# A Multimodal, Regenerative Approach to Traumatic Brain Injury

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# Disclaimer

I have no relevant financial relationships with any commercial interests to disclose.

The content of this presentation has been peer reviewed for fair balance and evidence based medicine.

# Multimodal Treatment Approach to TBI

I. Hyperbaric Oxygen Therapy
II. Intranasal Cocktail (PRP, Insulin, B12, Glutathione, Stem Cells)
I. Cranial Osteopathy
II. IV Nutrition
III. MCT Oil and Ketogenic Diet

# Learning Objectives

1) Learn about the individual mechanisms and benefits of each regenerative modality to treat TBI

2) Learn the unifying factor present in most TBI treatment modalities

# Introduction: Multimodal TBI Therapy

Mainstream treatment of the TBI patient has largely involved occupational and physical rehabilitation, speech therapy, pharmaceutical drugs, and cognitive maintenance exercises.

Under the mainstream model, most TBI patients resign to simply cope (rather than seek to improve) with their condition as they reach a plateau of overall treatment benefit.

# Introduction: Alternative TBI Treatments-Problems

1) Many alternative TBI treatments do not directly actually seek to regenerate the damaged brain function TBI but rather simply treat symptoms (aka hormone replacement therapy).

# Introduction: Alternative TBI Treatments-Problems

2) Very seldom do alternative TBI treatment clinics combine even regenerative treatments in a multimodal manner in order to maximize patient benefit (e.g. It is rare for TBI treatment clinics to both utilize stem cells and hyperbaric oxygen therapy).

# Introduction: Alternative TBI Treatments-Problems

3) Some singular alternative TBI treatments can be prohibitive for patients and their families, both in cost and time. (e.g. The 40 treatment model of medical HBOT at 1.5 ATA for TBI is too expensive for most mTBI patients or their third party payers, such as the U.S. Military).

# Multimodal TBI Therapy: Thesis

It is hypothesized that the practical, effective combination of multiple TBI therapies can produce synergistic benefits to the patient that exceed the use of one particular TBI treatment.


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# Multimodal TBI Therapy: Hyperbaric Oxygen Therapy

Breathing 100% oxygen at increased atmospheric pressures allows the body to absorb about 10-15 times its normal supply of oxygen.

This “high dose” oxygen, stimulates the growth of tissue, bone and blood vessels, reduces inflammation, and mobilizes stem cells.

# Multimodal TBI Therapy: Hyperbaric Oxygen Therapy

Two hours of HBOT at 2 ATA doubles the patients own circulating stem cells; 40 hours of HBOT at 1.5-2.0 ATA increases circulating stem cells to 8 fold (800%).

This stem cell increase results from an increase in nitric oxide in the bone marrow. Nitric oxide stimulates enzymes that mediate stem/progenitor cell release.

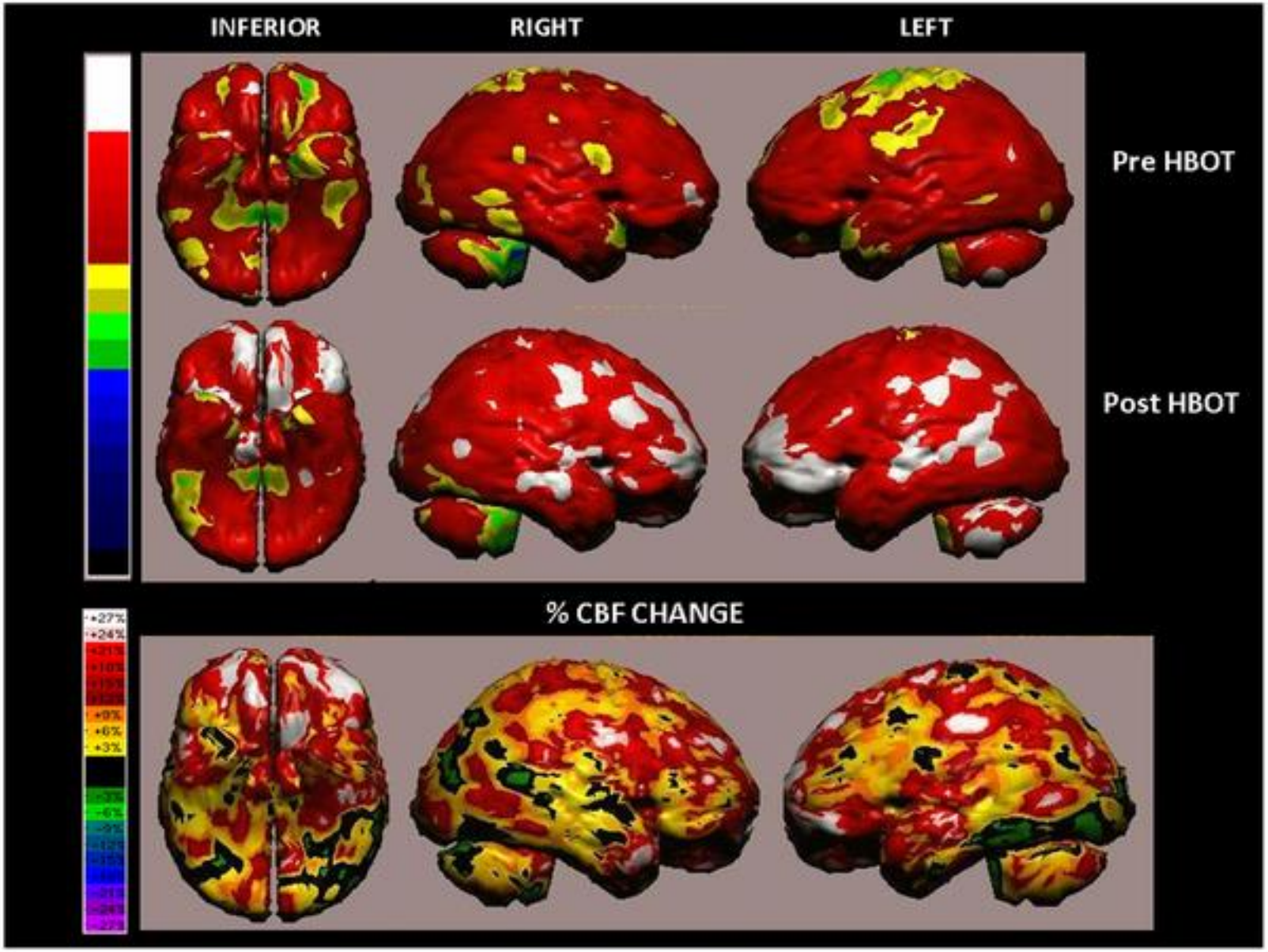
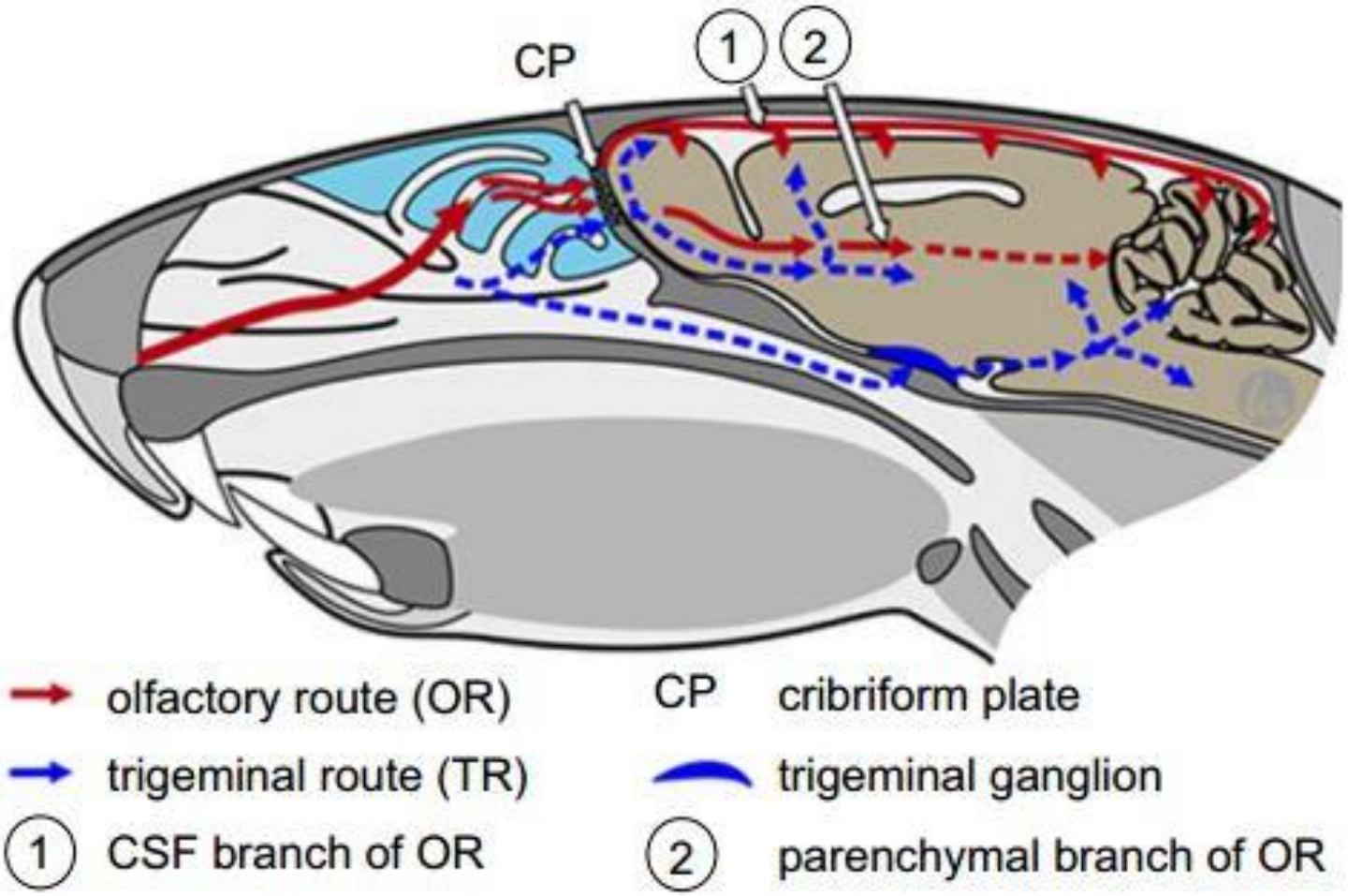



Figure 1. Volume rendered Brain SPECT perfusion maps of Example 1, a 51-year-old woman from the treated group suffering mTBI that had occurred 2 years prior to inclusion in the study.

Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, et al. (2013) Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial. PLoS ONE 8(11): e79995. doi:10.1371/journal.pone.0079995




Danielyan, L., Beer-Hammer, S., Stolzing, A., Schäfer, R., Siegel, G., Fabian, C., ... & Novakovic, A. (2014). Intranasal delivery of bone marrow-derived mesenchymal stem cells, macrophages, and microglia to the brain in mouse models of Alzheimer's and Parkinson's disease. *Cell transplantation*,*23*(1), S123-S139.

# Multimodal TBI Therapy: Intranasal Therapies: Insulin

Intranasal (IN) insulin and stem cells are emerging treatments for TBI and Alzheimer's disease.

IN insulin:

- improves brain ATP production
- decreases CSF cortisol
- improves neuronal viability in the hippocampus
- increases the expression of anti-inflammatory microglia
- reduces beta-amyloid and tau protein deposition

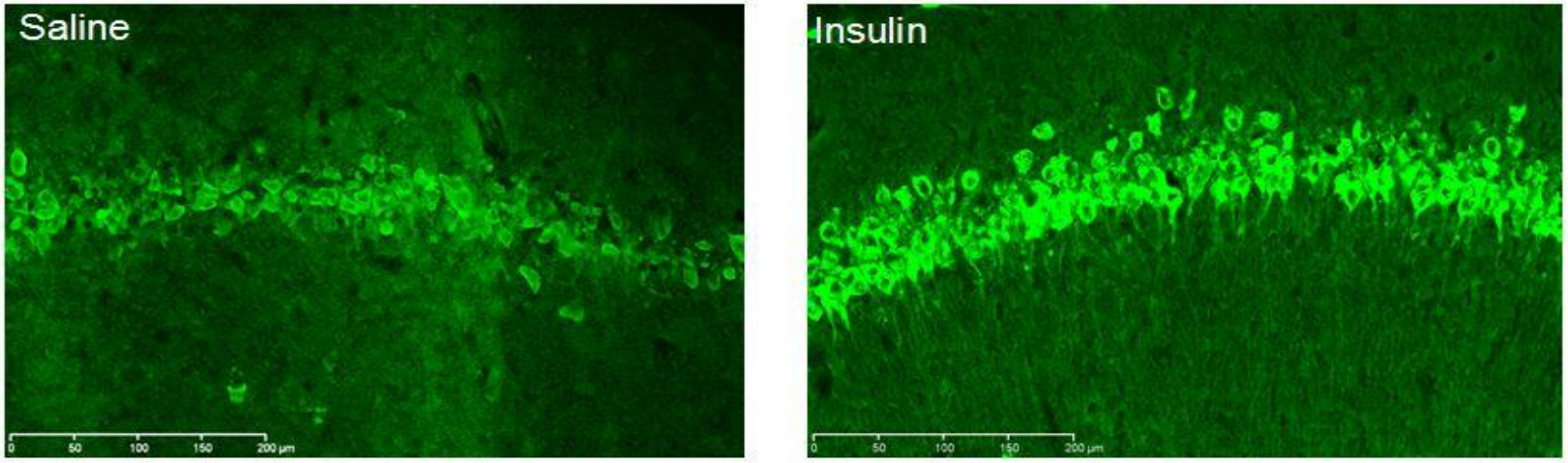



Figure 2. Neun staining was increased with intranasal insulin treatment

TBI results in neuronal cell death. Neuronal cell death in the hippocampus impairs memory function. NeuN, an immunohistochemical marker of neurons, was used to examine the effect of intranasal insulin on neurons after injury. Qualitative assessment of histology showed improved neuronal viability in the hippocampus of the insulin treated rats.

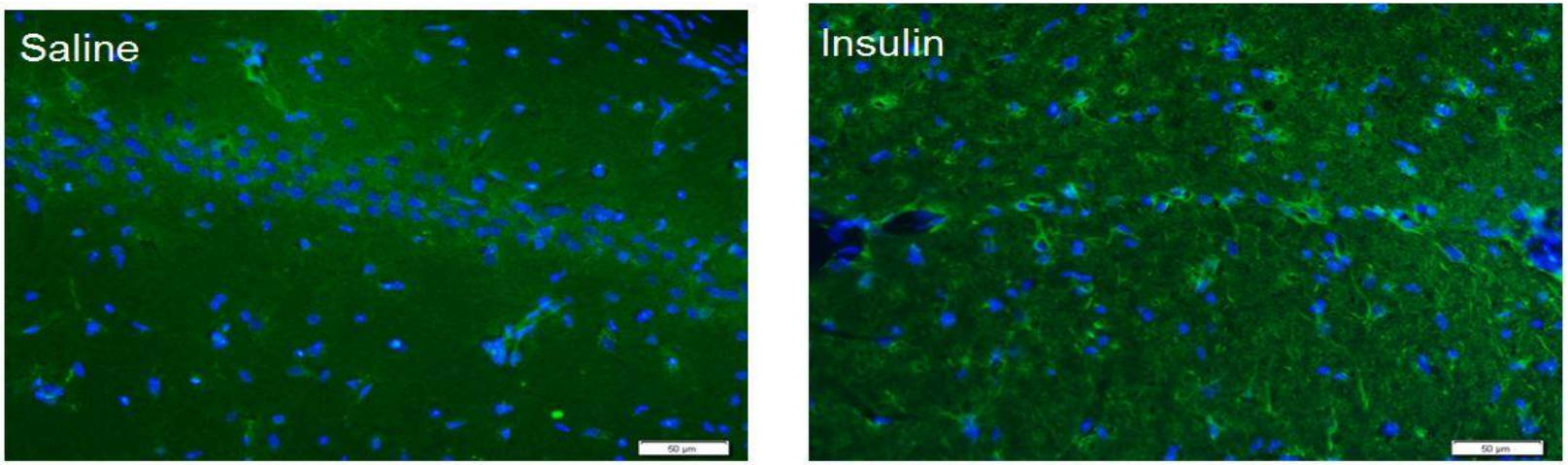



Figure 3. Intranasal Insulin increases the expression of anti-inflammatory microglia in the hippocampus

Brabazon, F. P., Khayrullina, G. I., Frey, W. H., & Byrnes, K. R. (2014, June). INTRANASAL INSULIN TREATMENT OF TRAUMATIC BRAIN INJURY. *In JOURNAL OF NEUROTRAUMA (Vol. 31*, No. 12, pp. A106-A106). 140 HUGUENOT STREET, 3RD FL, NEW ROCHELLE, NY 10801 USA: MARY ANN LIEBERT, INC.

# Multimodal TBI Therapy: Intranasal Therapies: Stem Cells

IN adult stem cells have been used to treat ischemic brain damage by reducing gray and white matter loss.

IN adult stem cells downregulate neuroinflammatory cytokines and rescue tyrosine hydroxylase (TH)-positive neurons in the substantia nigra in AD and PD patients.

# Multimodal TBI Therapy: Intranasal Therapies: Nutrients

IN glutathione has been used to reduce oxidative stress and enhance cellular detoxificaton in Parkinson's disease patients.

IN methylcobalamin has been shown to improve QEEG Theta activity in ADHD and autism patients.

# Multimodal TBI Therapy: Intranasal Therapies: Plasma

Autologous plasma contains growth factors and cytokines to aid the injured brain

- VEGF, EGF increases angiogenesis
- PDGF, TGF-p enhance collagen growth
- IGF-1 stimulates protein synthesis

Enhanced collagen IV in neurons of the brain has been shown to have a neuroprotective effect and reduce amyloid-beta proteins.

# Multimodal TBI Therapy: Intranasal Therapies: Plasma

Plasma cytokines

- control inflammatory mediators cox1, cox2
- guide stem cells to areas of injury

Human plasma lysate administered to rats (via the middle cerebral artery) after ischemic stroke was shown to reduce infarct volume.

# Multimodal TBI Therapy: Cranial Osteopathy

Cranial osteopathy is based on the fact that the central nervous system, including the brain and spinal cord, has a subtle, rhythmic pulsation which can be manipulated by a skilled practitioner.

This rhythmic pulsation (aka CRI) can be blocked in brain injuries that such that CSF and blood flow is impeded and the brain loses nourishment.

Cranial osteopathy has been found effective at treating the vertigo and headaches associated with TBIs.

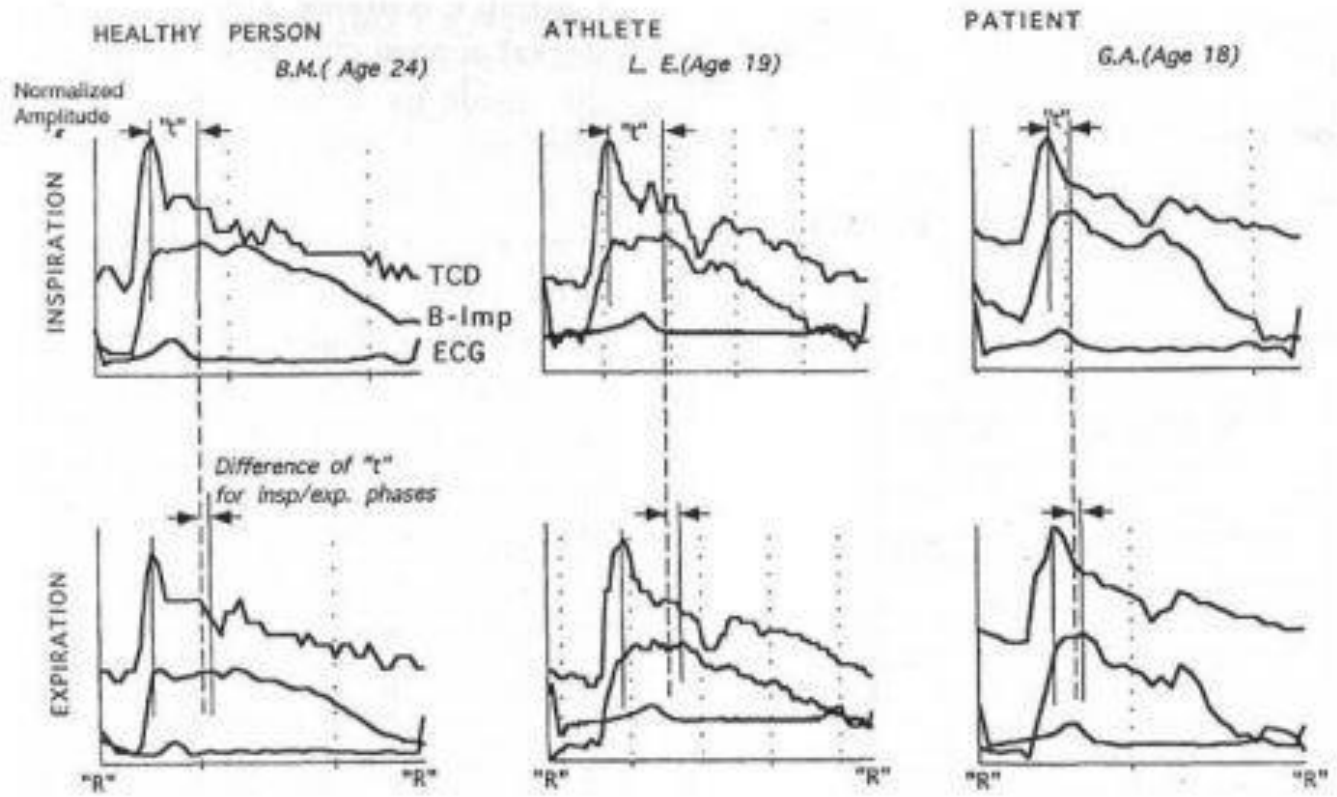



*Figure 5: The difference of "t" between inspiratory and expiratory phases of the secondary respiration in a Healthy person, Athlete trained in diving and Patient after head injury.*

Time shift between peaks of TCD and B-Imp is determined by the replacement of some portion of CSF out from (or into) zone of B-Imp electrodes. Thus this time interval represents the mobility of CSF inside the cranium during the pulse cycle. At this period no active processes could operate. Investigations under different conditions have shown that "t" reflects CSF mobility.

Moskalenko, Y., Frymann, V., Kravchenko, T., & Weinstein, G. (2003). Physiological background of the Cranial Rhythmic Impulse and the Primary respiratory Mechanism. *Am Acad Osteopath J*, *13*(2), 21-33.

# Multimodal TBI Therapy: Cellular Nutrition

Vitamin D deficiency has been found in over 65% of TBI patients suffering from chronic fatigue.

B vitamin supplementation (particularly B12, folate, B6) has been found to improve memory, mood, and energy levels and has been used to prevent stroke and Alzeheimer's disease.

# Multimodal TBI Therapy: Cellular Nutrition

Ketogenic diets are a proven treatment for patients suffering from epilectic seizures.

Ketogenic diets studied in brain trauma (CCI) produce corticol sparing and less apoptotic neuro-degeneration and overall improvements in cognitive and motor functioning.

# Multimodal TBI Therapy: Cellular Nutrition

It is theorized that ketones work because they increase the available calming neurotransmitter GABA, thereby reducing neuronal hyperpolarization and the excititatory neurotransmitter glutamate. With less glutamate, there is less oxidative stress and improved neuroprotection.

MCT oils are a rich source of ketone bodies.

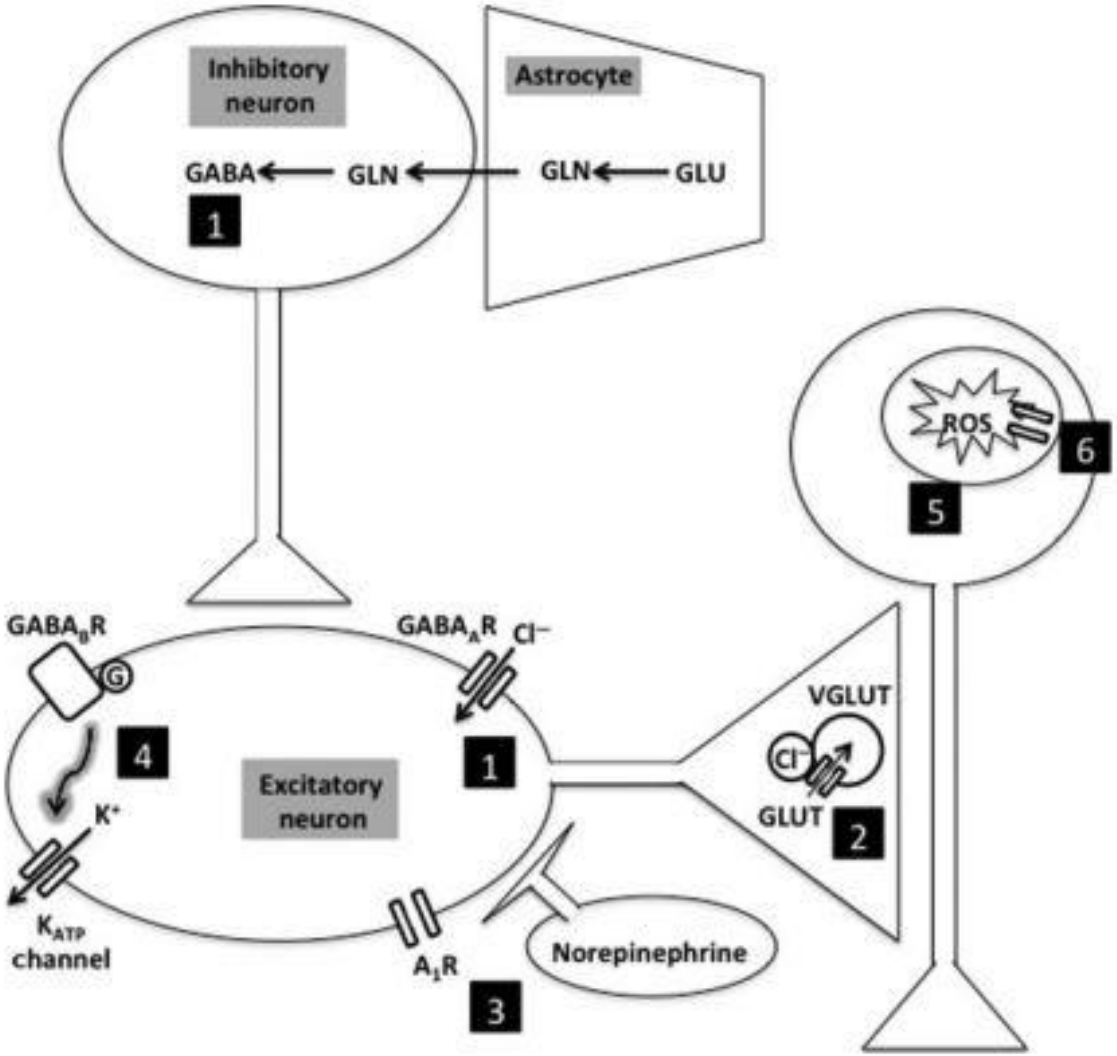



**Fig. 2** Possible anticonvulsant effects of ketone bodies on the brain. (1) Increased GABA synthesis through alteration of glutamate cycling in glutamate-glutamine cycle or altered neuronal responsiveness to GABA at $GABA_A$ receptors. (2) Decreased glutamate release by competitive inhibition of vesicular glutamate transporters. (3) Other neurotransmitters, including norepinephrine and adenosine. (4) Increased membrane potential hyperpolarization via $K_{ATP}$ channels possibly mediated by $GABA_B$ receptor signaling. (5) Decreased reactive oxygen species production from glutamate exposure. (6) Electron transport chain subunit transcription. $A_1R$, adenosine receptor; Cl, chloride; GLN, glutamine; GLU, glutamate; GABA, γ-aminobutyric acid; $GABA_BR$, γ-aminobutyric acid beta receptor; $GABA_AR$, γ-aminobutyric acid alpha receptor; VGLUT, vesicular glutamate transporter; ROS, reactive oxygen species.

McNally, M. A., & Hartman, A. L. (2012). Ketone bodies in epilepsy. *Journal of neurochemistry*, *121*(1), 28-35.

# Multimodal TBI Therapy: Protocol

1) HBOT at 1.3 ATA to 1.75 ATA from 5 to 40 sessions
   - use of home HBOT chambers is acceptable for a portion of the therapy for far-away patients

2) Intranasal therapies utilized 1 to 4 x during HBOT treatment series (IN plasma, insulin, glutathione, B12) administered first followed by IN platelet-derived, pluripotent stem cells within 7 days of IN plasma
   - patients are also sent home with 10 days IN insulin

# Multimodal TBI Therapy: Protocol

3) IV Nutrition Administered 1-4 x during HBOT treatment series
   - Myer's cocktail with potassium, magnesium, calcium, B-complex, B5, B6, and B12, ascorbate followed by a glutathione push

4) Oral Nutrition and Supplementation
   - Blueberries, Vitamin D3, elk antler supplementation recommended daily 3 weeks before treatment
   - Ketogenic dietary counseling and MCT oils are begun on day 1 of HBOT series

# Multimodal TBI Therapy: Clinical Results

Out of ten patients treated, every patient has reported:

- More mental clarity
- Improved memory
- Improved executive function/decision making
- More stable emotions and less stress
- Better ability to cope with pain
- More physical and mental energy

# Multimodal TBI Therapy: Clinical Results

Out of ten patients treated, some patients have reported:

- Less sound and light sensitivity
- Improved eyesight
- Improved sleep and libido
- Improved motor function (ability to open clenched fist, ability to walk)

# Multimodal TBI Therapy: Conclusion

Robert Cantu, MD states

> "The brain is in a metabolic crisis in a concussion, potassium ion from inside the cell going extracellular, calcium ions going intracellular, neurotransmitters widely released in a chaotic manner. It takes energy to pump that potassium back, put the neurotransmitters back on so the cell can function."

# Multimodal TBI Therapy: Conclusion

This multi-modal TBI therapy has a unifying theme of providing substrates to the brain that correct the metabolic crisis, in a way of stabilizing neurotransmitter release and repairing damaged neurons.

Ultimately, a TBI is a problem of energy metabolism. Healing from TBI requires solving that energy crisis.

# What Physical and Cognitive Rest Really Mean After a Concussion


http://www.brainline.org/content/multimedia.php?id=9022

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