxidant formation, thus reducing ROS and preventing neuronal death. This literature review on hyperbaric oxygen therapy (HBOT) for recovery of spatial memory in traumatic brain injury (TBI) rats highlights important limitations, including the reliance on animal models, which do not directly translate to potential human outcomes, and the need for more comprehensive investigations into optimal treatment protocols and potential adverse effects. Additionally, it calls for further clinical research to connect cellular mechanisms of HBOT with measurable functional improvements in TBI recovery. Identifying these cellular mechanisms not only fills a critical gap in the literature but also paves the way for targeted therapeutic strategies that enhance HBOT's efficacy in TBI recovery.

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