

The Next Generation in Brain Recovery and Neuroregeneration

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ABSTRACT

For several decades traditional medicine has perpetuated the notion that, unlike other tissues in the human body, the brain and nervous system, once injured, lack the capacity to repair and heal themselves. In fact, clinical and scientific evidence show that the nervous system has significant healing ability.

Millions of Americans are affected by both acute and chronic traumatic brain injury (TBI), but there is no standard-of-care recovery therapy. Medications used in TBI patients are mostly off-label and treat symptoms but do not promote healing. Even worse, without healing, neurodegenerative processes begin.

Methods of reducing inflammation and promoting neural recovery include hyperbaric oxygenation therapy (HBOT) and nutritional doses of magnesium, lithium, and zinc.

Traumatic Brain Injury (TBI)

According to U.S. Centers for Disease Control and Prevention statistics, approximately 1.7 million people in the U.S. suffer a traumatic brain injury (TBI) each year.¹ Nearly 75% of TBIs that occur each year are concussions or other forms of mild traumatic brain injury (mTBI).² In 2010, direct and indirect medical costs of TBI totaled an estimated \$76.5 billion in the U.S.³ In the U.S. alone, more than 5.3 million people live with disabilities caused by TBI.^{3,4} The traditional approach to recovery is observation and supportive care. Supportive care often includes medications to treat the various symptoms and consequences of TBI such as depression, anxiety, night terrors, chronic headaches, poor balance, difficulties concentrating, and sleep disturbances. Current medications do little more than treat symptoms. They do not promote healing, do not inhibit cell death or any neurodegenerative process, and are often associated with negative side effects.

Basic Pathophysiology of Traumatic Brain Injury

The first stages of cerebral injury after TBI are characterized by tissue damage, axonal shearing, contusions, and impaired regulation of cerebral blood flow (CBF) and metabolism. During the first 10 days succeeding a TBI, known as the acute phase, the following excitotoxic events occur: terminal membrane depolarization along with excessive release of excitatory neurotransmitters (i.e. glutamate, aspartate)

leading to over-activation of N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolopropionate (AMPA), and voltage-dependent Ca^{2+} and Na^{+} channels. Subsequent Ca^{2+} and Na^{+} influx leads to an increase in catabolic intracellular processes and a high level of oxidative stress.⁵

The next stage, known as the subacute phase (more than 10 days, less than a year post-injury) is defined by tissue damage, and if healing is not progressing, Wallerian degeneration begins. A potentially reversible phase of intra-axonal damage proceeds to further axon fragmentation and demyelination of intact axons. Repair might still be possible, but if the process is unchecked, cell death is likely.⁶

The chronic phase of post-concussion is persistent and ongoing. Depending on the severity of the trauma (or repeated traumas), symptoms such as long-lasting cognitive impairment, depression, anxiety, sleep disturbances, and progressive neurodegeneration and decline may occur years after the injury.^{7,8} Cell death has occurred, and processing speed is invariably compromised.

Biochemical Restoration

The past few decades have seen great advances in our knowledge of nutritional biochemistry and nutrient-based therapeutics, and a new treatment model known as "biochemical restoration" has emerged. In biochemical restoration, the goal is to correct underlying nutrient and hormone deficiencies and toxic burdens (e.g. mercury and other heavy metals as well as persistent organic pollutants) that drive inflammation and mitochondrial disease and dysfunction. Mitochondria are responsible for creating more than 90% of the energy the body needs to sustain life, and all healing and growth processes require healthy mitochondrial function. These vital organelles require a multitude of nutrients (e.g. Mg, Li, Se, Zn, Cu, Mn, Mo, B-vitamins, essential fatty acids, cholesterol, hormones, and oxygen) for optimal function and ATP production.

Biochemical restoration can activate or reactivate healing processes.

Magnesium, Lithium, and Zinc: Essential for Neuronal Repair

Like magnesium and zinc, lithium is an essential mineral required for a number of biochemical and regulatory functions in the body. All three minerals are needed for neuronal healing processes (e.g. neurogenesis, neuroregeneration,

reducing neuro-inflammation), and modulation of the body's excitatory NMDA receptor.⁹⁻¹⁷ Magnesium and zinc are cofactors in more than 600 chemical reactions in the human body, while lithium has a wide range of nutritional effects that are intercorrelated with the functions of several enzymes, hormones, and vitamins, as well as with growth and transforming factors.¹⁸⁻¹⁹

Low doses of lithium were found to increase brain-derived neurotrophic factor (BDNF) expression in cortical neurons (10% at 0.02mM) and hippocampal neurons (28% and 14% at 0.02 mM and 0.2 mM, respectively). Extracellular BDNF of cortical neurons increased 30% at 0.02 mM and 428% at 0.2 mM, and in hippocampal neurons, BDNF increased 44% at 0.02 mM.²⁰

Small, nutritional doses of lithium from 5-40 mg/d have been used since the 1970s to treat depression, anxiety, headaches, migraines, chronic pain, alcoholism, drug addiction, stroke, and autism, to halt or slow progression in Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis (ALS), and to prevent suicide.^{18,19} Nutritional deficiencies result from poor diet or lithium antagonists such as caffeine or alcohol, which promote the loss of many water soluble nutrients (e.g. lithium, magnesium, zinc, B-vitamins, and ascorbic acid).

Brain magnesium levels fall rapidly following the acute phase of a TBI, and replenishing levels to their normal values has been shown to prevent and reverse neurological injury.^{14,15} Magnesium has also been shown to promote sciatic nerve regeneration¹⁶ and rapid recovery from major depression.¹⁷

Zinc is needed for healthy brain function, and has been shown to possess anxiolytic and antidepressive effects similar to those of magnesium and lithium.^{21,22} Like magnesium and lithium deficiency, zinc deficiency increases oxidative stress and contributes to general inflammation,²³ while zinc supplementation can reverse this. Other symptoms of zinc deficiency include mental lethargy, learning difficulties, delayed wound healing, low testosterone, and neurosensory disorders.^{21,23} Zinc deficiency has been shown to impair hippocampal neurogenesis, while decreasing neuronal survival.²⁴⁻²⁷ Supplementing with zinc during the acute and subacute phases of TBI also decreases the damaging effects of oxidative stress and inflammation.²³⁻²⁸

Molecular mechanisms are being elucidated.²⁹ One of lithium's beneficial effects resides in its ability to modulate the NMDA receptor. A large part of its wide-ranging action lies in its inhibition of the phosphorylating enzyme glycogen synthase kinase-3 (GSK3),^{30,31} thereby protecting brain cells from a wide range of assaults, including oxidative stress, DNA damage, impairment of mitochondrial function, and excitotoxicity.^{32,33} GSK3 regulates the functions of more than 100 proteins, many of which are involved in neuronal resilience. GSK3 also regulates the actions of more than 25 different transcription factors, exerting a large effect on the levels of proteins in neurons. Lithium increases resistance

to oxidative stress by reversing GSK3's inhibition of the antioxidant boosting, neuroprotective transcription factor Nrf2.^{29,34}

Replenishing these nutrients is important in all phases of TBI, including the chronic phase, to prevent cell damage as well as to stimulate the healing process by increasing neural growth factors such as BDNF²⁰ and stem-cell mobilization.^{35,36}

Hyperbaric Oxygenation for Neurologic Recovery

Hyperbaric oxygenation therapy (HBOT) involves breathing pure oxygen (100 v/v%) in a pressurized chamber. It is a well-established and effective treatment for decompression sickness, serious infections, inflammation, and wound healing. Many recent reports provide evidence for its effectiveness in promoting repair of neurologic injuries, whether traumatic or anoxic.³⁷⁻⁴⁷

HBOT at 1.5 atmospheres absolute (ATA) is a commonly used treatment pressure in outpatient clinics in the U.S. and has been used internationally. A treatment pressure of 1.5 ATA with 100% oxygen tremendously enhances the oxygen carrying capacity of blood, promotes healing, and has an excellent safety record.³⁷⁻⁴⁰

The minimal elevated pressure a patient can sense (about 1.3 ATA, depending on the rate of change) can induce an elevation in tissue oxygenation of 50% or more when the patient is breathing room air. This is important to recognize because "sham" treatment under such conditions has been used as a "placebo" in experimental trials, when in fact it is a low-dose treatment.

It has been said that over-oxygenation at pressures at or above 2.0 ATA can inhibit healing or even have toxicity. If so, HBOT above 2.0 ATA may be less effective than 1.3 ATA, explaining the "unexpected" improvements in control groups when 1.3 ATA was used for the control.⁴⁸ There is controversy about the optimal pressure to use. Dr. Paul Harch at Louisiana State University Health Sciences Center is working with the LSU Neurology Department to develop protocols for a variety of neurological conditions.

Mechanism of Action of HBOT

HBOT creates oxygen radicals, which stimulate healing mechanisms including production of neurotrophic growth factors⁴⁹ and vascular endothelial growth factor,⁵⁰ neural stem cell proliferation and mobilization,⁵¹⁻⁵⁴ and modification of gene expression.⁵⁰

In a 2014 study, researchers at M.D. Anderson Cancer Center found that "HBOT not only increased antioxidant enzyme expression, such as Cu/Zn-superoxide dismutase, catalase, and glutathione peroxidase, but also significantly decreased pro-oxidant enzyme levels...thereby decreasing net oxygen radical production by means of negative feedback."⁵⁵ Note that free radicals have a hormetic effect, i.e. a biphasic response in which low levels stimulate beneficial

processes and high levels are damaging.

HBOT improves cerebral plasticity, allowing the repair of chronically impaired brain functions and improved quality of life in mTBI patients with prolonged post-concussion syndrome and in post-stroke patients, years after the brain insult.^{43,56}

HBOT has also been shown to inhibit NO-induced apoptosis (programmed cell death) via enhanced expression of heat shock protein⁵⁸ and the up-regulation of the anti-apoptotic protein Bcl-2 (increasing the Bcl-2/Bax ratio) in degenerated human intervertebral disc cells.⁵⁹ Bcl-2 is localized to the outer membrane of mitochondria, where it plays an important role in promoting cellular survival and inhibiting the actions of pro-apoptotic proteins (e.g. Bax, Bak).

Summary

While there is currently no standard-of-care therapy that has been recognized to treat brain injury, which is too often considered hopeless, this could change with biochemical restoration therapy and hyperbaric oxygenation therapy (HBOT). These modalities have neuro-protective effects while promoting vital healing processes in the brain and nervous system in both acute and chronic phases.

Published research shows that these modalities have great potential. Much further research is needed to establish the most appropriate dosing and pressures.

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Disclosure: Dr. Marshall's company NeuroLith Nutraceuticals LLC has developed nutritional supplements designed to enhance brain healing, based on research cited here; patents pending.

REFERENCES

1. Faul M, Xu L, Wald MM, Coronado VG. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006*. Atlanta, Ga.: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010. Available at: https://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf. Accessed May 15, 2017.
2. National Center for Injury Prevention and Control. *Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem*. Atlanta, Ga.: Centers for Disease Control and Prevention; 2003. Available at: <https://www.cdc.gov/traumaticbraininjury/pdf/mtbireport-a.pdf>. Accessed May 15, 2017.
3. CDC. Traumatic Brain Injury & Concussion. Available at: <https://www.cdc.gov/traumaticbraininjury/severe.html>. Accessed May 15, 2017.
4. Thurman D, Alverson C, Dunn K, Guerrero J, Sniezek J. Traumatic brain injury in the United States: a public health perspective. *J Head Trauma Rehabil* 1999;14:602-615.
5. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth* 2007;99(1):4-9.

6. Armstrong RC, Mierzwa AJ, Marion CM, Sullivan GM. White matter involvement after TBI: clues to axon and myelin repair capacity. *Exp Neurol* 2016;275(Pt 3):328-333.
7. Fehily B, Fitzgerald M. Repeated mild traumatic brain injury: potential mechanisms of damage. *Cell Transplant* 2016 Aug 5. doi: 10.3727/096368916X692807. [Epub ahead of print].
8. Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. *Mol Cell Neurosci* 2015;66(Pt B):75-80.
9. McIntosh TK, Vink R, Yamakami I, Faden AI. Magnesium protects against neurological deficit after brain injury. *Brain Res* 1989;482:252-260.
10. Vink R. Magnesium and brain trauma. *Magn Trace Elem* 1991-1992;10(1):1-10.
11. Heath DL, Vink R. Traumatic brain axonal injury produces sustained decline in intracellular free magnesium concentration. *Brain Res* 1996;738(1):150-153.
12. Heath DL, Vink R. Optimization of magnesium therapy after severe diffuse axonal brain injury in rats. *J Pharmacol Exp Ther* 1999;288(3):1311-1316.
13. Vink R, Cernak I. Regulation of intracellular free magnesium in central nervous system injury. *Front Biosci* 2000;5:D656-D665.
14. Hoane MR, Knotts AA, Akstulewicz SL, Aquilano M, Means LW. The behavioral effects of magnesium therapy on recovery of function following bilateral anterior medial cortex lesions in the rat. *Brain Res Bull* 2003;60(1-2):105-114.
15. Hoane MR. Magnesium therapy and recovery of function in experimental models of brain injury and neurodegenerative disease. *Clin Calcium* 2004;14(8):65-70.
16. Pan HC, Sheu ML, Su HL, et al. Magnesium supplement promotes sciatic nerve regeneration and down-regulates inflammatory response. *Magn Res* 2011;24(2):54-70.
17. Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Med Hypotheses* 2006;67(2):362-370.
18. Marshall T. Lithium as a nutrient. *J Am Phys Surg* 2015;20:104-109.
19. Schrauzer GN. Lithium: occurrence, dietary intakes, nutritional essentiality. *J Am Coll Nutr* 2002;21(1):14-21.
20. De-Paula VJ, Gattaz WF, Forlenza OV. Long-term lithium treatment increases intracellular and extracellular brain-derived neurotrophic factor (BDNF) in cortical and hippocampal neurons at subtherapeutic concentrations. *Bipolar Disord* 2016;18(8):692-695.
21. Prasad AS. Zinc: an overview. *Nutrition* 1995;11(1 Suppl):93-99.
22. Mlyniec K, Davies CL, de Agüero Sánchez IG, et al. Essential elements in depression and anxiety. Part I. *Pharmacol Rep* 2014;66(4):534-544.
23. Krebs NF, Miller LV, Hambidge KM. Zinc deficiency in infants and children: a review of its complex and synergistic interactions. *Paediatr Int Child Health* 2014;34(4):279-288.
24. Corniola RS, Tassabehji NM, Hare J, Sharma G, Levenson CW. Zinc deficiency impairs neuronal precursor cell proliferation and induces apoptosis via p53-mediated mechanisms. *Brain Res* 2008;1237:52-61.
25. Gao HL, Zheng W, Xin N, et al. Zinc deficiency reduces neurogenesis accompanied by neuronal apoptosis through caspase-dependent and -independent signaling pathways. *Neurotox Res* 2009;16(4):416-425.
26. Suh SW, Won SJ, Hamby AM, et al. Decreased brain zinc availability reduces hippocampal neurogenesis in mice and rats. *J Cereb Blood Flow Metab* 2009;29(9):1579-1588.
27. Pfaender S, Föhr K, Lutz AK, et al. Cellular zinc homeostasis contributes to neuronal differentiation in human induced pluripotent stem cells. *Neural Plast* 2016 (2016), article ID 3760702. doi:10.1155/2016/3760702.
28. Cope EC, Morris DR, Scrimgeour AG, Van Ledingham JW, Levenson CW. Zinc supplementation provides behavioral resiliency in a rat model of traumatic brain injury. *Physiol Behav* 2011;104(5):942-947.
29. Jope RS, Nemeroff CB. Lithium to the rescue. *Cerebrum* 2016;2016. pii: cer-02-16. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4938258/>. Accessed May 16, 2017.
30. Jope RS, Bijur GN. Mood stabilizers, glycogen synthase kinase-3 β and cell survival. *Mol Psych* 2002;7(Suppl 1):S35-S45.
31. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci USA* 1996;93:8455-8459.
32. Beurel E, Jope RS. The paradoxical pro and anti-apoptotic actions of GSK3 in the intrinsic and extrinsic apoptosis signaling pathways. *Prog Neurobiol* 2006;79:173-189.
33. Hanson ND, Nemeroff CB, Owens MJ. Lithium, but not fluoxetine or the corticotropin-releasing factor receptor 1 receptor antagonist R121919, increases cell proliferation in the adult dentate gyrus. *J Pharmacol Exp Ther* 2011;337:180-186.

34. Alural B, Ozerdem A, Allmer J, Genc K, Genc S. Lithium protects against paraquat neurotoxicity by NRF2 activation and miR-34a inhibition in SH-SY5Y cells. *Front Cell Neurosci* 2015;9:209.
35. Sun DM, Young W. Lithium stimulation of cord blood stem cell proliferation and growth factor production. Patent assigned to Rutgers, the State University of New Jersey, New Brunswick, N.J. (US). US 8,852,938.
36. Young W. Review of lithium effects on brain and blood. *Cell Transplant* 2009;18(9):951-975.
37. Harch PG, Andrews SR, Fogarty EF, et al. A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. *J Neurotrauma* 2012;29(1):168-185.
38. Harch PG, Andrews SR, Fogarty E, et al. Preliminary Report on Hyperbaric Oxygen Treatment (HBOT) of U.S. Military Veterans with Traumatic Brain Injury (TBI) and Post-Traumatic Stress Disorder (PTSD): the LSU IRB #7051 Pilot Trial. Feb 14, 2011.
39. Harch PG, Kriedt C, Van Meter KW, Sutherland RJ. Hyperbaric oxygen therapy improves spatial learning and memory in a rat model of chronic traumatic brain injury. *Brain Res* 2007;1174:120-129.
40. Efrati S, Ben-Jacob E. Reflections on the neurotherapeutic effects of hyperbaric oxygen. *Expert Rev Neurother* 2014;14:233-236.
41. Boussi-Gross R, Golan H, Volkov O, et al. Improvement of memory impairments in post-stroke patients by hyperbaric oxygen therapy. *Neuropsychology* 2015;29:610-621.
42. Efrati S, Fishlev G, Bechor Y, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients—randomized, prospective trial. *PLoS One* 2013;8.
43. Boussi-Gross R, Golan H, Fishlev G, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury—randomized prospective trial. *PLoS One* 2013;8(11):079595.
44. Hadanny A, Efrati S. The efficacy and safety of hyperbaric oxygen therapy in traumatic brain injury. *Expert Rev Neurother* 2016;16(4):359-360.
45. Hadanny A, Golan H, Fishlev G, et al. Hyperbaric oxygen can induce neuroplasticity and improve cognitive functions of patients suffering from anoxic brain damage. *Restor Neurol Neurosci* 2015;33(4):471-486.
46. Tal S, Hadanny A, Berkovitz N, et al. Hyperbaric oxygen may induce angiogenesis in patients suffering from prolonged post-concussion syndrome due to traumatic brain injury. *Restor Neurol Neurosci* 2015;33(6):943-951.
47. Hadanny A, Efrati S. Oxygen—a limiting factor for brain recovery. *Crit Care* 2015;19:307.
48. Harch PG. Hyperbaric oxygen therapy for post-concussion syndrome: contradictory conclusions from a study mischaracterized as sham-controlled. *J Neurotrauma* 2013; 30(23):1995-1999.
49. Tai PA, Chang CK, Niu KC, et al. Attenuating experimental spinal cord injury by hyperbaric oxygen: stimulating production of vasoendothelial and glial cell line-derived neurotrophic growth factors and interleukin-10. *J Neurotrauma* 2010;27(6):1121-1127.
50. Liu X, Zhou Y, Wang Z, et al. Effect of VEGF and CX43 on the promotion of neurological recovery by hyperbaric oxygen treatment in spinal cord-injured rats. *Spine J* 2014;14(1):119-127.
51. Feng Z, Liu J, Ju R. Hyperbaric oxygen treatment promotes neural stem cell proliferation in the subventricular zone of neonatal rats with hypoxic-ischemic brain damage. *Neural Regen Res* 2013;8(13):1220-1227.
52. Yang YJ, Wang XL, Yu XH, et al. Hyperbaric oxygen induces endogenous neural stem cells to proliferate and differentiate in hypoxic-ischemic brain damage in neonatal rats. *Undersea Hyperb Med* 2008;35(2):113-129.
53. Wei L, Wang J, Cao Y, et al. Hyperbaric oxygenation promotes neural stem cell proliferation and protects the learning and memory ability in neonatal hypoxic-ischemic brain damage. *Int J Clin Exp Pathol* 2015;8(2):1752-1759.
54. Wang XL, Yang YJ, Xie M, et al. Proliferation of neural stem cells correlates with Wnt-3 protein in hypoxic-ischemic neonate rats after hyperbaric oxygen therapy. *Neuroreport* 2007;18(16):1753-1756.
55. Zhang Q, Gould LJ. Hyperbaric oxygen reduces matrix metalloproteinases in ischemic wounds through a redox-dependent mechanism. *J Invest Dermatol* 2014;134(1):237-246.
56. Efrati S, Fishlev G, Bechor Y, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients—randomized, prospective trial. *PLoS One* 2013;8(1):e53716.
57. Holbach KH, Wassman H, Hoheluchter KL. Reversibility of the chronic post-stroke state. *Stroke* 1976;7:296-300.
58. Ueng SW et al. Hyperbaric oxygen treatment prevents nitric oxide-induced apoptosis in articular cartilage injury via enhancement of the expression of heat shock protein 70. *J Orthop Res* 2013;31:376-384.
59. Mazumdar J, O'Brien WT, Johnson RS, et al. O2 regulates stem cells through Wnt/ β -catenin signalling. *Nat Cell Biol* 2010;12:1007-1013.

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