The Functional And Nutritional Medicine Approach To Brain Injury – A Focus On Restoring Endocrine And Metabolic Function

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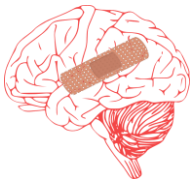
Disclosures

- Practicing ND
- Medical Director – *Advanced Orthomolecular Research*
- Scientific advisory board – *Complete Concussion Management*

Overview

- Overview of metabolic, endocrine and neurological changes
  - from the perspective of potential therapeutic targets
- Potential Pharmaceutical Interventions
- Nutrition to support neuro – recovery
- Potential Natural Interventions - to support neuro



CLINICAL PATHOPHYSIOLOGY

Mg competes w/ Ca^{2+} for access to NMDA

2 phases to mTBI - Excitatory & Spreading Depression

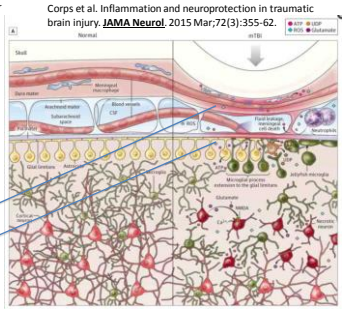
Responsible for sx

Barnett EC, McBurney MI, Ciappio ED. Adv Nutr. 2014 May 14;5(3):268-277

Relevant Physiology of Acute mTBI

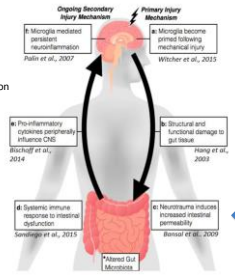
- Acute mTBI
  - 80-90% resolve in 10-14 days
- Secondary effects of acute mTBI
  - ionic flux
  - disruption of cellular function
  - free radical damage
  - Activation of microglia = inflammation
  - Derangement of blood flow
    - Excess SNS and ANS dysfunction
  - Leaky blood-brain barrier

Corps et al. Inflammation and neuroprotection in traumatic brain injury. **JAMA Neurol**. 2015 Mar;72(3):355-62.



- McConeghy KW, Hatton J, Hughes L, Cook AM A review of neuroprotection pharmacology and therapies in patients with acute traumatic brain injury. CNS Drugs. 2012 Jul 1;26(7):613-36.

Sustained Neuroinflammation



Starts 3hrs after TBI, peaks 72hrs, lasted 7 days

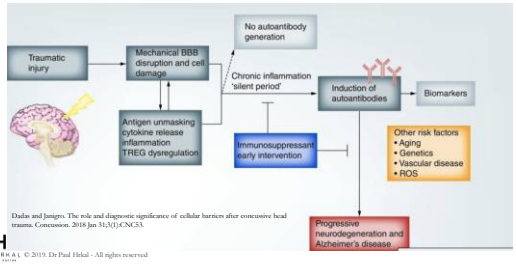
Sundman, M. H., Chen, N.-K., Subbian, V. & Chou, Y.-H. The bidirectional gut-brain-microbiota axis as a potential nexus between traumatic brain injury, inflammation, and disease. Brain Behav. Immun. 66, 31–44 (2017)

Gut –Brain Connection

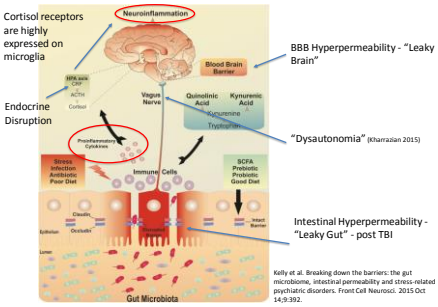
- Gut lining resembles the BBB in many respects
  - ± 75% similarity in structural composition
- Immune system – cross reaction of Gut lining and BBB proteins
  - "Autoimmune reaction"
- Neuro trauma induces a more permeable BBB and GI barrier
- **Leaky gut causes leaky brain!**
  - Common sx include: depression, anxiety, **brain fog** etc etc.

Rea, K., Dinan, T. G. & Cryan, J. F. The microbiome: A key regulator of stress and neuroinflammation. Neurobiol Stress 4, 23–33 (2016).
Lopez-Ramirez, et al. MicroRNA-155 negatively affects blood-brain barrier function during neuroinflammation. *FASEB J.* June 2014 28:2551-2565; doi:10.1096/fj.13-240880

Autoimmune-TBI Connection

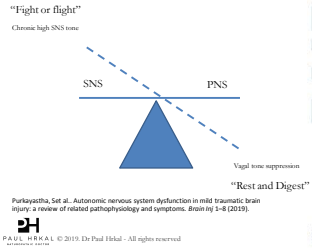


Dadas and Janigro. The role and diagnostic significance of cellular barriers after concussive head trauma. Concussion. 2018 Jan 31;3(1):CNC53.

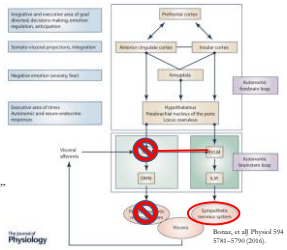


Kelly et al. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front Cell Neurosci. 2015 Oct 14;9:392.

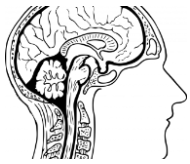
Dysautonomia: High SNS and Low PNS Tone



Purkayastha, Set al.. Autonomic nervous system dysfunction in mild traumatic brain injury: a review of related pathophysiology and symptoms. *Brain Inj* 1–8 (2019).



Benzo, et al J Physiol 594 5781–5790 (2016).



POST CONCUSSION SYNDROME

Post Concussion Syndrome (PCS)

- Headaches, dizziness, fatigue, cognitive impairment and neuropsychiatric symptoms, such as irritability and reduced tolerance to stress
- >30% of all concussions will go on to have long-standing symptoms (30 days+)
  - 33% (pediatrics)
- Cause: officially "unknown" BUT here is what we DO know
  - Soft tissue damage of neck
  - **Autonomic dysfunction**
  - **Metabolic, endocrine and blood flow dysfunction**
  - Biopsychosocial factors
  - lower pre-injury cognitive reserve
  - **Persistent inflammation**
    - elevated CRP (3 months) linked to greater depression, fatigue and cognitive impairment

"Post Inflammatory Brain Syndrome"?

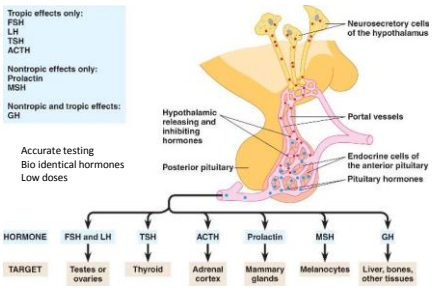
Rathbone et al 2015

- Zemek et al. Clinical Risk Score for Persistent Postconcussion Symptoms Among Children With Acute Concussion in the ED. JAMA. 2016 Mar 8;315(10):1014-25. doi: 10.1001/jama.2016.1203.
- Collins-Praino et al. The effect of an acute systemic inflammatory insult on the chronic effects of a single mild traumatic brain injury.Behav Brain Res. 2018 Jan 15;336:22-31. doi: 10.1016/j.bbr.2017.08.035. Epub 2017 Aug 10.
- S.H. Su, W. Xu, M. Li, L. Zhang, Y.F. Wu, F. Yu, et al., Elevated C-reactive protein levels may be a predictor of persistent unfavourable symptoms in patients with mild traumatic brain injury: a preliminary study, Brain Behav. Immun. 38 (2014)

Hormone – TBI connection

- Hypopituitarism post TBI - assessment and treatment pioneered by Dr Mark Gordon MD
- 50-76% of mod-severe TBI patients have loss of pituitary function right after injury
  - 58% of patients recover their normal pituitary function within one year
  - 52% develop new pituitary hormone deficiencies after one year
- 2017 study: 16% of their mTBI patients developed new pituitary dysfunction over the 6-12 months after injury
  - Most frequently cited dysfunction is growth hormone deficiency
  - Other data suggests as high as 37.5% in mTBI
- Hypopituitarism affects healing of brain!!

- Agha A, Phillips J, O'Kelly P, Tormey W, Thompson CJ. The natural history of post-traumatic hypopituitarism: implications for assessment and treatment. Am J Med. 2005 Dec;118(12):1416.
- Frendl et al. Plasminogen Activator Inhibitor Type 1: A Possible Novel Biomarker of Late Pituitary Dysfunction after Mild Traumatic Brain Injury. J Neurotrauma. 2017 Sep 20. [Epub ahead of print]
- See reference list for more



Accurate testing
Bio identical hormones
Low doses

Summary of Key Underlying Metabolic Factors

- Excitotoxicity and ionic imbalance
- ATP/Energy deficiency
- Neuroinflammation – Acute → Chronic
- Dysautonomnia

} Gut-Brain Axis

- Derangement of blood flow
- Leaky blood-brain barrier
- Endocrine imbalances

"It is much more important to know what sort of person has a disease, than what sort of disease a person has"

Sir William Osler

"Anita" – 35 y/o female – Aug 2017

- July 4th - Impact to occipital area, no symptoms – 4 days later hit her head on same area triggered severe headache ("10/10") for 10 days
- Trouble initiating sleep
- Screen time, acupuncture agg., nature and quiet amel.
- O: TBI score: 29, Neuro and visual screener WNL
- ROS: low TSH, eczema

"Anita" – 35 y/o female – Aug 2017

- Went to hospital after severe headache
  - CT scan "all clear", sent home
- Using Advil to manage headache PRN

Current Conventional Treatments For Concussions and PCS

Pharmacotherapy For Concussions

- **Pharmacological interventions:**
- **Berlin Consensus:** "*Currently, there is limited evidence to support the use of pharmacotherapy*"
- Currently, no neuroprotective treatment options exist that improve neurological outcomes after concussion
- Pharma interventions centred on symptom management
- **Berlin Consensus:** "concussed athletes should not only be free from concussion-related symptoms, but also should not be taking any pharmacological agents/medications that may mask or modify the symptoms of SRC"

- Blaylock R and Maroon J. Natural plant products and extracts that reduce immunocsicitotoxicity-associated neurodegeneration and promote repair within the central nervous system. Surg Neurol Int. 2012; 3: 19.
- McCrossgle KR, Hatton J, Hughes L, Cook AM A review of neuroprotection pharmacology and therapies in patients with acute traumatic brain injury. CNS Drugs. 2012 Jul 1;26(7):613-36.

Pharmacotherapy For Symptoms of TBI

- No evidence supporting **mild** TBI treatment
- Poor or no evidence for interventions targeting symptoms of all types of TBI
  - Depression – sertraline 59% of the treatment-arm had improvements in their depression score but not statistically sig. difference
  - Amantadine – irritability – 1 positive, 1 negative study
    - Unknown MOA but reduces excitotoxicity
  - Donepezil – improved short term memory
    - But may inhibit hippocampal neurogenesis
  - Methylphenidate - improvement in cognitive complaints and PTSD
    - Caution due to addiction, aggression psychosis….

Bhatnagar et al. Pharmacotherapy in rehabilitation of post-acute traumatic brain injury. Brain Res. 2016 Jun 1;1640(Pt.A):164-79.

Pharmacotherapy For Neuroprotection

Intervention	Rationale	Outcome
Calcium channel blockers	Reduce vasospasm in aneurysmal subarachnoid hemorrhage	No benefits found*
Steroids (dexamethasone)	Reduce edema	risk of death or severe disability was higher in the steroid group
NMDA-receptor antagonists	Reduce excitotoxicity of glutamate	No benefits found, trials stopped due to lack of efficacy
Oxygen free-radical scavengers	Antioxidant (synthetic)	No follow up trials due to lack of efficacy
Immune system modulation (cyclosporin, fingolimod)	Suppress the immune system right after TBI	No benefit (and no negative effects), some promise - ongoing trials
Statins	Anti-inflammatory, reduction on iNOS	Improvement in cognition after 3 weeks - ongoing trials
Hypothermia	decreasing cerebral edema and swelling	ineffective in large clinical trials, limitations due to sys effects

Chakraborty et al. Neuroprotection Trials in Traumatic Brain Injury. Curr Neurol Neurosci Rep. 2016 Apr;16(4):29

Statins and mTBI

- Atorvastatin for 7 days post-injury
- 28 patients received atorvastatin and 24 received placebo
- Rivermead Post-Concussion Symptoms Questionnaire at 3 months
- Atorvastatin administration for 7 days post-injury was safe, but there were no significant differences in neurological recovery post-mTBI with atorvastatin

Robertson et al. Phase II Clinical Trial of Atorvastatin in Mild Traumatic Brain Injury. J Neurotrauma. 2017 Feb 27. PMID: 28006970

Table 1. Pharmacological Agents Currently Prescribed for PCS and Known Side Effects

Pharmacological Agent	Commercial Name	Mechanism	Approved Indications	Side Effects
D-amphetamine	Dexedrine® (GlaxoSmithKline), Adderall® (Actavis)	Directly releases dopamine and NE	Narcolepsy, ADHD	Anxiety, GI upset, insomnia, irritability, euphoria, starting episodes
Methylphenidate	Ritalin® (Novartis)	Enhances dopaminergic transmission	Narcolepsy, ADHD	Insomnia, decreased appetite, GI upset, headaches, dizziness, motor tics, irritability, anxiousness, tearfulness
Modafinil	Provigil® (Cephalon)	Increases release of catecholamines and histamine	Narcolepsy	Headache, asthenia
Bupropion	Wellbutrin® (GlaxoSmithKline)	Blocks dopamine reuptake	Depression	Seizures, dilirium, hallucinations
Atomoxetine	Strattera® (Eli Lilly and Company)	Blocks noradrenergic reuptake	ADHD	Dizziness, asthenia, GI upset, nausea, decreased appetite, insomnia
Gabapentin	Neurontin® (Pfizer), Fanatrex® (Fusion Pharmaceuticals), Horizant® (GlaxoSmithKline), Gralise® (Depomed, Inc.)	GABA analog	Epilepsy, seizures, neuropathic pain	Dizziness, headache, blurred vision, anxiety, memory problems, motor tics, nauses, increased appetite
Fluoxetine	Prozac® (Eli Lilly and Company), Sarafem® (Warner Chilcott Laboratories), Selfemra® (Eli Lilly and Company)	Selective serotonin reuptake inhibitor	Depression, OCD, panic attacks	Anxiety, nausea, motor tics, decreased appetite, weakness

Maroon et al. Phys Sportsmed. 2012 Nov;40(4):73-87.

Most common side effects: Dizziness, blurred vision, irritability, poor concentration and memory, headache and anxiety…

Amantadine	Symadine® (Cipla), Symmetrel® (DuPont)	Releases dopamine and NE, NMDA receptor antagonist	Parkinson disease	Dizziness, blurred vision, anxiety, insomnia
Escitalopram	Lexapro® (Forest Laboratories)	Selective serotonin reuptake inhibitor	Depression, anxiety	Nausea, dizziness, GI upset, increased appetite, hallucination, arrhythmia
Trazodone	Desyrel® (Bristol-Myers Squibb Company), Oleptro™ (Labopharm Inc.)	Increases, releases serotonin	Depression	GI upset, nausea, changes in appetite, blurred vision, impaired concentration/memory, motor tics, arrhythmia
Amitriptyline	Elavil® (AstraZeneca), Endep® (Roche Laboratories)	Serotonin and NE reuptake inhibitor	Depression	Nausea, GI upset, weakness, blurred vision, changes in appetite, dizziness, arrhythmia, motor tics, seizures, hallucination, unusual bleeding
Topiramate	Topamax® (Janssen Pharmaceuticals, Inc.), Topiragen® (Upsher-Smith Laboratories, Inc.)	Blocks voltage-gated sodium channels	Seizures, migraines	Lack of coordination, impaired memory/concentration, irritability, headache, depression, weakness, motor tics, GI upset, hair loss, change in appetite
Ibuprofen	Motrin® (Johnson & Johnson), Advil® (Pfizer)	COX inhibitor	Osteoarthritis, analgesia, fever, inflammation	GI upset, GI ulcers, GI bleeding, dizziness, nausea, loss of appetite, arrhythmia, headache, confusion

Maroon et al. Phys Sportsmed. 2012 Nov;40(4):73-87.

Conventional Options for Inflammation

- Inflammation → NSAIDs, COX_2 inhibitors
  - Acute mTBI - Ibuprofen (+ acetaminophen) reduced headaches and sped return to school (Petrella 2017)
  - Chronic Ibuprofen may worsen cognition post TBI (Bryson et al 2006)
    - New "nano" delivery, fat soluble systems of ibuprofen promising acute application
  - Targeted anti-inflam's may be better
    - i.e. TNF-α inhibitors
  - Long term side effects
    - Gastric side effects
    - Inhibits formation of healing cytokine cascade - cartilage

- Patterson ZR, Holahan MR Understanding the neuroinflammatory response following concussion to develop treatment strategies. Front Cell Neurosci. 2012 Dec 12;6:58
- Bryson, K. D., Iwata, A., Pratt, M. E., and Smith, D. H. (2006). Chronic ibuprofen administration worsens cognitive outcome following traumatic brain injury in rats. Exp. Neurol. 201, 301–307.
- Petrella et al. Paediatr Child Health. 2017 Mar;22(1):2-6. The use of ibuprofen and acetaminophen for acute headache in the postconcussive youth: A pilot study.. PMID: 29483787

PROs and CONs to Pharma Approach

PROs

- Usually faster acting
- May help reduce symptoms

CONs

- Single target MOA
- Doesn't address underlying pathophysiology
- Side effects
- Nutrient depletions
  - i.e. Benzos - Melatonin
- Unproven efficacy

RE-THINKING TBI/PCS:
THE FUNCTIONAL MEDICINE APPROACH

"Anita" – 35 y/o female – Aug 2017

- 2nd impact after 4 days
- Visited family MD after hospital
  - Told to rest and avoid screens
  - No active care or manual therapy recommended

My Approach…

- Understanding and addressing underlying metabolic dysfunction
  - Step by step
- An integrative, evidence informed approach
  - Diet and lifestyle
  - Multi faceted treatment plan
    - Botanicals, endocrine support, nutrients, IV therapy etc.

Acute and Sub Acute Management

- Have they been assessed by qualified MD, physio or DC?
  - Neuro, neck, vestibular, vision
- Use a sx tracking questionnaire as baseline
- Consider acute pathophysiology
  - Goal reduce excitotoxicity and ***balance*** inflammation
- Diet: Brain recovery diet – SIMPLE, clean, easy to follow
- Foundational nutrients – consider functional pathophys.
- Botanical antioxidants - titrate up until sx resolve
- IV therapy – rapid repletion and delivery of nutrients

"Anita" – 35 y/o female – Aug 2017

- Tx: Paleo diet for 2 weeks, no gluten
  - Patient disclosed she "doesn't feel good after gluten"
- Why paleo?
  - Easy adherence in acute cases

The Foundations For a Brain Recovery Diet

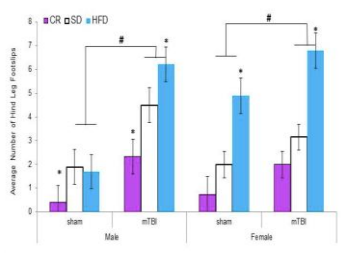
- No diet studied for treatment of mTBI in humans…yet
- But related evidence suggests benefits
  - Prevention – Brain Resilience
  - Therapeutic – reduce inflammation, increase antioxidant and energy (mitochondrial) systems
- Consider "metabolic state of patient"
  - PLUS extra inflammatory and oxidative damage in TBI

Can Diet Prevent Effects of TBI?

- 2015 study - Alberta children's hospital
- Study goal: Could high fat diet (HFD) or Calorie restricted (CR) alter susceptibility or resiliency to poor outcomes following an mTBI in animals
- Findings
  - CR diet appeared to create resiliency to the injury
  - HFD decreased in all measures compare to STD and CR
  - HFD demonstrated greater susceptibility to poor outcomes after the mTBI
  - CR group had higher BDNF, SIRT1 and other neuroprotective genes compare to HFD
  - CR increased telomere length, HFD decreased brain levels

Mychasiuk et al. *Front. Behav. Neurosci.* 9:17. 2015

Can Diet Prevent Effects of TBI?



Mychasiuk et al. *Front. Behav. Neurosci.* 9:17. 2015

Impact of nutrition on inflammation, tauopathy, and behavioral outcomes from chronic traumatic encephalopathy

Jin Yu[1], Hong Zhu[1], Saeid Taheri[1], William Mondy[1], Stephen Perry[2] and Mark S. Kindy[1,3,4*]

Abstract

Background: Repetitive mild traumatic brain injuries (mTBI) are associated with cognitive deficits, inflammation, and stress-related events. We tested the effect of nutrient intake on the impact of mTBI in an animal model of chronic traumatic encephalopathy (CTE) to study the pathophysiological mechanisms underlying this model. We used a between group design mTBI closed head injuries in mice, compared to a control and nutrient-treated groups.

Methods: Our model allows for controlled, repetitive closed head impacts to mice. Briefly, 24-week-old mice were divided into five groups: control, mTBI, and mTBI with nutrients (2% of NF-216, NF-316, and NF-416). mTBI mice received four concussive impacts over 7 days. Mice were treated with nutrient diets for 2 months prior to the mTBI and until euthanasia (6 months). Mice were then subsequently euthanized for macro- and micro-histopathologic analysis for various times up to 6 months after the last TBI received. Animals were examined behaviorally, and brain sections were immunostained for glial fibrillary acidic protein (GFAP) for astrocytes, Iba-1 for activated microglia, and AT8 for phosphorylated tau protein.

Results: Animals on nutrient diets showed attenuated behavioral changes. The brains from all mice lacked macroscopic tissue damage at all time points. The mTBI resulted in a marked neuroinflammatory response with persistent and widespread astrogliosis and microglial activation, as well as significantly elevated phospho-tau immunoreactivity to 6 months. Mice treated with diets had significantly reduced inflammation and phospho-tau staining.

Conclusions: The neuropathological findings in the mTBI mice showed histopathological hallmarks of CTE, including increased astrogliosis, microglial activation, and hyperphosphorylated tau protein accumulation, while mice treated with diets had attenuated disease process. These studies demonstrate that consumption of nutrient-rich diets reduced disease progression.

Keywords: Animal model, Chronic traumatic encephalopathy, Concussion, Pathophysiology, Repetitive, Diet, Inflammation, Neurodegeneration, Behavior

- 5 groups of mice (15 per group):

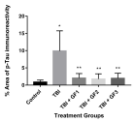
1. Control
2. Repeated mTBI (rmTBI)
3. rmTBI with diet 1 (fruits & veggie)
4. rmTBI with diet 2 (fruits)
5. rmTBI with diet 3 (veggie)

- Those in the diet groups started the diet 2 months before the injuries occurred and then kept it going for the duration of the study.

- Mice were given 4 concussions in 7 day period and were then tested in a variety of ways until they were euthanized and processed to look for inflammation and signs of CTE at 6 months

Impact of nutrition on inflammation, tauopathy, and behavioral outcomes from chronic traumatic encephalopathy

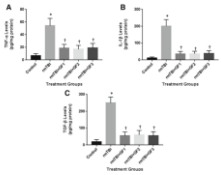
- Results:
  - Tau – control mice showed very little phosphorylated tau (p-tau), whereas rmTBI mice showed at dramatic increase, however with the diets, there was a significant reduction in p-tau pathology



Yu et al., 2018

Impact of nutrition on inflammation, tauopathy, and behavioral outcomes from chronic traumatic encephalopathy

- Results:
  - Inflammatory cytokines: TNF-a, Interleukin-1B, and TGF-B were all elevated in rmTBI vs. controls at 6 months. rmTBI resulted in "CTE-like" effects elevated cytokine levels that were still increased 6 months later
    - The diets significantly reduced or attenuated all of these markers
      - Reduced TNF-a by 67%
      - IL-1B was reduced by 85%
      - TGF-B was reduced by 80%



Yu et al., 2018

Impact of nutrition on inflammation, tauopathy, and behavioral outcomes from chronic traumatic encephalopathy

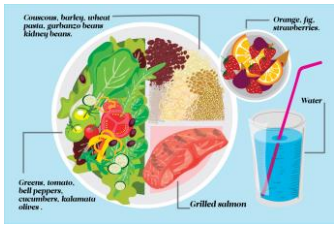
- Results:
  - Repetitive mild traumatic brain injury (rmTBI) results in increased risk-taking and depression-like behaviors at 2 weeks, 1 month, and 6 months – the animals treated with the diets had returned to control levels by 2 weeks and remained so up to 6 months.
  - Sleep – also significantly impacted by rmTBI, but attenuated by the diet

Conclusion

Here, we show that treatment of mice with diets enriched in fruits and vegetables (phytochemicals) can alter the pathogenesis of CTE. Although treatment was started prior to the CTE, the indications are that the presence of these diets helped to attenuate the disease process, reduce inflammation, and improve outcomes. These data suggest that diets enriched in phytochemicals and other entities will help to limit the extent of injury following TBIs and reduce the potential progression to CTE in individuals.

Yu et al., 2018

Human Evidence – Neuroprotective Diets



- Mediterranean Diet
  - Excellent evidence as preventative for Alzheimer's Dz
    - Reduces inflammatory markers, cardio preventive, boosts BDNF levels

- Sánchez-Villegas et al. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: the PREDIMED-NAVARRA randomized trial. Nutr Neurosci. 2011 Sep;14(5):195-201.

Image credit: https://www.nl.com/health/wellness/mediterranean-diet-infographic/

MIND Diet

- MIND diet - "Mediterranean-DASH Intervention for Neurodegenerative Delay" – *Rush University*
  - N:923, 4.5 years
  - 53% reduction of Alzheimer's disease risk
  - Even moderate adherence had some benefit** (35% RR)
- **3 servings of whole grains**
- **A salad plus one other vegetable**
- **A glass of wine daily**
- **Nuts as a snack daily**
- **Blueberries or strawberries**
- **Chicken or fish**
- **Beans (every other day)**

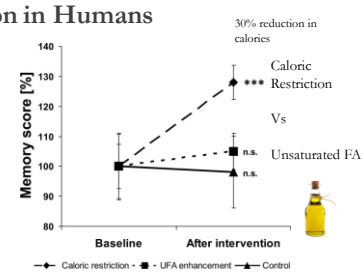
- Avoiding foods like butter and cheese, red meat, pastries, sweets and fried or processed foods.

Morris et al. Alzheimers Dement. 2015 Sep;11(9):1007-14. MIND diet associated with reduced incidence of Alzheimer's disease.

Caloric restriction in Humans

- Memory enhancing effect is "well-established" in human and animal studies (aging)

- Human Study (50)
  - Improved memory (verbal) after 3 months



- Witte AV, Fobker M, Gellner R, Knecht S, Floel A. Caloric restriction improves memory in elderly humans. Proc Natl Acad Sci U S A. 2009 Jan 20;106(1):1255-60.

Why Is Caloric Restriction / KD Effective?

1. Improved insulin signalling = neuroprotective (Witte et al 2008)
2. Increases neurotrophic factors (Connor and Dragunow 1998)
   - BDNF and IGF-1 promote nerve growth and repair
3. Ketones improve Mitochondrial function (Maalouf et al 2009)
   - More cellular energy
4. Reduces Inflammation

- Witte AV, Fobker M, Gellner R, Knecht S, Flöel A. Caloric restriction improves memory in elderly humans. Proc Natl Acad Sci U S A. 2009 Jan 27;106(4):1255-60.
- Maalouf,M.,Rho,J.M.& Mattson,M.P. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Res. Rev. 59, 293–315 (2009).

Ketogenic diet / Ketones

- Pre and post injury animal studies show improved structural and functional outcomes
  - Increase endogenous antioxidants and decreases ROS, some functional benefits
  - Ketones preferred fuel source of brain after TBI
    - Lactate is also being studied
- Human clinical data comes from epilepsy studies, nothing on TBI
  - Limitations
    - Adherence is poor
    - Side effects: hypoglycemia, excessive acidosis, gastroesophageal reflux, nephrolithiasis, and hypercholesterolemia
  - Ketone esters are expensive and numerous sides effects
    - nausea, abdominal distention, headache, diarrhea, and dizziness

Prins ML, Matsumoto JH. The collective therapeutic potential of cerebral ketone metabolism in traumatic brain injury. *Journal of Lipid Research*. 2014;55(12):2450-2457. doi:10.1194/jlr.R046706.

Food Induced Inflammation

- Refined Sugars, Carbs and Fats (saturated)
  - Promotes inflammation, oxidative stress and insulin resistance
  - Meats rich in saturated fat and arachidonic acid – pork, beef, cow's milk, lamb, liver
  - Egg/sausage Muffin sandwich and hash browns increase inflammation
    - NF-κβ increased by 150% for 2 hours

- Aljada et al. Increase in intranuclear nuclear factor kappaB and decrease in inhibitor kappaB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect. Am J Clin Nutr. 2004 Apr;79(4):682-90.

Oligoantigenic / Hypoallergenic Diet

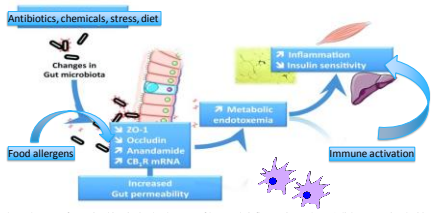
Lancet Neurol. 2010 Mar;9(3):318-30. doi: 10.1016/S1474-4422(09)70290-X.

Gluten sensitivity: from gut to brain.

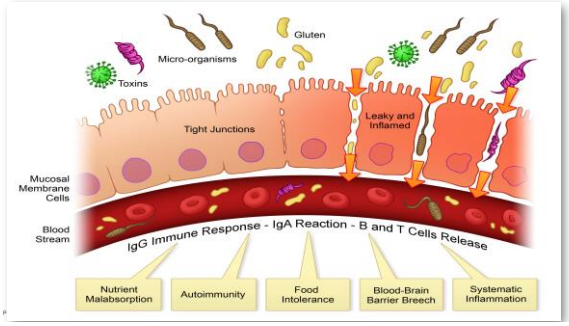
Hadjivassiliou M[1], Sanders DS, Grünewald RA, Woodroofe N, Boscolo S, Aeschlimann D.

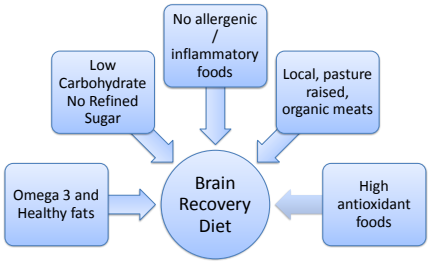
- Auto-antibodies produced after TBI
- Food allergens promote immune activation AKA "inflammation"
  - In the gut AND in distant tissue - *Cross-reactivity*
  - Celiac and gluten sensitivity liked to arthritis, depression, ADHD, autism etc.
  - Gluten free improves joint pain, migraines, depression

Gut – Inflammation Connection



Cani et al. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. Gut Microbes. 2012 Jul-Aug;3(4):279-88. Epub 2012 May 14.





Brain Super Foods

Foods That Block Inflammation

Markers of inflammation (IL-6, NF-κβ) increased and blood flow decreased after 2-4 hours

When ½ avocado was consumed at the same time inflammation did NOT increase and blood flow was preserved

Li Z et al. Hass avocado modulates postprandial vascular reactivity and postprandial inflammatory responses to a hamburger meal in healthy volunteers. Food Funct. 2013 Feb 26;4(3):384-91.

Dietary Antioxidants

Antioxidant	Demonstrated Action
Açai berry pulp	Neuro-protective, anti-inflammatory
Apple juice	Decreases oxidative damage and improves mental performance
Concord grape juice	Increases verbal performance
Blueberries, flavonoids	Antioxidant, anti-inflammatory, improves blood flow etc.
Resveratrol (wine)	Inhibition of activated microglia, vascular health, anti-inflam.

POTENTIAL NATURAL INTERVENTIONS

Nutritional Supplements for the Treatment and Prevention of Sports-Related Concussion—Evidence Still Lacking

Thomas H. Trojian, MD, MMB, FACSM[1]; David H. Wang, MD, MS[2]; and John J. Leddy, MD, FACSM, FACP[3]

Abstract

Concussions are common neurologic events that affect many athletes. Very little has been studied on the treatment of concussions with supplements and nutraceuticals. The U.S. Food and Drug Administration (FDA) reminds us that no supplement has been proven to treat concussions. Many animal studies show that supplements have potential for improving the effects of a brain injury but none have been shown to be of consistent benefit in human studies. Animal studies on severe traumatic brain injury (TBI) may not therefore be applicable transfer to sports-related concussions (SRC).

Of the many supplements reviewed in this article, omega-3 fatty acids (ω3 FA) have potential for SRC treatment but in the one human trial those taking higher dosages preinjury had more concussions. In animal studies, postinjury administration was as effective as pretreatment. *N*-acetyl-cysteine has demonstrated a positive short-term effect on blast injuries in soldiers if administered within 24 h, but there are no studies in SRC. Caffeine, conversely, may be detrimental if taken after SRC. Lower serum levels of vitamins D, C, or E preinjury have worse outcomes in animal studies. Preinjury correction of deficiencies may be of benefit. Current human trials for nicotinamide ribose, melatonin, and branched chain amino acids (BCAA) may soon provide more evidence for the use of these supplements to reduce the impact of SRC in athletes.

Introduction

A concussion is an injury that disrupts the normal function of the brain that can be caused by a blow to the head or body resulting in a rapid acceleration and deceleration of the calvarium (38). Concussions are common in collision sports resulting in variable recovery times in athletes. The cerebral physiology is adversely affected causing significant neurometabolic derangements (13). After a head injury, there is a posttraumatic depolarization and potassium efflux from cells that trigger the release of excitatory amino acid (EAA)-like glutamine, which in turn activate N-methyl-t-aspartate (NMDA) receptors and form a pore through which calcium enters the neuron (111). A large influx of calcium into the cell triggers the lysis of EAA and the formation of reactive oxygen species (ROS) (111). The negative effects of ROS overproduction and activation of inducible nitric oxide synthase is seen in repeat mild traumatic brain injury (mTBI) (105).

The release of cytokines and EAA are normally contained to the area of inflammation associated with the injury (73). Secondary injury to the brain occurs within minutes, days, but can evolve over weeks after the initial insult, which is the result of cascades of these metabolic, cellular, and molecular events (77). These events occur alongside the alterations of endogenous neurochemical, inflammatory, and neuroinflammatory mechanisms. All of these alterations are linked directly or indirectly to neuroinflammation (73). Such mechanisms ultimately lead to brain cell death or rescue, elasticity, tissue damage, and at-

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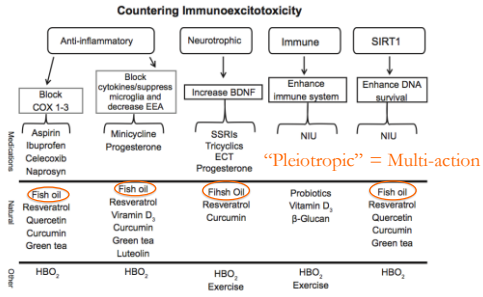
Trojian TH, Wang DH, Leddy JJ. Nutritional Supplements for the Treatment and Prevention of Sports-Related Concussion-Evidence Still Lacking. Curr Sports Med Rep. 2017 Jul/Aug;16(4):247-255.



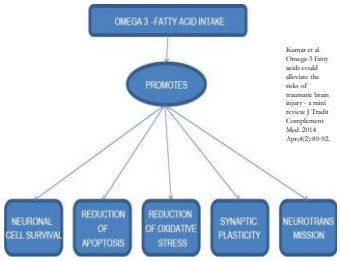
"Pleiotropic" = Multi-action

Maroon et al. Phys Sportsmed. 2012 Nov;40(4):73-87.

Fish Oils - Omega 3 FA's

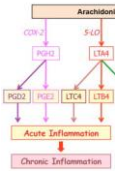
- Brain is 60% fat
- DHA – (25-30% of fat content)
  - *EPA – functional
  - Influence fluidity (structure), cell signaling
  - Anti-inflammatory and PRO-resolving
  - BDNF = nerve growth

Tassoni D, Kaur G, Weisinger RS, Sinclair AJ. The role of eicosanoids in the brain. Asia Pac J Clin Nutr. 2008;17 Suppl 1:220-8.



Kumar et al. Omega-3 Fatty acids could alleviate the risks of traumatic brain injury - a mini review. J Tradit Complement Med. 2014 Apr;4(2):89-92.

Omega 3s



Serhan CN, Petasis NA. Resolvins and protectins in inflammation resolution. Chem Rev. 2011 Oct 12;111(10):5922-43.
Harrison et al. Resolvins AT-D1 and E1 differentially impact functional outcome, post-traumatic sleep, and microglial activation following diffuse brain injury in the mouse. Brain Behav Immun. 2015 Jul;47:131-40.

Omega 3 – TBI Studies

- Animal models
  - improves cognitive function
  - reduces neuronal edema
  - stabilizes cellular energy homeostasis
  - increases dendrite growth
  - deficient levels impair recovery

- Mills JD, Bailes JE, Sedney CL, Hutchins H, Sears B. Omega-3 fatty acid supplementation and reduction of traumatic axonal injury in a rodent head injury model. J Neurosurg. 2011 Jan; 114(1):77-84.
- Wu A, Ying Z, Gomez-Pinilla F. Omega-3 fatty acids supplementation restores mechanisms that maintain brain homeostasis in traumatic brain injury. J Neurotrauma. 2007 Oct; 24(10):1587-95

The Omega-3 index in NCAA-D1 collegiate football Athletes

- Red blood cell content of Omega-3's as measured by Omega-3 index in collegiate football player.
- The Omega-3 index is separated into 3 categories
  - 0 - <4% - high risk (undesirable)
  - 4% - 8% - intermediate risk
  - >8% - low risk (desirable)

Results

- The mean Omega-3 index among all athletes was 4.4% - this means EPA and DHA accounted for less than 5% of all fatty acids present in red blood cells
- 34% of athletes had Omega 3 index of >4% (high risk) with 66% of remaining athletes in intermediate risk category. ONLY 1 athlete had an Omega-3 index of 8.

Anzalone, A. et al. The Omega-3 Index in National Collegiate Athletic Association Division I Collegiate Football Athletes. J Ath Train 54, 7–11 (2019).

Omega 3 Considerations

- Pre-injury dietary supplementation with fish oil may have a neuroprotective effect
  - Prevents some of the metabolic cascade
  - "Brain resilience"
- Possible mechanisms for post injury supplementation
  - Human trials underway, results pending
  - Pleotropic action – i.e. BDNF
- Very Safe – minimal side effects
  - belching, bad breath, "fishy burp," heartburn, nausea, and loose stools

- Wu A, Ying Z, Gomez-Pinilla F. Omega-3 fatty acids supplementation restores mechanisms that maintain brain homeostasis in traumatic brain injury. J Neurotrauma. 2007 Oct; 24(10):1587-95
- Barrett EC, McBurney MI, Ciappio ED. ω-3 Fatty Acid Supplementation as a Potential Therapeutic Aid for the Recovery from Mild Traumatic Brain Injury/Concussion. Adv Nutr. 2014 May 14;5(3):268-277
- Barringer N, Conkright W. Omega-3 Fatty Acid Ingestion as a TBI Prophylactic. J Spec Oper Med. 2012 Fall;12(3):5-7.

Omega 3 and TBI - Summary

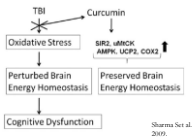
- Helpful as preventive supplement, high doses possibly helpful after injury
- Aim for balance omega 6:3 ratio in diet
  - Food based sources better than supplements
- Diet: wild fish, pasture fed beef, wild game
  - Precursor: Flaxseed, chia
- Poor quality/cheap products
  - PCBs and heavy metals high in fish
  - Oxidation and rancidity
    - Benefits outweigh negatives
- *More studies needed**

Barringer N, Conkright W. Omega-3 Fatty Acid Ingestion as a TBI Prophylactic. J Spec Oper Med. 2012 Fall;12(3):5-7.

Curcumin

Turmeric Root (~2-6% Curcuminoids) → Curcuminoids → Curcumin (70%)

- Spice: turmeric
  - Active ingredient: CURCUMIN
- Actions
  - Reduces inflammation - NF-κB, COX_2, PGE_2
  - Increases B-amyloid clearance, reduces hs-CRP
- "Pleotropic" nutrient
  - Multiple pathways and actions



Sharma Set al. 2009. Neuroscience. 2009 Jul 21;161(4):1037-44.

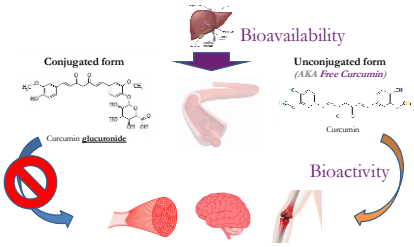
- Bengmark S. Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases. JPEN J Parenter Enteral Nutr. 2006 Jan-Feb; 30(1):45-51.
- Baum et al. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. J Clin Psychopharmacol. 2008 Feb; 28(1):110-3.

Curcumin - Concussions

- Multifaceted neuro-protective MOA
  - Multiple points in TBI cascade
- Animal studies
  - Pre-traumatic supplementation improved
    - cognitive deficits
    - stabilized cellular energy homeostasis
  - Post supplementation reduced
    - lipid peroxidation and protein oxidation
    - Reduced edema
    - Improved behavioral impairment
    - Reduces microglia activation

- Petraglia AL, Winkler EA, Bailes JE. Stuck at the bench: Potential natural neuroprotective compounds for concussion. Surg Neurol Int. 2011;2:146.
- Zhu et al. Curcumin attenuates acute inflammatory injury by inhibiting the TLR4/MyD88/NF-κB signaling pathway in experimental traumatic brain injury. J Neuroinflammation. 2014 Mar 27;11:59.

Bioavailability vs Bioactivity



Creatine

- Creatine → Phosphocreatine
  - Studies confirm increase in brain levels
- Energy production – ATP/mitochondria
  - maintenance of ion gradients
  - intracellular calcium homeostasis
  - neurotransmission etc
  - GABA function
- Improves memory in AD

- Béard E, Braissant O Review Synthesis and transport of creatine in the CNS: importance for cerebral functions. J Neurochem. 2010 Oct; 115(2):297-313.

Creatine – TBI

- In animals pre-supplementation reduces cortical damage, markers of cellular injury and lowered lactic acid
- Humans: Post supplementation improve amnesia, communication abilities and cognitive function
  - Mod-severe TBI
- Acute concussion may increase levels
  - Brain uses it to "fuel" recovery
- PCS (chronic) may decrease

- Sullivan PG, Geiger JD, Mattson MP, Scheff SW Dietary supplement creatine protects against traumatic brain injury. Ann Neurol. 2000 Nov; 48(5):723-9.
- Sakellaris et al. J Trauma. 2006 Aug; 61(2):322-9
- George et al. J Neurotrauma. 2014 Jun 1;31(11):1018-28.

Creatine – Summary

- Theoretical application
  - Offset energetic crisis
- Inexpensive, easy to obtain
  - Good preliminary recommendation
- Other benefits
  - Recovery, muscle function
- Safe long term use

Concussion and Sleep

- Meta-analysis with 21 studies with mild to severe TBI estimated that **50%** of patients with a TBI are affected by a sleep-disturbance
  - insomnia (29%), hypersomnia (28%), obstructive sleep apnea (25%), periodic limb movement during sleep (19%), and narcolepsy (4%
- Kempf et al. (2010), in a prospective longitudinal study found that **67%** of the cohort (n-51) still had disturbances with their sleep–wake cycle **even at 3 years** after a mild to severe TBI.
  - 45% of patients in this study had no other associated psychiatric symptoms, such as anxiety or depression, which could have an affect on sleep

Mathias, J.L., Alvaro, P.K., 2012. Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: a meta-analysis. Sleep Med. 13 (7), 898–905.
Kempf, J., Werth, E., Kaiser, P.R., Bassetti, C.L, Baumann, C.R., 2010. Sleep-wake disturbances 3 years after traumatic brain injury. J. Neurol. Neurosurg. Psychiatry 81 (12), 1402–1405.

Melatonin

- Regulates circadian rhythm
  - TBI patients have dysfunctional rhythm
- "Neuroantioxidant"
- Animal studies in TBI
  - "significantly attenuated trauma-induced neuronal death"
    - Very large dose
  - Reduced edema and BBB permeability post TBI

- Ozdemir et al. Protective effect of melatonin against head trauma-induced hippocampal damage and spatial memory deficits in immature rats. Neurosci Lett. 2005 Sep 16;385(3):234-9. Dehghan F, Khaksari
- Hadad M, Asadikram G, Najafipour H, Shahrokhi N. Effect of melatonin on intracranial pressure and brain edema following traumatic brain injury: role of oxidative stresses. Arch Med Res. 2013 May;44(4):251-8.

Melatonin Summary: More Than Just Sleep

- Sleep onset and maintenance
- Anxiolytic and analgesic
  - migraines, irritable bowel syndrome, and peri-operative pain and anxiety
- Gut function (also produced locally)
  - HCL production, motility, GERD
- Antioxidant and anti-inflammatory effects
  - COX2 inhibition
- Studied to reduce migraines
- Anti-cancer effect
  - Improves chemo sensitivity, reduces METs etc.
- Chronically low levels linked to mental illness
  - Depression and schizophrenia

Antioxidants

Worldviews Evid Based Nurs. 2016 Oct;13(5):380-389. doi: 10.1111/wvn.12167. Epub 2016 May 31.

Systematic Review of Traumatic Brain Injury and the Impact of Antioxidant Therapy on Clinical Outcomes.

Shen Q[1], Hiebert JB[2], Hartwell J[3], Thimmesch AR[4], Pierce JD[5].

- Progesterone, vitamin C and E, NAC
- "By incorporating antioxidant therapies into practice, clinicians can help attenuate the oxidative posttraumatic brain damage and optimize patients' recovery."

Shen et al. Systematic Review of Traumatic Brain Injury and the Impact of Antioxidant Therapy on Clinical Outcomes. Worldviews Evid Based Nurs. 2016 Oct;13(5):380-389. doi: 10.1111/wvn.12167. Epub 2016 May 31.

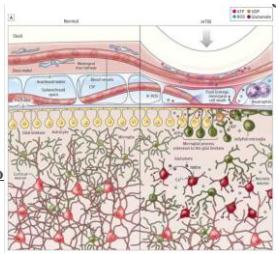
N-acetylcysteine (NAC)

- Precursor to glutathione
- Animal studies: *N*-acetylcysteine reversed the behavioral deficits associated with mTBI and moderate TBI
- RCT - Patients who received *N*-acetylcysteine within 24 hours had significantly improved recovery during a 7-day period when compared with a placebo control group
  - Large dose with loading dose – 1.5g twice daily

- Hoffer et al. Amelioration of acute sequelae of blast induced mild traumatic brain injury by N-acetyl cysteine: a double-blind, placebo controlled study. PLoS One. 2013; 8(1):e54163.
- Eakin et al. Efficacy of N-acetyl cysteine in traumatic brain injury. PLoS One. 2014; 9(4):e90617

Remember…

- The concept of free radical–mediated damage of CNS tissue after injury has existed for several decades….
- … **Administration of effective antioxidants has the potential to significantly limit the spread of damage and inflammation if given soon after brain injury.**



Corps et al. Inflammation and neuroprotection in traumatic brain injury. **JAMA Neurol**. 2015 Mar;72(3):355-62. doi: 10.1001/jamaneurol.2014.3558.

Limitations and Considerations

1. Limited evidence, preliminary studies
2. Poorly conducted studies
   - misunderstood functional physiology
3. Bioavailability problem: delivery to the brain
4. Concurrent risk factors and pre-injury status
   - Antioxidant and micronutrient levels
   - Heavy metals, age, genetics etc.

"Anita" – 35 y/o female – Aug 2017

- Mg Theronate, theanine, High Dose EPA/DHA, melatonin, vitamin D
- Curcumin - 1 cap twice daily and then increase buy 1 cap every day until headache and brain fog resolves
- Referral for cervical assessment and manual treatment (3 tx)
- IV therapy – 1g (5cc) GSH push in (5cc) saline +

Substance	Lot#	Exp.	mg/mL	CC (mL)	mOsmol/mL	mOsm x Vol
Magnesium Chloride			200	3.00	2.95000	8.85
Zinc Chloride			10	1.00	0.07300	0.073
Saline			1	30.00	0.32000	9.6
Dexapanthenol			250	2.00	1.21700	2.434
B Complex			10	1.00	1.13800	1.138
Pyridoxine			100	2.00	0.00110	0.0022
B12 Methylcobolamin			1000	1.00	0.00074	0.00074
5-MTHF			1	1.00	0.02000	0.02
L-Taurine			200	3.00	0.00000	0

"Anita" – 35 y/o female – Aug 2017

- Follow up - 1.5 months later
- Ended up at 3 caps TID of curcumin
- 100% resolution of sx
- TBI score at 5 = baseline

Clinical Approaches to Chronic TBI/PCS

Reminder: Acute and Sub Acute Management

Have these been addressed?

- Have they been assessed by qualified MD, physio or DC?
  - Neuro, neck, vestibular, vision
- Use a sx tracking questionnaire as baseline
- Consider acute pathophysiology
  - Goal reduce excitotoxicity and ***balance*** inflammation
- Diet: Brain recovery diet – SIMPLE, clean, easy to follow
- Foundational nutrients – consider functional pathophys.
- Botanical antioxidants - titrate up until sx resolve
- IV therapy – rapid repletion and delivery of nutrients

Foundation

- Brain Recovery Diet Principles
  - 1st line: Healthy fat, reduce refined carbs, no sugars olioantigenic diet
  - 2nd line: keto / Paleo / Sugar and refined carb free
- Foundation (also used to improve Brain resilience)
  - Magnesium
  - Vitamin E, Vitamin D
  - Omega 3 fish oil (3:2 ratio of EPA to DHA)

First Line – Acute

- Active
  - High dose fish oil (DHA)
  - Creatine
  - Brain available curcumin/flavonoid antioxidants
  - melatonin
  - Glutathione/NAC
  - Magnesium

Potential Preventive Therapies

Intervention	Rationale	Dose	Food sources
Omega 3	Large % deficient Key in resolution of inflammation Strong physiological function Pre-clinical data on prevention and intervention in TBI	2-6 g Does NOT cause blood thinning	Cold water fish, nuts and seeds
Vitamin D	Large % deficient Anti-inflam Neuroprotective Balance immune sys - microglia	2000 IU maintenance 6000IU repletion	none
Magnesium	Large % deficient Low levels cause inflammation Strong physiological function Levels fall after TBI Studied IV after TBI	200-400mg of amino acid form Very safe in high doses	Almonds Pumpkin seeds greens
Vitamin E	Large % deficient Fat soluble antioxidant Animal studies show reduced brain damage and improved function. Use formula with all 8 forms.	400IU of mixed tocopherols and tocotrienols twice daily	Avocado Nuts Seeds Wheat germ

Deficiencies

- Phytonutrients, minerals, vitamins, omega fatty acids
- Most common / important deficiency
  - **Magnesium**/potassium – reflect poor fruit and veggie intake
    - 68% population def, 90% of athletes
  - **Vitamin D** – reflects poor outdoor activity
    - 40-50% of North Americans insufficient, 25% def.
  - **Omega 3** – reflect poor fats in diet
    - 80% of Americans deficient

PCS Management

- Don't just focus on "brain" protocols or products
  - i.e. products the "boost" brain function
- Brain foundation nutrients and diet are essential
  - Mg, Vit D, NAC etc.
- Stabilize metabolic function first
  - May need to use acute TBI interventions to reduce sx.
  - Testing: Start with blood chemistry, then more advanced endocrine
- Create a hypo inflammatory environment
  - Starts with diet → gut brain axis
- Need to create referral network of TBI-literate practitioners

Functional Medicine and Systems Biology Model of PCS

Brain Behav Immun. 2015 May;46:1-16. doi: 10.1016/j.bbi.2015.02.009. Epub 2015 Feb 28.

A review of the neuro- and systemic inflammatory responses in post concussion symptoms: Introduction of the "post-inflammatory brain syndrome" PIBS.

Rathbone AL[1], Thermaradinam S[2], Jiang S[3], Rathbone MP[4], Kumbhare DA[5].

- Calm Immunoexcitotoxicity
- Break cycle of chronic neuroinflammation
- Restore balanced autonomic function
- Promote healthy gut-brain axis, microbiome function
- Stimulate cerebral blood flow
- Support cellular energy/mitochondrial function
- Balance endocrine function

- Maroon JC, Lepore DB, Blaylock RL, Bost JW. Postconcussion syndrome: a review of pathophysiology and potential nonpharmacological approaches to treatment. Phys Sportsmed. 2012 Nov;40(4):73-87.
- Blaylock RL, Maroon J. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy–A unifying hypothesis. Surg Neurol Int. 2011;2:107.

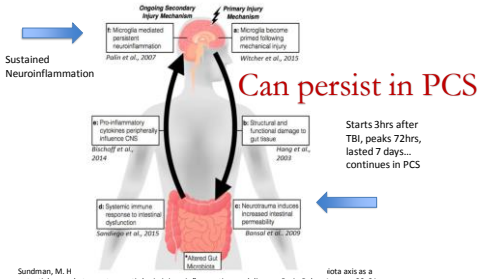
N.C. 21 female – may 2017

- Impact on vertex of head bungie jumping 2013 = whiplash
- 2015 another bungie jumping impact
- 2nd impact (hit head on counter) 1 day later
- Feb 2016 – sx re-aggravated at concert – loud music and lights
- Tried many other therapies – HBOT, acu.
- O: orthostatic hypotension
- TBI score: 34
- Comorbidities
  - severe constipation
  - PMS

N.C. 21 female – may 2017

- Key treatment targets

1. Calm neuro inflammation – cause of "cognitive sx"
   - Consider GI sx = sign of gut-brain axis dysfunction and source of inflammation
2. Foundational nutrients and diet for neuro-metabolic healing
3. Address



Sustained Neuroinflammation

Can persist in PCS

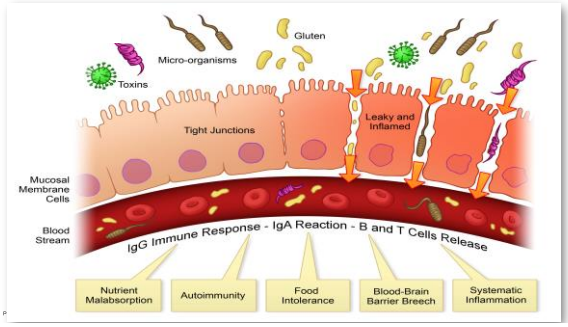
Starts 3hrs after TBI, peaks 72hrs, lasted 7 days… continues in PCS

Sundman, M. H iota axis as a potential nexus between traumatic brain injury, inflammation, and disease. Brain Behav. Immun. 66, 31–44 (2017)

Gut –Brain Connection

- Gut lining resembles the BBB in many respects
  - ± 75% similarity in structural composition
- Immune system – cross reaction of Gut lining and BBB proteins
  - "Autoimmune reaction"
- Neuro trauma induces a more permeable BBB and GI barrier
- **Leaky gut causes leaky brain!**
  - Common sx include: depression, anxiety, **brain fog** etc etc.

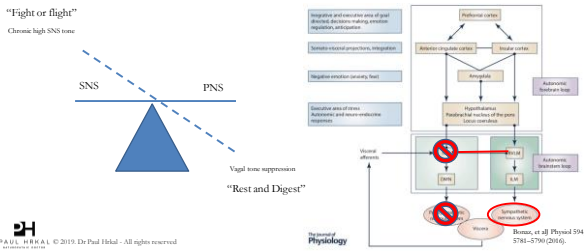
Rea, K., Dinan, T. G. & Cryan, J. F. The microbiome: A key regulator of stress and neuroinflammation. Neurobiol Stress 4, 25–33 (2016).
Lopez-Ramirez, et al. MicroRNA-155 negatively affects blood-brain barrier function during neuroinflammation. *FASEB J.* June 2014 28:2551-2565; doi:10.1096/fj.13-248880



Healing Your "Leaky" Gut (And Brain)

- Avoid food allergies, lower HPA overactivity etc.
  - **Gluten** is one of the biggest disruptors of GI and Brain lining
  - Avoid Alcohol – increases micropores
- Healing foods
  - Cabbage, Aloe vera
  - Slippery elm, marshmallow, licorice – teas
  - Broccoli sprouts, wild blueberries
- **L-glutamine –** primary fuel for enterocytes
  - Increased need during stress
- **Zinc** – plays critical role in the maintenance of normal intestinal permeability and control of inflammation.

Dysautonomia: High SNS and Low PNS Tone



Restoring Vagus Nerve Function

Table 1. Main potential therapeutic treatments currently considered as acting upstream to decrease TNFα release

Therapy	Target/therapy sub-type	Mechanism	References
Pharmacological therapy	GTS-21	α7nAChR agonists	van Westerloo *et al.* (2006) The *et al.* (2007)
	AR-R17779		
	Galantamine	Central cholinergic pathway stimulation	Pavlov *et al.* (2009); Ji *et al.* (2014)
	Semapimod (CNI 1493)	p38 mitogen-activated protein kinase inhibitor	Borovikova *et al.* (2000*a*); Berrak *et al.* (2002*b*)
Nutritional therapy	Fat nutrition	Stimulation of vagal afferent fibres through fat-induced CCK release and, in return, of the CAP	Luyer *et al.* (2005)
	Choline	Precursor in the biosynthesis of ACh and selective natural α7nAChR agonist	Parrish *et al.* (2008)
	Ghrelin	Activation of the CAP	Mao *et al.* (2015*a*,*b*,*c*)
Complementary therapy	Acupuncture	Stimulation of vagal efferent fibres and CAP	Gamus (2011)
	Hypnosis		
	Meditation		
	Tai chi		
Physical activity and exercise		Stimulation of vagal efferent fibres and CAP	Heffernan *et al.* (2009); Jae *et al.* (2009*a*,*b*)

Benefit of keto diet and intermittent fasting ?

Bonaz, et al J Physiol 594, 5781–5790 (2016).

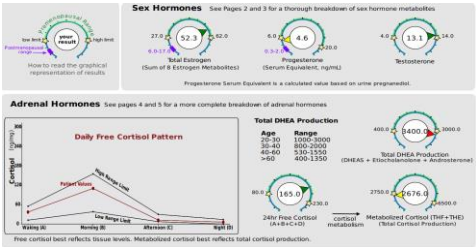
N.C. 21 female

- Tx
  - Foundation: Mg theronate, **theanine,** creatine, taurine
  - Endocrine: Adaptogenic formula, lion's mane
  - GI: Glutamine, **zinc carnosine**, ginger
- Cell phone and screen time hygiene
- Continue hypoallergenic diet
- Referral to functional DC for neck assessment

N.C. 21 female

- Follow up 1 month later
- TBI score: 13 (62% improvement)
- Still has restless sleep, constipation 90% improved
- PMS still key concern = key underlying issue
- Blood chemistry: Iron def, vitamin D insufficiency (59 nmol/L)
- Dried urine hormone testing:

Dried Urine Hormone Testing:



Progesterone

- Neuro-active hormone
  - Modulates calcium, excitotoxicity, GABA and edema
- Promising results of phase II clinical trials
  - Acute admin, mod-severe TBI - Improved recovery
- 2014 – phase III trials
  - Double blind, placebo controlled, 2000+ px, IV acute TBI, 6 month f/u
  - **Both** found no difference compare to placebo
  - Howard et al 2017 – dose and duration NOT long enough
- Synergy: Vitamin D makes progesterone work better

- Wright et al. ProTECE: a randomized clinical trial of progesterone for acute traumatic brain injury. Ann Emerg Med. 2017 Apr;69(4):391-402, 402.e1-2.
- Skolnick et al. A clinical trial of progesterone for severe traumatic brain injury. N Engl J Med. 2014 Dec 25;371(26):2467-76.
- Wright et al. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med. 2014 Dec 25;371(26):2457-66.
- Howard RB, Sayeed I, Stein DG. Suboptimal Dosing Parameters as Possible Factors in the Negative Phase III Clinical Trials of Progesterone for Traumatic Brain Injury.J Neurotrauma. 2017 Jun 1;34(11):1915-1918.

N.C. 21 female

- Correct Iron and vitamin D
- Support progesterone – 30mg/dose nightly 2 months
  - Supports GABA activity in the brain = sleep, anxiety and PMS
  - Synergetic with Vit D
- Continue adrenal, adaptogenic support
- 2 month follow up
  - Back to full academic function
  - Feels 95% back to normal
  - TBI score 8, stress aggravated sx

Conclusion

- Clinical summary handout

Concussions and Brain Injury – Intervention Summary

1. Functional and comprehensive assessment – rule our emergent conditions
2. Give anti-inflammatory diet
   a. Additional neuroprotective principles
      i. Reduce caloric intake by 30% (reduce all refined carbs and sugars
      ii. Focus on brain super foods
         1. Berries
         2. Cold water fish low in contaminants, high in omega 3's (**S**almon, **M**ackerel. **A**nchovies, **S**ardines, **H**erring)
3. Supplements to impact metabolic changes – try for 30-60 days
4. Refer for advanced integrative care
   a. Comprehensive diet, supplements and IV therapy

Intervention	Comments and Research	Dosage	Safety
Fish oil – DHA * keep in fridge	Promising application based on physiology – decreases inflammation and increases BDNF. Stronger data as preventative Only animal studies in mTBI Human trials pending	Animal equivalent dosage is 387mg DHA daily but should use higher dose. Clinical: 1.5-3g DHA twice daily for 30 days	Doses up to 7.5g daily have been studied with no side effects. Caution with blood thinners but doses below 6g daily do not affect platelets.
Curcumin	Broad-spectrum anti-oxidant and anti-inflammatory herb.	1200mg daily, divided doses, std to 95% curcuminoids	Avoid in active gastric ulcer. Caution with

Next Steps…

- Network of latest evidence based TBI management certified clinics
  - https://completeconcussions.com/
  - 200+ clinics, 600 clinicians – Canada, USA, Australia, UK
- Coming 2019 – Certification course (online) in Advanced Functional and Metabolic Medicine for TBI
  - Become certified to be connected to CCMI network of clinics
  - Referral network
- Email me for more info - paulhrkalnd@gmail.com
  - I will share my ***Brain recovery diet patient handout***

Thank You

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