



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.

LEARNING OBJECTIVE

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



MAINSTREAM TREATMENTS

- Occupational and physical rehabilitation, speech therapy, pharmaceutical drugs, and cognitive maintenance exercises.
- Patients resign to simply cope with their condition as they reach a plateau of overall treatment benefit.

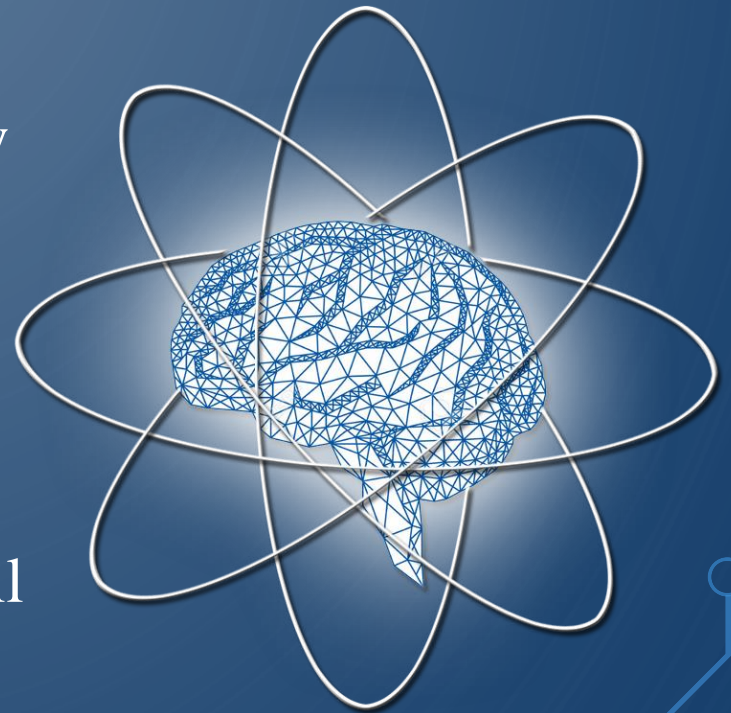
ALTERNATIVE TREATMENTS



- Do not seek to regenerate the damaged brain function TBI but rather simply treat symptoms (aka hormone replacement therapy).
- Do not combine regenerative treatments in a multimodal manner in order to maximize patient benefit.
- Singular treatments can be prohibitive for patients and their families, both in cost and time.

REGENERATIVE, MULTIMODAL APPROACH TO TBI

- I. Hyperbaric Oxygen Therapy
- II. Intranasal Therapies
- III. IV Nutrition
- IV. Cranial Osteopathy
- V. Ketogenic Diet and MCT Oil



TBI THERAPY: THESIS

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

The image shows a hyperbaric oxygen chamber, which is a large, cylindrical metal container used for medical treatments. Inside the chamber, there is a bed with a blue sheet and a white pillow. The chamber's interior is illuminated by a grid of lights on the ceiling. The entire scene is framed by a blue circuit-like pattern with nodes and lines, suggesting a technological or medical theme.

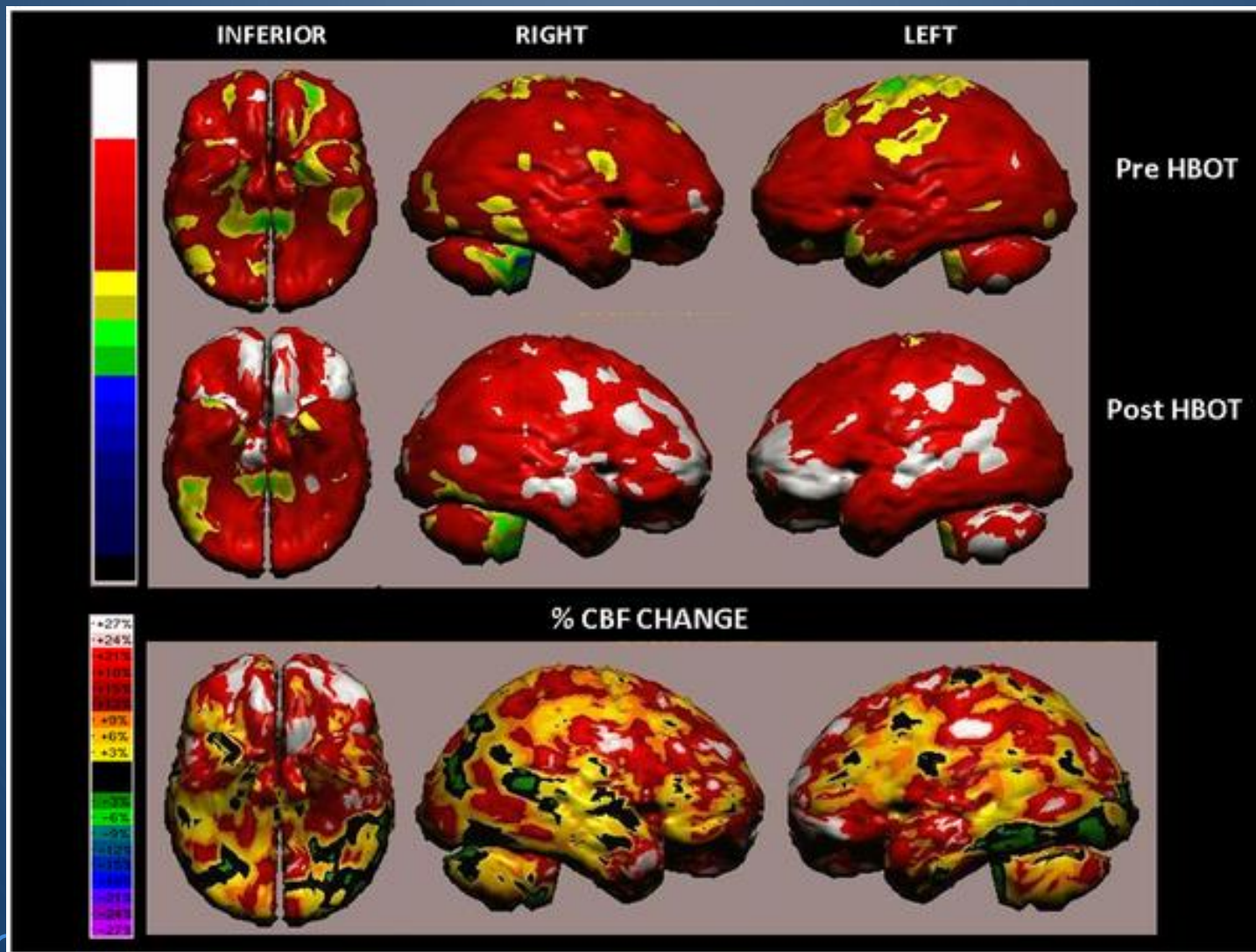
**PART I:
HYPERBARIC OXYGEN THERAPY**

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.

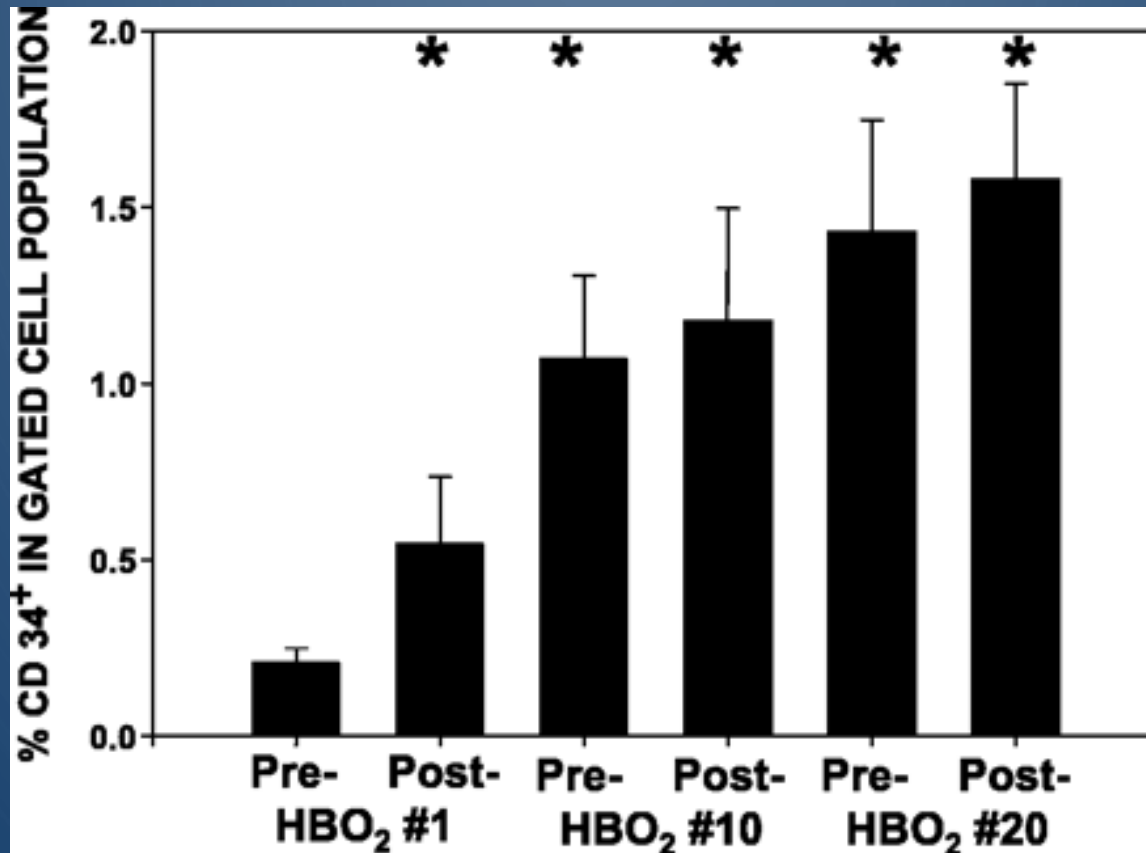
Volume rendered Brain SPECT perfusion maps of Example 1, a 51-year-old woman from the treated group suffering mTBI that had occurred 2 years prior to inclusion in the study.



TBI THERAPY: HYPERBARIC OXYGEN THERAPY

- 2 hours of HBOT at 2 ATA triples the patients own circulating stem cells (SPCs) and doubles CD34+ cells in the peripheral circulation (Thom, 2005).
- 20 sessions of HBOT at 2 ATA increases circulating CD34+ stem cells to 8 fold (800%) (Thom, 2005).
- 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.

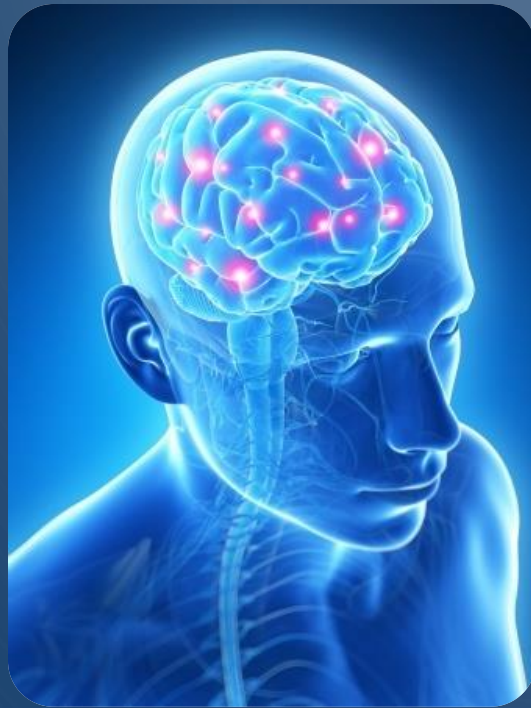
Mean CD34⁺ population in blood of humans before and after HBO₂ treatments. Data are the fraction of CD34⁺ cells within the gated population using leukocytes obtained from 26 patients before and after their 1st, 10th, and 20th HBO₂ treatment. *Repeated-measures one-way ANOVA, $P < 0.05$ vs. the pre-HBO₂ first treatment value.



“

[Hyperbaric oxygen therapy] is the safest way clinically to increase stem cell circulation, far safer than any of the pharmaceutical options.

”

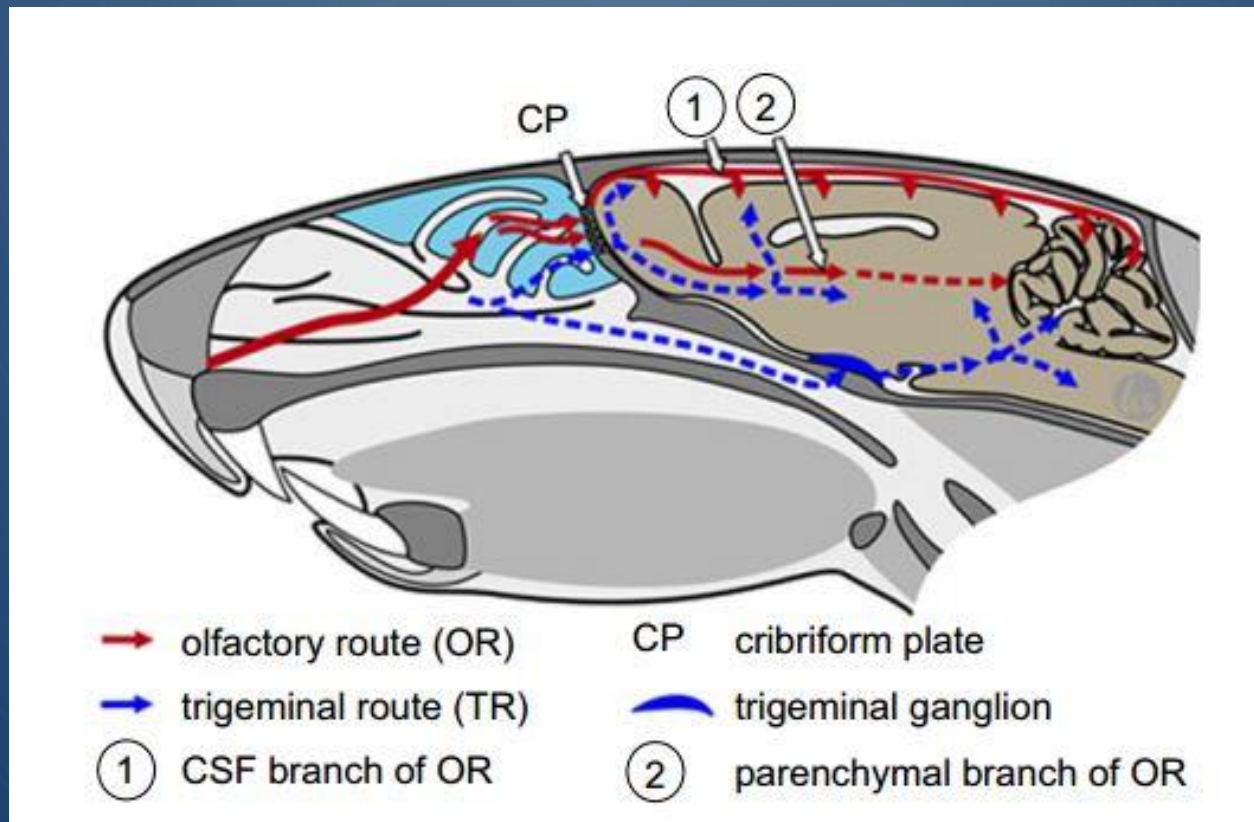


Stephen Thom, MD, Ph.D. (2005)

PART II:
INTRANASAL THERAPIES
(INSULIN, PRP, STEM CELLS,
B12, AND GLUTATHIONE)

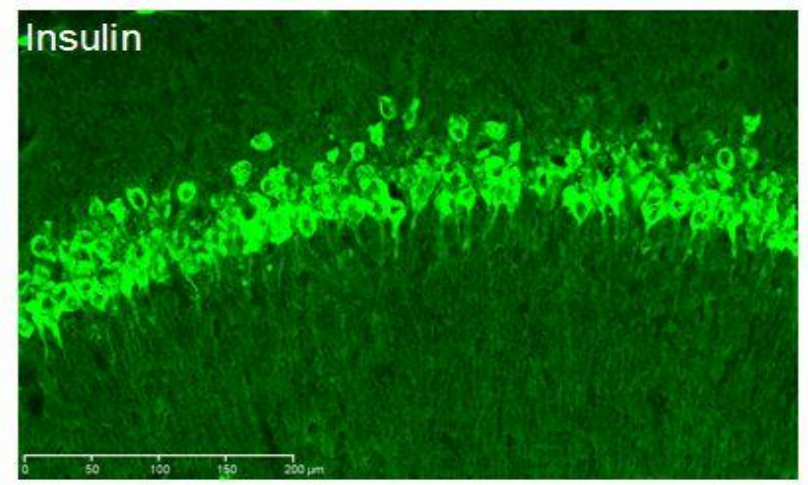
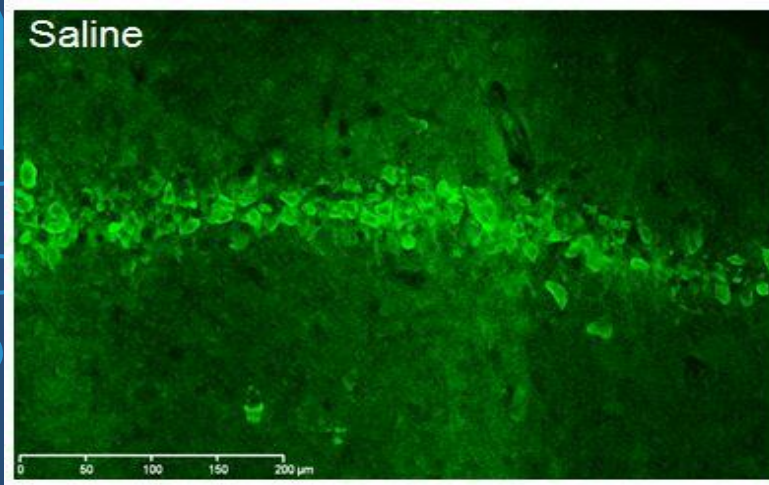


Schematic drawing of two routes of IN delivery of cells to the brain. After crossing the cribriform plate (CP), the olfactory route (OR, red arrows) divides into two branches: (1) the CSF branch and (2) the parenchymal branch. Solid arrows represent the paths of migration of cells into the brain evidenced in this study, whereas dashed arrows reflect possible hypothetical routes of cell delivery. The hypothetical trigeminal route (TR) consists also of at least two branches one of which crosses the cribriform plate into the parenchyma, where it diverges to the rostral and caudal parts of the brain. The second branch projects from the nasal mucosa to the trigeminal ganglion, where the exogenously applied cells are further distributed to the forebrain, OB and caudal brain areas including the brainstem and the cerebellum.

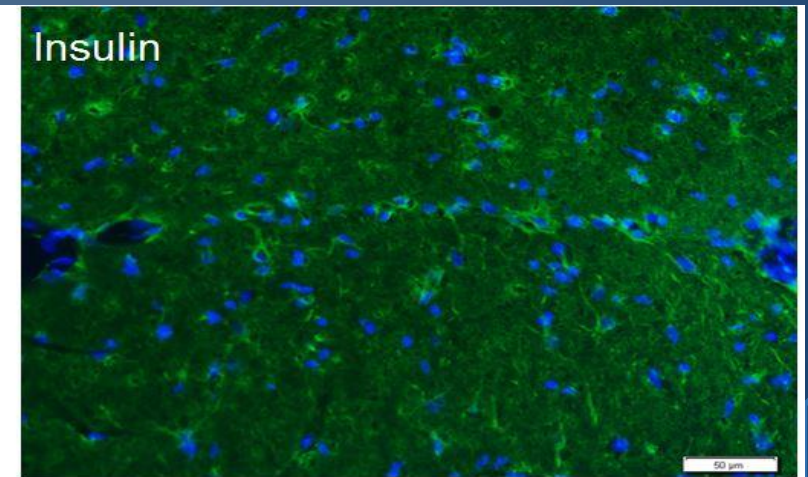
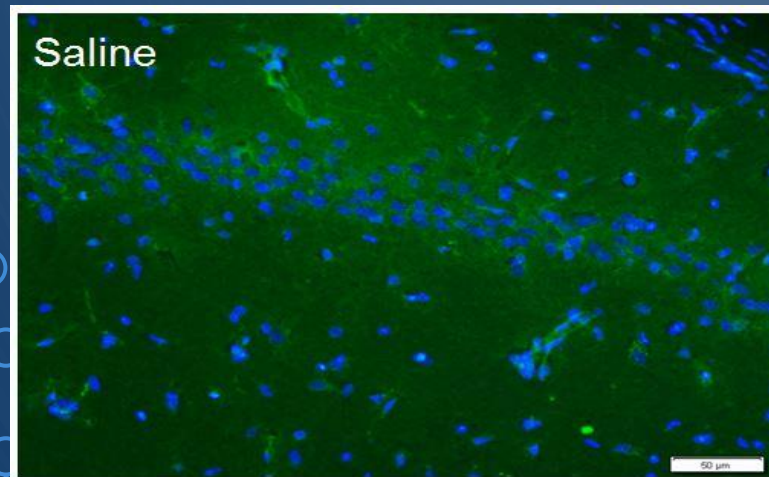


TBI THERAPY: INTRANASAL THERAPIES- INSULIN

- 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

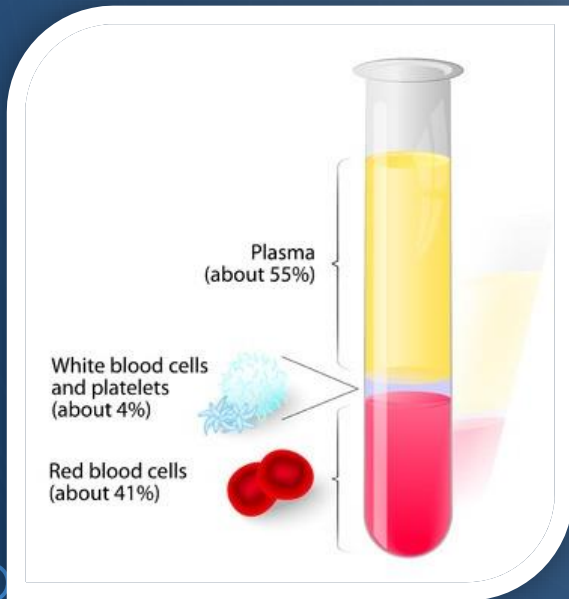


NeuN, an immunohistochemical marker of neurons, was used to examine the effect of intranasal insulin on neurons after injury. Qualitative assessment of histology showed improved neuronal viability in the hippocampus of the insulin treated rats.



Intranasal insulin increases the expression of anti-inflammatory microglia in the hippocampus.

TBI THERAPY: INTRANASAL THERAPIES- PLATELET RICH PLASMA (PRP)



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

- VEGF, EGF increases angiogenesis
- PDGF, TGF- β 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.

TBI THERAPY: INTRANASAL THERAPIES- PLATELET RICH PLASMA (PRP)

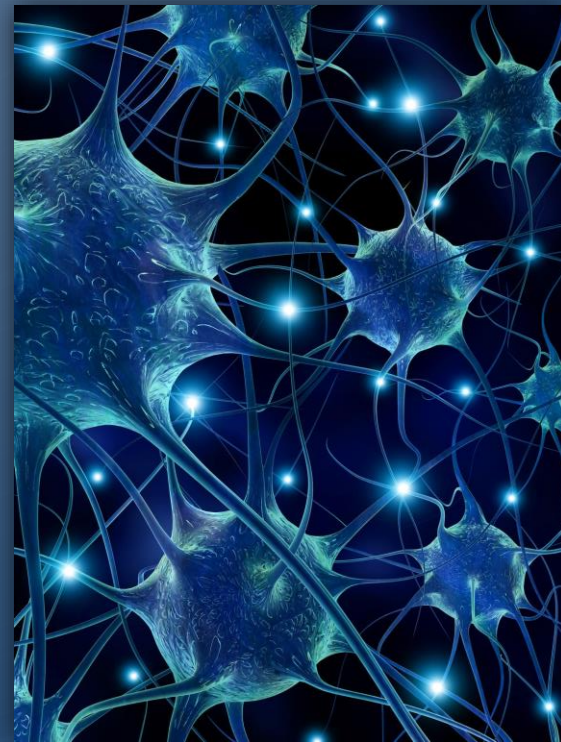
- The infusion of concentrated platelets, once activated, results in an exponential increase in numerous growth factors at the sight of infusion
- Plasma cytokines:
 - Control inflammatory mediators cox1, cox2
 - Guide stem cells to areas of injury

TBI THERAPY: INTRANASAL THERAPIES- PLATELET RICH PLASMA (PRP)

- “Basic fibroblast growth factor (bFGF) or epidermal growth factor (EGF) infusion enhances injury-induced cell proliferation in the dentate gyrus (DG) and improves cognitive function in rats following fluid percussive injury” (Sun, 2014).
- “Other studies have found that infusion of S100 β or VEGF can also enhance neurogenesis in the hippocampus and improve the functional recovery of animals following TBI” (Kleindienst et al., 2005; Lee and Agoston, 2010; Thau-Zuchman et al., 2010 cited from Sun, 2014).

TBI THERAPY: INTRANASAL THERAPIES- STEM CELLS

- Peripheral blood derived pluripotent stem cells that are released from the bone marrow are used.
- Plasma contains hundreds of thousands of these cells per ml in peripheral blood depending on age.

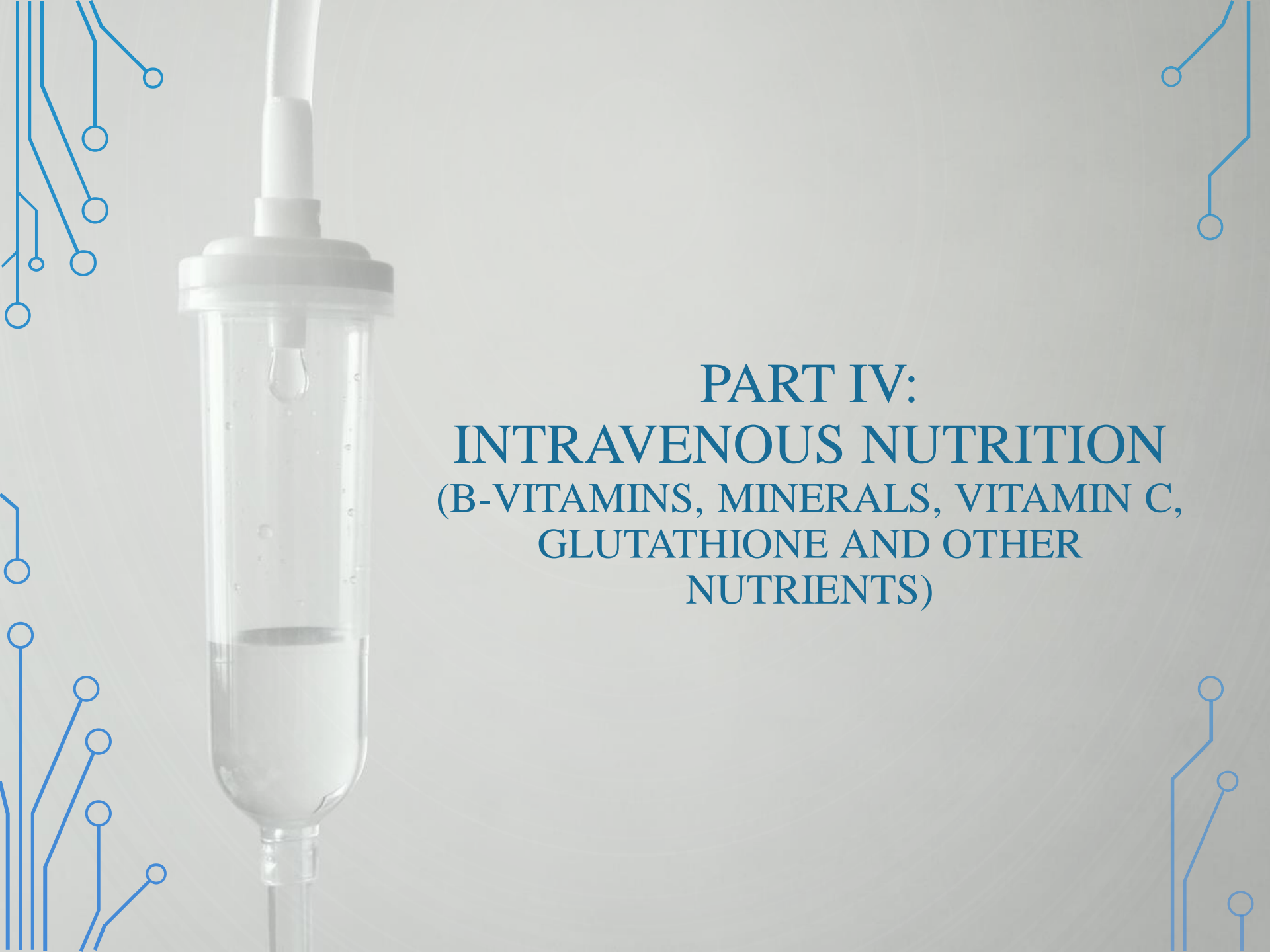


TBI THERAPY: INTRANASAL THERAPIES- STEM CELLS

- 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.

TBI THERAPY: INTRANASAL THERAPIES- NUTRIENTS

- IN glutathione has been used to reduce oxidative stress and enhance cellular detoxification in Parkinson's disease patients.
- IN methylcobalamin has been shown to improve QEEG Theta activity in ADHD and autism patients.



**PART IV:
INTRAVENOUS NUTRITION
(B-VITAMINS, MINERALS, VITAMIN C,
GLUTATHIONE AND OTHER
NUTRIENTS)**

TBI THERAPY: INTRAVENOUS 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 Alzheimer's disease.

PART IV: CRANIAL OSTEOPATHY



TBI THERAPY: CRANIAL OSTEOPATHY

- 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 in which 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.

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. 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.

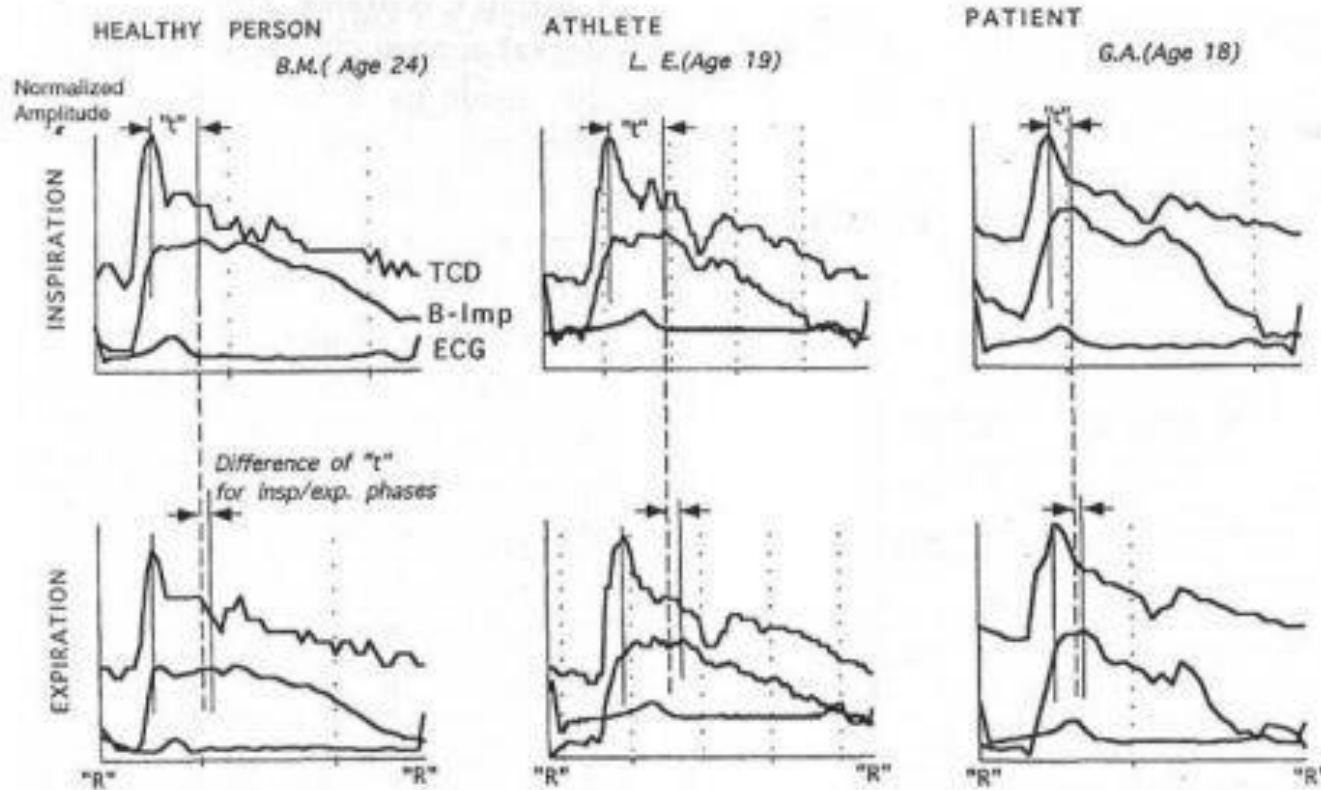


Figure 5: The difference of "t" between inspiratory and expiratory phases of the secondary respiration in a Healthy person, Athlete trained in diving and Patient after head injury.

PART V: MCT OILS AND THE KETOGENIC DIET



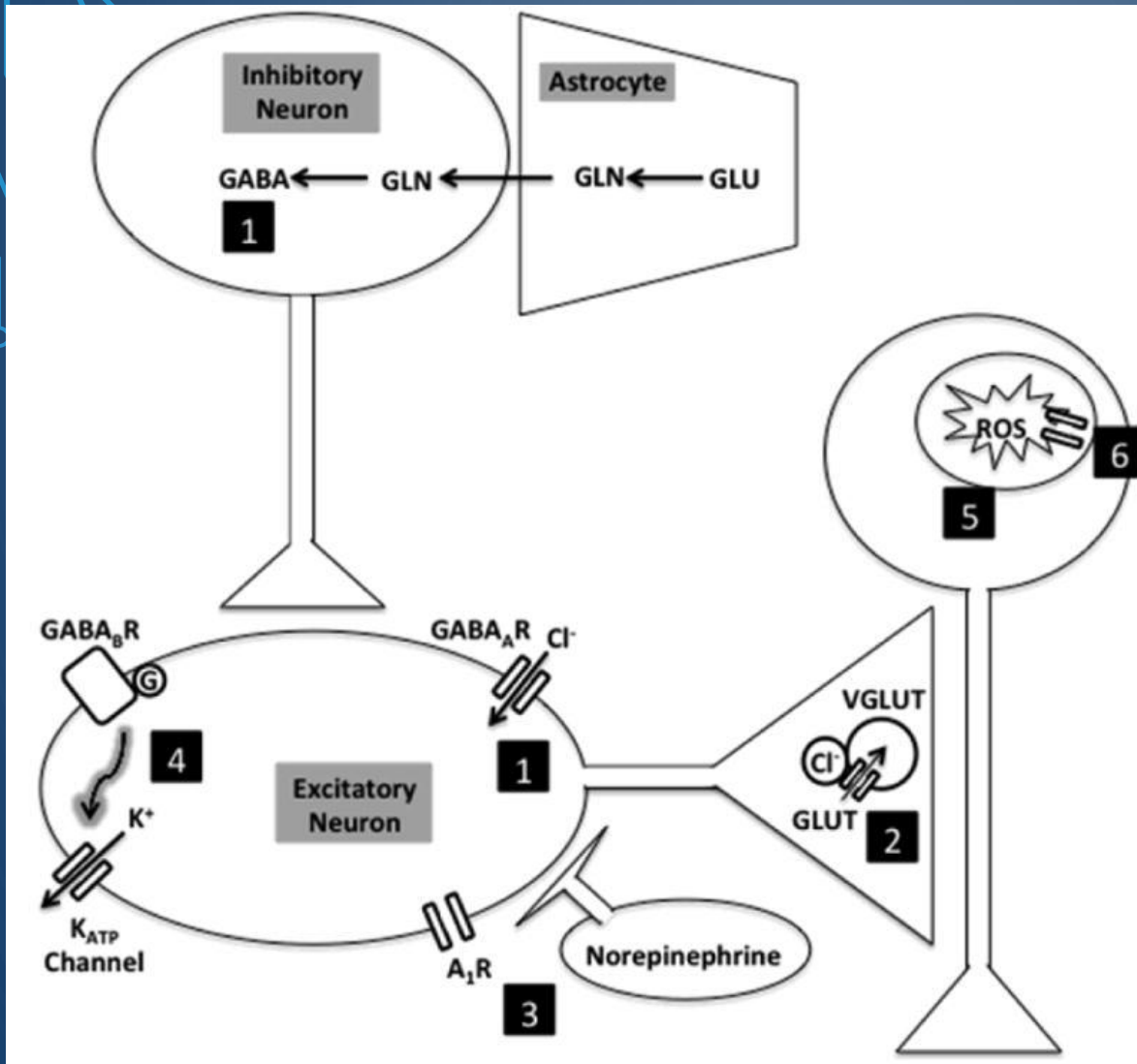
TBI THERAPY: KETOGENIC DIET

- Proven treatment for patients suffering from epileptic seizures.
- Ketogenic diets studied in brain trauma (CCI) produce cortical sparing and less apoptotic neuro-degeneration and overall improvements in cognitive and motor functioning.

TBI THERAPY: MCT OILS

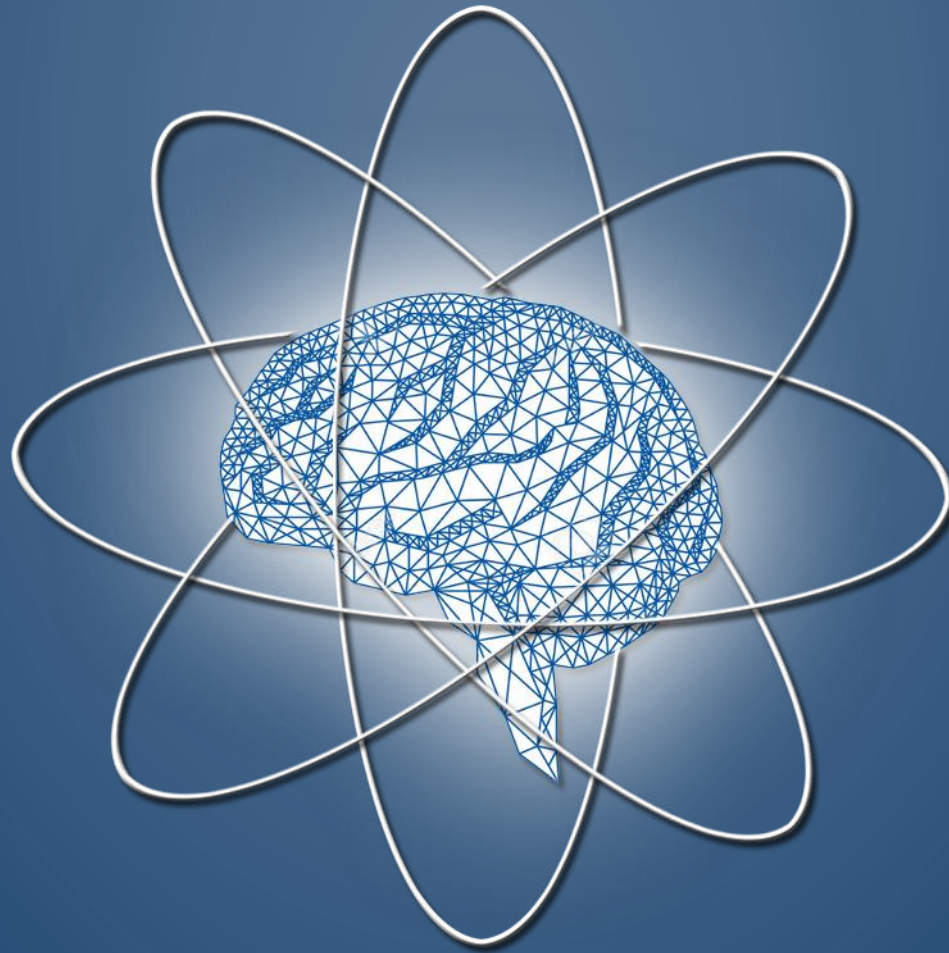
- Increase the available calming neurotransmitter GABA, thereby reducing neuronal hyperpolarization and the excitatory neurotransmitter glutamate.
 - With less glutamate, there is less oxidative stress and improved neuroprotection.
- MCT oils are a rich source of ketone bodies.

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.

Abbreviations: A₁R, 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.



THE TBI THERAPY PROTOCOL

TBI THERAPY: PROTOCOL

- HBOT: at 1.3 ATA to 1.75 ATA from 10 to 40 sessions
- 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 to self administer
- Cranial osteopathy: administered throughout HBOT treatment series

TBI THERAPY: PROTOCOL

- 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
- Ketogenic Diet, MCT Oils and Supplementation
 - Blueberries, Vitamin D3, and elk antler recommended daily 3 weeks before and after treatment
 - Ketogenic dietary counseling and MCT oils are begun on day 1 of HBOT series and continued for 3 months after treatment

TBI THERAPY: CLINICAL RESULTS

Out of 20 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

TBI THERAPY: CLINICAL RESULTS

Out of 20 patients treated, some patients have reported:

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

A man with a beard, wearing a black beanie, a black t-shirt, blue jeans, and a large brown backpack, stands on a rocky ledge overlooking a vast valley. The background is a soft-focus landscape of rolling hills and greenery. The image is framed by blue circuit-like lines and circles in the corners.

TBI THERAPY: CASE REPORT

“I was so hypersensitive to light and sound that I had to wear ear plugs, headphones, sunglasses, giant sun hat, and a scarf just to attend the appointment. I could not drive. After the intranasal PRP treatment, it was like a stream of information had been let loose like a dam that had busted. I felt for the first time in a year that I had some clarity. I was excited and able to read more than 2-3 sentences without triggering a migraine. I found that I was able to get back on the computer and learn more about my trauma and recent treatments. Within the following days it was like an awakening. It seemed like a light switch was turned back on inside my head. The ability to think and plan returned.”

TBI THERAPY: CONCLUSION

This regenerative, multi-modal TBI therapy protocol has a unifying theme of providing regenerative substrates to the injured brain that correct its metabolic crisis—by increasing oxygen, nutrients, cofactors, growth factors, and stem cells—to ultimately repair damaged neurons, enhance neurogenesis, increase blood flow, improve glucose utilization, decrease inflammation, and stabilize neurotransmitter release.

References

- 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.
- 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.
- 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.
- European Society of Endocrinology. (2010). Vitamin D deficiency associated with chronic fatigue in brain injured patients. ScienceDaily. Retrieved August 15, 2016 from www.sciencedaily.com/releases/2010/04/100427182609.htm
- Gladstone Institutes. (2008). Collagen May Help Protect Brain Against Alzheimer's Disease. *ScienceDaily*. Retrieved August 15, 2016 from www.sciencedaily.com/releases/2008/12/081210150713.htm
- Gunther, N. & Queen, E. (2013). What Physical and Cognitive Rest Really Mean After a Concussion. *Brainline*. Retrieved from <http://www.brainline.org/content/multimedia.php?id=9022>
- Haller, H., Cramer, H., Werner, M., & Dobos, G. (2015). Treating the sequelae of postoperative meningioma and traumatic brain injury: a case of implementation of craniosacral therapy in integrative inpatient care. *The Journal of Alternative and Complementary Medicine*, 21(2), 110-112.
- Huskisson, E., Maggini, S., & Ruf, M. (2007). The role of vitamins and minerals in energy metabolism and well-being. *Journal of international medical research*, 35(3), 277-289.
- Kurtz, S. (2008). *U.S. Patent Application No. 12/077,296*. Retrieved August 15, 2016 from <https://www.google.com/patents/US20090012039>
- McNally, M. A., & Hartman, A. L. (2012). Ketone bodies in epilepsy. *Journal of neurochemistry*, 121(1), 28-35.
- Mischley, L. K., Conley, K. E., Shankland, E. G., Kavanagh, T. J., Rosenfeld, M. E., Duda, J. E., ... & Padowski, J. M. (2016). Central nervous system uptake of intranasal glutathione in Parkinson's disease. *npj Parkinson's Disease*, 2, 16002.
- 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.
- Rho, J. M., & Stafstrom, C. E. (2012). The ketogenic diet as a treatment paradigm for diverse neurological disorders. *Frontiers in pharmacology*, 3, 59.
- Sun, D. (2014). The potential of endogenous neurogenesis for brain repair and regeneration following traumatic brain injury. *Neural regeneration research*, 9(7), 688.
- Thom, S. R., Bhopale, V. M., Velazquez, O. C., Goldstein, L. J., Thom, L. H., & Buerk, D. G. (2006). Stem cell mobilization by hyperbaric oxygen. *American Journal of Physiology-Heart and Circulatory Physiology*, 290(4), H1378-H1386.
- Tithon-Biotech (n.d.). Retrieved from <http://tithonbiotech.com/index/>
- UHN Staff. (2015). Vitamins for Memory Loss and Stroke Prevention – These 3 Are Critical. University Health News Daily. Retrieved August 15, 2016 from <http://universityhealthnews.com/daily/memory/vitamins-for-memory-loss-and-stroke-prevention-these-3-are-critical/>
- Van Velthoven, C. T., Kavelaars, A., van Bel, F., & Heijnen, C. J. (2010). Nasal administration of stem cells: a promising novel route to treat neonatal ischemic brain damage. *Pediatric research*, 68, 419-422.

