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 blow 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-isoxazolpropionate (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 regeneration[16] 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 BDNF[20] 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 factors[49] 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 protein[58] 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.

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