

Traumatic Brain Injury: Natural Therapeutics and New Perspectives for Clinical Practice

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Traumatic brain injuries (TBI) and concussions are garnering greater medical and research interest as public awareness grows, especially in the impact on younger and more vulnerable populations. A recent study found there are approximately 30,000 concussions or head related injuries reported annually among the 12 to 19 year-old age group with over 80% being sports related.¹ While these numbers increase each year, the majority of concussions are still not being reported so the true numbers are most likely underestimated.¹

An explosion of recent research has uncovered some of the pathophysiological pathways involved in TBI. While one unified theory has yet to be confirmed, there is emerging evidence that brain trauma causes neurotransmitter and calcium release which initiates a cascade of neuroinflammation, excitotoxin production, mitochondrial dysfunction and immune activation.² The pathways found in TBI have also shed light on the potential mechanisms involved in other chronic neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's diseases (PD).³

Until recently, little has been known about the long-term effects of TBIs and sub-concussive injuries. The symptoms of most concussions (mild to moderate severity) resolve spontaneously after 1-2 weeks but a small proportion (less than 10%) progress to more advanced stages with persistent symptoms and cognitive impairment.⁴ The spectrum of post-concussive conditions includes acute TBI symptoms, post-concussion syndrome (PCS), prolonged post-concussion syndrome (PPCS), mild cognitive impairment (MCI), chronic traumatic encephalopathy (CTE), and dementia pugilistica (DP).⁴ Incomplete recovery, premature return to competition and multiple injuries may contribute to the prolonged duration of symptoms and greatly increase the chance and severity of future concussions and persistent symptoms or cognitive impairment.⁴ This highlights the importance of complete assessment, monitoring and a conservative return to activity. It also underscores the need and opportunity for treatment possibilities that are able to address the multifaceted pathophysiological aspects of TBI.

The current treatment and management of TBI and PCS is rest, reduction of sensory inputs, and symptomatic treatment (i.e. depression).² Conventional and pharmaceutical approaches have shown limited benefits due to their singular mechanisms. Currently, no neuroprotective treatment options exist that improve neurological outcomes after TBI.⁵ Now many researchers are starting to study a wide range of natural compounds and vitamins that have promising broad-spectrum, neuroprotective and anti-inflammatory activity. Curcumin, green tea, essential fatty acids, resveratrol, vitamins C and E are some of the compounds with potential therapeutic benefit in the treatment and management of TBI.³ This article will explore a number of the most promising natural and non-pharmacological treatment options to address the symptoms and pathophysiological pathways found in TBI.

Physiology of Traumatic Brain Injury

Physical and mechanical trauma sustained during a TBI initiates a complex cascade of neurochemical and neurometabolic events.⁴ Physical damage to nerve axons leads to ionic imbalance and indiscriminate release of the excitatory neurotransmitter, glutamate. The excessive release of glutamate over-stimulates of the N-methyl-D-aspartate (NMDA) receptors causing excess calcium to accumulate in the mitochondria, which leads to impaired energy production, cell death and reduced blood flow.⁴ Glutamine itself can be excitotoxic and causes neuronal depolarization leading to apoptosis. In the attempt to restore ionic equilibrium, adenosine triphosphate (ATP) dependent sodium and potassium pumps work excessively, which in turn increases glucose metabolism, draining cellular energy stores and causing a buildup of lactic acid.⁴ This period of hypermetabolism can last from minutes to hours following the TBI.⁴ Almost immediately after the injury activated or "primed" immune cells secrete inflammatory cytokines and chemokines locally around the area of trauma. While the goal of these inflammatory molecules is to promote repair and healing, it appears they are ultimately harmful, leading to a cycle of chronic inflammation and immune activation.⁴

Following the brief hypermetabolic period, brain tissue rapidly progresses into a hypometabolic state as mitochondria function is impaired. The subsequent hypometabolic state can last seven days or longer (30 days in severe cases) depending on the severity or frequency of the TBI.⁴ While symptoms may disappear within one week, metabolic recovery generally takes a number of weeks to months after a moderate to severe TBI.⁴ It can take even longer if there was a second injury before full recovery. A very prevalent

problem is that many athletes underplay or hide their symptoms in order to return to play earlier. The risk of a concussion appears to increase when the brain has suffered a prior concussive injury.

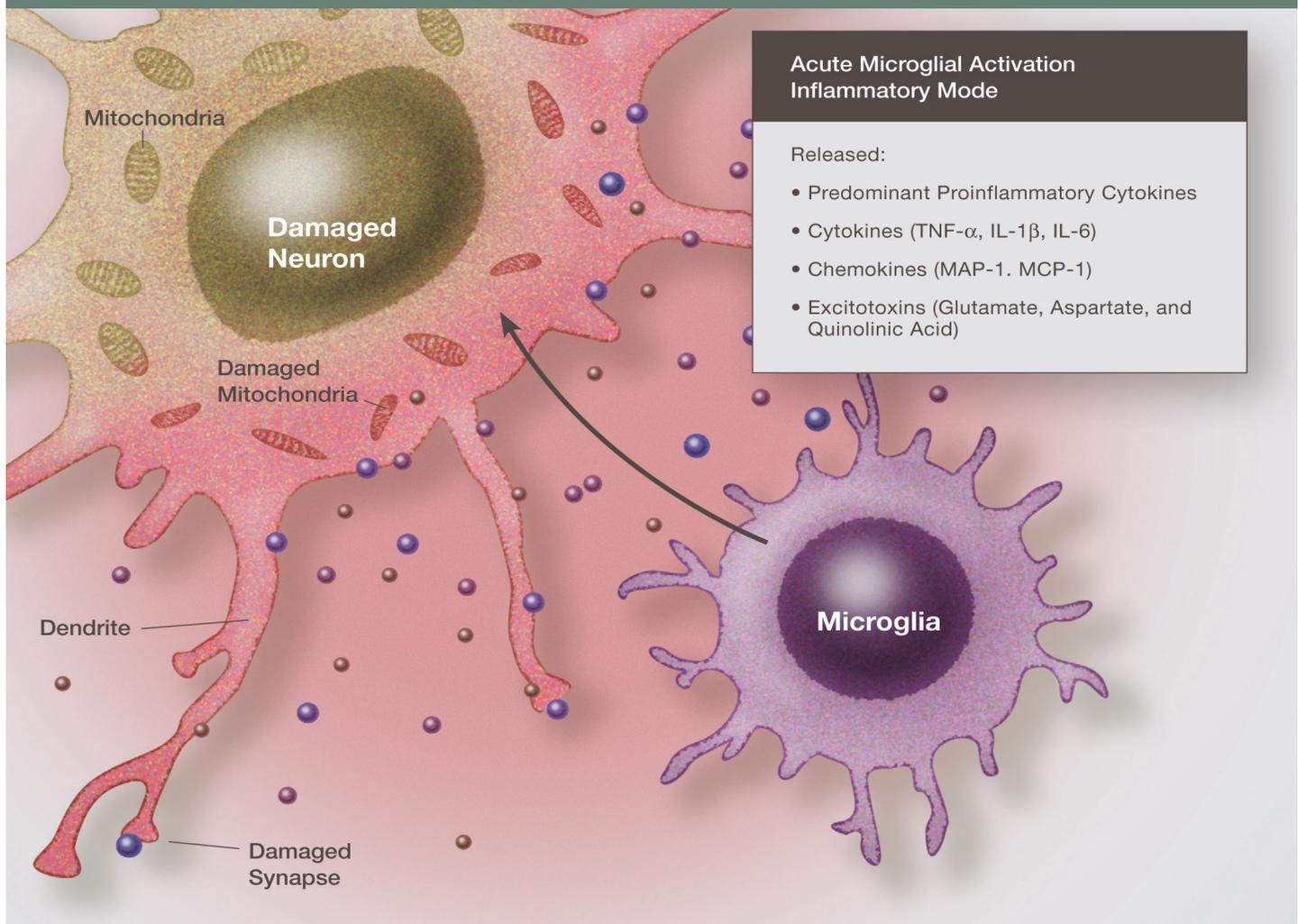
Immunoexcitotoxicity and Inflammation in Neurodegeneration

While this article is focused primarily on TBI, the emerging research on immune system activation also has clinical relevance for chronic conditions such as AD, autism and PD. These conditions have also been linked to activated immune system states and it appears that TBI, PCS, CTE, PD and AD may share this common pathophysiological characteristic. The chronic inflammation described in AD has been attributed to the activation of microglia.⁶ A very similar process occurs in PCS, which in turn leads to CTE, a condition which shares many common hallmarks (such as Tau tangles) of AD.⁷ While reducing inflammation is of great clinical importance, modulating immune activation may be even greater since it appears to be the key initiating factor causing the vicious cycle of neuroinflammation.

Even though all immune cells are capable of producing cytokines, the primary immune cell in the brain to become activated is the microglia (they are the macrophages of the brain).⁸ Any changes or disruption of neuronal homeostasis (i.e. TBI) can cause the microglia to become activated from their resting state. Other factors such as toxic environmental exposures (e.g. heavy metals, pesticides), systemic immune stimulation, microbial infections, ischemia/hypoxia and brain aging have also been linked to activated or “primed” microglia.⁹⁻¹¹ This suggests that other cumulative and lifestyle factors can predispose someone to a greater degree of trauma and/or poorer prognosis after a TBI. While normal neurophysiology suggests a possibility of switching activated microglia back to a resting or reparative mode, it is unknown if it is possible in chronic situations or in the prolonged presence of the initiating factors listed above.¹²

Resting or resident microglia are mainly phagocytic and secrete trophic factors needed in brain repair and neuroprotection. Paradoxically, activated microglia, can secrete a number of anti- and proinflammatory cytokines, chemokines, nitric oxide,

Figure 1: Blaylock RL, Maroon J. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy-A unifying hypothesis. *Surg Neurol Int* 2011;2:107



prostaglandins, free radicals, and three types of excitotoxins.⁸ Figure 1 illustrates an activated microglia and how it mediates damage to other neurons.⁸ Dr Russell Blaylock first coined the term “immunoexcitotoxicity” to describe the importance of the immune system in producing excitotoxins that drive the damaging cascade in both acute and chronic brain disease.¹³ Immunoexcitotoxic cascades generate large amounts of free radicals and lipid peroxidation products, which cause damage to a number of tissues and cellular components, including microvessels, the blood–brain barrier (BBB), mitochondria, cell membranes, nuclear and mitochondrial DNA.^{3,14} The reduced integrity of the BBB may enhance the penetration of environmental toxins, heavy metals and microbes into the brain and further contribute to the viscous cycle of neuroinflammation and chronic dysfunction. Therefore, modulating the immune and inflammatory response, quenching free radicals and supporting mitochondrial function in TBI, PCS, CTE, and AD are emerging as key therapeutic targets in both acute and chronic neurological conditions.

Natural Compounds for Neuroprotection and Recovery

Since the pathophysiology of TBI, PCS, and CTE is a complex process there are a number of possible natural interventions that may be applicable at different stages. Before getting into specifics, it is important to note that much of the interventional research

has been done in pre-clinical and animal models. Extrapolation to human subjects is promising but still falls short of definitive, clinical application. Secondly, many of the studies on commonly used natural substances (i.e. vitamin E) do not use adequate dosing or the most biologically active forms.³ There is an underlying misunderstanding of how antioxidants and vitamins function in the human body, which is reflected in poor study design and methodology (i.e. only using one antioxidant in isolation as an intervention). It is possible this has confounded potentially beneficial results, which in turn may have limited the therapeutic impact of the natural compounds used in the studies.³

Curcumin

Curcumin is the active compound found in the spice turmeric. It has attracted much interest as a potential treatment of many chronic diseases including AD, cancer and heart disease due to its powerful anti-inflammatory, antimutagenic and antioxidant properties.¹⁵ It has been shown to inhibit inflammatory pathways such as NF- κ B, cyclooxygenase (COX), and lipoxygenase (LOX) enzymes and to stimulate nuclear factor erythroid-2 (Nrf2), which increases the transcription of anti-inflammatory cytokines.¹⁵ Since curcumin possesses a broad spectrum effect that can impact many aspects of a complex neuroinflammatory cascade it now is being heavily studied in AD.¹⁶ While results and clinical implications are still preliminary, curcumin extracts are showing positive benefit in neuro-recovery,



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membrane stabilization and reduction of oxidative stress in TBI models.¹⁷⁻²⁰ Other potential therapeutic effects include increasing brain growth factors, chelating heavy metals, reducing cholesterol, suppressing abnormal beta amyloid and Tau protein production, protecting mitochondria and reducing glutathione depletion.³ The unfortunate problem with curcumin is that due to its poor water solubility, its absorption in the digestive tract is limited. Newer lipophilic encapsulations appear to improve delivery into plasma and the brain tissue.²¹ Curcumin stands as one of the most promising neuroprotective and therapeutic agents in TBI, PCS, CTE due to its excellent safety profile and wide ranging mechanism of action.

Green Tea, Resveratrol and other Polyphenols

Green tea, like curcumin, is a well-known and widely consumed herb with broad-spectrum antioxidant activity. Its neuroprotective properties can be attributed primarily to epigallocatechin-3-gallate (EGCG), the amino acid L-theanine and to a lesser degree, caffeine.²² EGCG has been shown to have antioxidant and anti-inflammatory effects in animal models of brain injury.^{23,24} A number of studies have found positive benefits for cognitive decline in elderly after supplementing with a green tea extract and L-theanine, but there have been no human trials conducted specifically on TBI or PCS.²⁵ One unique aspect of green tea is that the L-theanine content may offer protection from excitotoxic injury through modulation of the glutamine receptor system.²⁶ There is a clear need for more research but there is promising evidence suggesting that even regular dietary consumption of green tea may have a neuroprotective effect in the event of a TBI.

A number of other polyphenols and plant compounds such as resveratrol, quercetin, anthocyanidins, flavonoids, luteolin, and baicalein, have been associated with a neuroprotective effects.³ Unlike pharmacological medications they have multiple modes of actions and work synergistically with each other. They also support the function of endogenous antioxidant systems such as glutathione and quench free radicals not affected by other antioxidants.²⁷ There have been a number of animal trials using polyphenols such as resveratrol, demonstrating an anti-inflammatory and neuroprotective effect in TBI but like green tea there have been no human trials to date.^{28,29} Since flavonoids are found in many colourful fruits and vegetables it would be a prudent and safe recommendation for patients with TBI to incorporate them into their diet.

Essential Fatty Acids and Phospholipids

Omega-3 polyunsaturated fatty acids have long been considered essential for brain development and function. Docosahexaenoic acid [(DHA) and to a lesser degree eicosapentaenoic acid (EPA)] is primarily found in nerve membrane and influences fluidity, cell signaling and inflammatory pathways.³⁰ Since the human body cannot efficiently convert plant based essential fatty acids to EPA and DHA, the supplementation of fish oil is the best source of the active components. It is important to note that while consuming fish high in omega-3 fatty acids is desirable, the high amount of heavy metals and polychlorinated biphenyls (PCBs) found in most

fish is a concern especially in brain function.³¹ A number of trials in animal models of TBI have found that DHA and omega-3 supplementation improves cognitive function, reduces neuronal edema, stabilizes cellular energy homeostasis and increases dendrite growth.^{32,33} One of these studies also showed that pre-injury dietary supplementation with fish oil also had a neuroprotective effect.³² While the anti-inflammatory and cardioprotective benefit of fish oil is widely accepted, there have been no human trials in TBI to date. In chronic conditions such as AD, the results have been inconsistent with a recently published study found no benefit in AD patients after DHA supplementation.³⁴ Mechanistically and functionally, DHA and EPA have promising therapeutic value for neuroprotection, when consumed from plant and fish sources or from high quality, contaminant-free fish oil.

Phospholipids are key structural components of the cellular membrane. Citicoline is a specific phospholipid with potential benefits for aiding in neuronal repair and increasing acetylcholine levels in the central and peripheral nervous system.³⁵ It has been studied as a potential intervention for stroke, TBI and AD.³⁶ Early trials showed promising results in TBI patients but a recent, large scale study found no benefit after 3 months of supplementation.^{37,38} An intriguing and unique use of phospholipids as an effective therapy may be achieved using adequate doses, duration and through intravenous administration.³⁶ Considering the full body of evidence, there does seem to be some (albeit inconsistent) neuroprotective action and a good safety profile for citicoline supplementation in TBI recovery but there remains a need for more research.

Vitamins E and C

One of the frequently studied natural compounds for brain health is vitamin E. It is a family of molecules that have a potent antioxidant effect in fatty tissue. A number of animal studies have found that vitamin E supplementation reduces lipid peroxidation and improves cognitive performance following repetitive, concussive brain injury.^{39,40} Interestingly, supplementation before the concussions also had a neuroprotective effect.⁴⁰

Unfortunately there have been conflicting studies on the benefit of vitamin E supplementation calling into question clinical application.⁴¹ Some of the conflicting results may be due to a number of flaws that exist in the use of vitamin E as an intervention in research trials. Vitamin E is a family of 8 molecules (four tocopherols and four tocotrienols) that function synergistically in human physiology. Most studies have used only low doses of alpha-tocopherol which has been shown to be the least active form of vitamin E and actually depletes the other forms.⁴¹ Gamma-tocopherol is the main anti-inflammatory component and has been found to be more effective than the alpha form in scavenging free radicals that cause inflammation.⁴¹ Emerging evidence suggests that the tocotrienol family has even more benefits than the tocopherols in brain and heart health.⁴² In addition, vitamin E works with other antioxidants such as vitamin C and coenzyme Q10 as part of an antioxidant network. Supplementation with a single antioxidant can lead to itself

becoming oxidized if adequate levels of supporting antioxidants are not present.⁴¹ These two factors may be the reason that led to poor outcomes in vitamin E intervention trials.²² It also highlights the need to supplement antioxidant together in order to support their proper biological function. Expanding on this approach, one trial found that intravenous vitamin E along with vitamin C stabilized severe brain injury and reduced cerebral edema.⁴³ Intravenous treatments such as vitamins E and C may be promising therapies in TBI as they are able to deliver high doses of antioxidant protection to brain tissue and appear to act synergistically.

Emerging Treatments

It is worth noting some of the other emerging, non-nutrient treatments that are being studied for TBI. Progesterone administration after acute TBI is currently undergoing phase III clinical trials and has shown positive outcomes.^{44,45} There also is some evidence that vitamin D, while having a large spectrum of potential cognitive benefits in its own right, has a synergistic role with progesterone. Correcting a vitamin D deficiency appears to improve the effectiveness of progesterone therapy in TBI.⁴⁶

Another intervention purported to have beneficial effects on TBI recovery is hyperbaric oxygen therapy (HBOT). While still controversial, a Cochrane review found there is some benefit from HBOT but it concluded that higher quality trials are needed to confirm positive outcomes.⁴⁷ While the therapy usually requires 40 or more consecutive treatments (that can be financially burdensome) there appears to be enough positive evidence to consider HBOT a potential treatment for TBI.

Clinical Conclusions

TBI is a common form of injury, which often goes unreported and is commonly mismanaged. Researchers are now just beginning to understand the complex pathophysiological cascade after a brain injury. Recent evidence suggests that a TBI (especially multiple event) predisposes a person to chronic neurological damage very similar to AD. The pathophysiology of TBI and CTE shed light on some of the possible therapeutic targets that may be effective in managing AD. Immune activation, excitotoxicity, and inflammation occur in both acute and chronic neurological injury and should be the primary targets for treatments. Treatments with a singular mechanism have had limited benefit but natural compounds offer promising options due to their broad spectrum of action.

While the evidence is far from conclusive, some simple conclusions can be drawn and applied to clinical practice. Some of the most promising natural compounds in active treatment of TBI are curcumin, green tea extract, and resveratrol. Intravenous therapies such as citicoline and vitamins E and C also offer benefit. From a preventative perspective, a diet high in polyphenols found in colourful fruits and vegetables and omega-3 fatty acids along with supplementation of vitamin E and DHA may improve recovery after a TBI. There remain other therapeutics such as caffeine, creatine, and magnesium that also merit consideration as potential intervention

for TBI. Although the discussion is beyond the scope of this paper, it would also be prudent to also consider and assess the stability of the cervical spine as TBI and PCS symptoms can also originate from damage to cervical ligaments.

Studies looking at natural and plant compounds show promising results but clearly show that there is a need for more, high quality research. The data remains equivocal with studies finding both positive and no benefits despite a promising, theoretical mechanism of action. This may reflect the diversity, dosing and quality of natural substances used in the trials. The complex nature of the neuroinflammatory cascade and the individuality of each person may also contribute to the wide range of findings. Despite the advances in the understanding of TBI and chronic neurological disease, we still do not fully understand the intricate interplay of cell signaling and inflammation. The one definitive point is that very few (if any) side effects and negative results have been found in trials with natural substances making their use safe when prescribed and monitored by a healthcare professional. Both researchers and clinicians can remain cautiously optimistic that more evidence will emerge to support natural therapies for TBI. 🍂

KEY FACTS

- Approximately 30,000 concussions or head related injuries have been reported annually among the 12 to 19 year-old age group but the majority of concussions are still not being reported so the true numbers are most likely underestimated.
- Traumatic brain injury stimulates a cascade of glutamate and calcium release which leads to neuroinflammation, excitotoxin production, mitochondrial dysfunction and immune activation.
- Immune system activation has been identified as a key factor in TBI but emerging research has found it also plays a role in chronic conditions such as Parkinson's disease, Alzheimer's disease and autism.
- Natural substances such as curcumin and green tea possess a broad spectrum, therapeutic effect that can simultaneously impact many aspects of a complex neuroinflammatory cascade. They are now being heavily studied in TBI, AD and other neurodegenerative disorders.
- The 8 molecules in the vitamin E work with other antioxidants such as vitamin C as part of an antioxidant network. Supplementation with a single antioxidant can lead to itself becoming oxidized if adequate levels of supporting antioxidants are not present.

About the Author

Dr. Paul Hrkal, ND is a board certified naturopathic physician and is an active member of the Canadian Association of Naturopathic Doctors and The Ontario Association of Naturopathic Doctors. Dr. Hrkal is an expert in nutrition and supplemental treatments and has additional training and certification in intravenous and injection therapy. He has a special interest in brain health, neurological disorders, cancer, chronic pain and sports medicine. He also is strong advocate of integrative medical education and lectures regularly to both healthcare practitioners and public audiences. He currently is a medical advisor for Advanced Orthomolecular Research and maintains a clinical practice in the Mississauga area at pureBalance Wellness centre in Mississauga.

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