

Feeding the Injured Brain

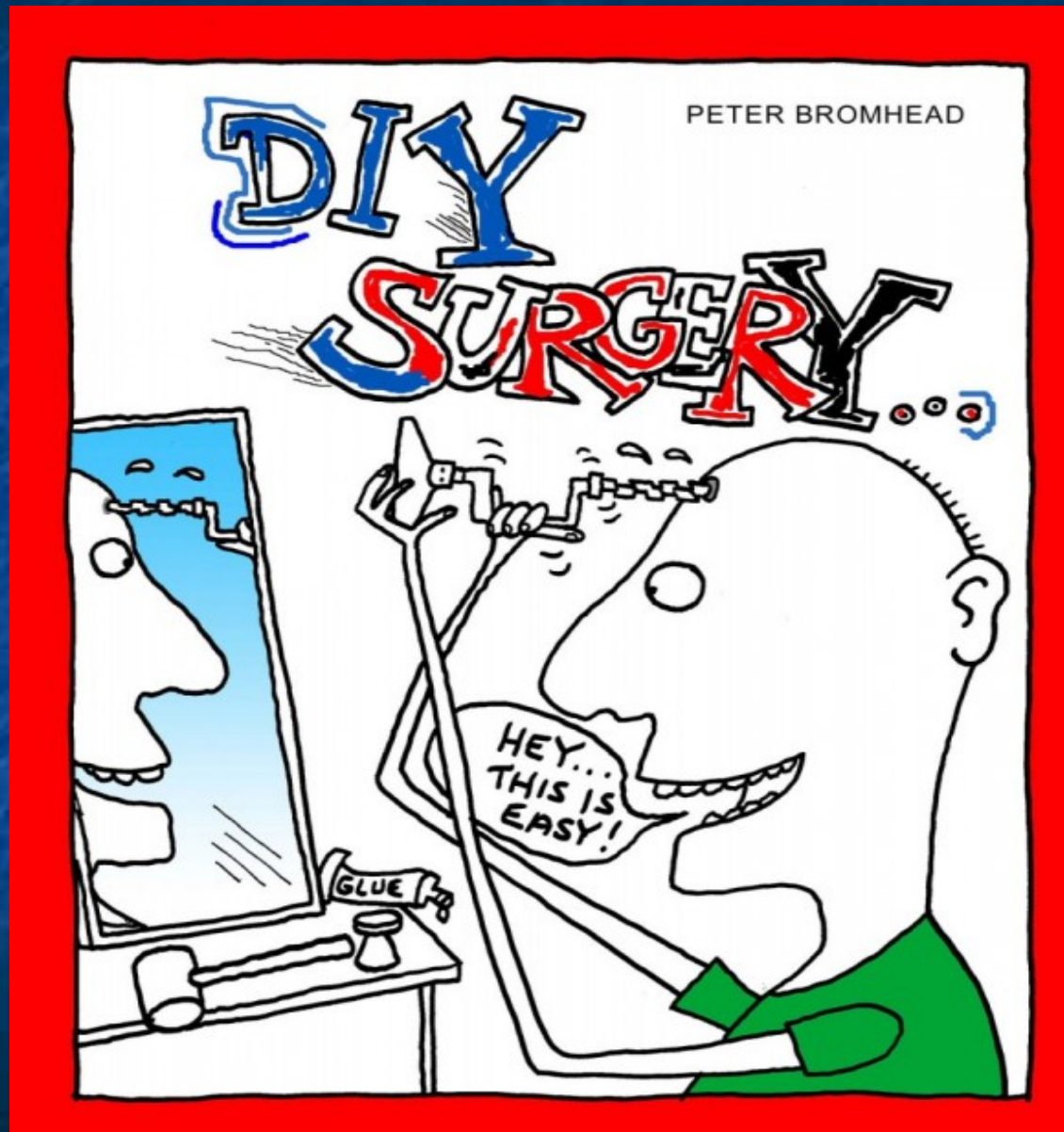


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Intro



Intro

- Treating head injury presents an ever-changing, complex series of interventions.
- Therapies are constantly being revised, no set standard.
- Shift of emphasis from primary control of ICP to a multi-faceted, individualized approach.
- Based on patient needs, stability and setting.
- New non-invasive approaches available.
- Goals— Improve outcome by incorporating nutrients, supplements & herbs as part of protocol.
- Focus— Optimize nutrition, improve cognition, reduce oxidative damage, promote oxygenation & perfusion, reduce inflammation & seizure potential.

Intro

- Additional benefits—
Maintain immune function, prevent wasting, reduce fatigue, stabilize mood, aid overall health.
- TBI is a risk factor for acquiring Alzheimer's and other degenerative diseases.
- Some interventions not in general use, some in modest use, some in wide use in other countries.
- Can be safely, effectively, integrated with medications, nutritional program and cognitive rehab to improve recovery.
- Cited animal and human studies.
- Give overview of the many possibilities to enhance neuronal function in TBI.

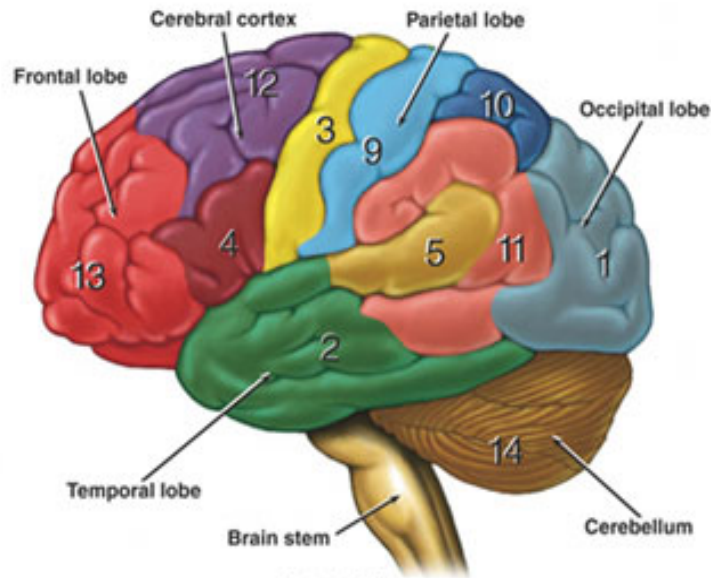
Anatomy and Functional Areas of the Brain

Functional Areas of the Cerebral Cortex

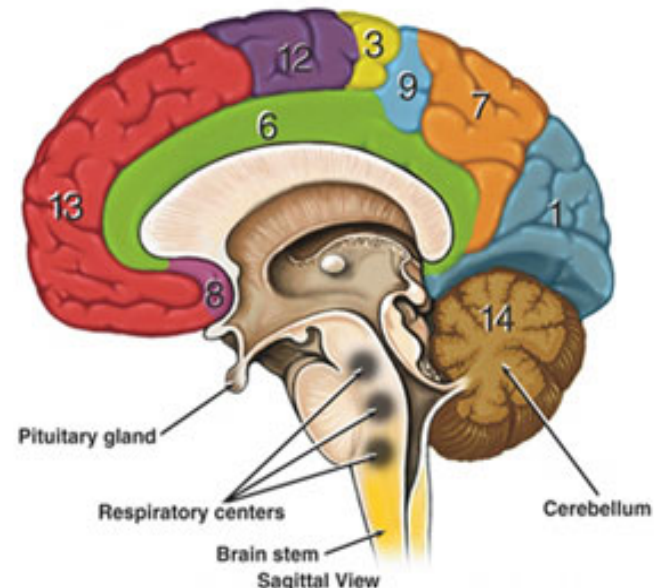
- 1 Visual Area:**
Sight
Image recognition
Image perception
- 2 Association Area**
Short-term memory
Equilibrium
Emotion
- 3 Motor Function Area**
Initiation of voluntary muscles
- 4 Broca's Area**
Muscles of speech
- 5 Auditory Area**
Hearing
- 6 Emotional Area**
Pain
Hunger
"Fight or flight" response
- 7 Sensory Association Area**
- 8 Olfactory Area**
Smelling
- 9 Sensory Area**
Sensation from muscles and skin
- 10 Somatosensory Association Area**
Evaluation of weight, texture, temperature, etc. for object recognition
- 11 Wernicke's Area**
Written and spoken language comprehension
- 12 Motor Function Area**
Eye movement and orientation
- 13 Higher Mental Functions**
Concentration
Planning
Judgment
Emotional expression
Creativity
Inhibition

Functional Areas of the Cerebellum

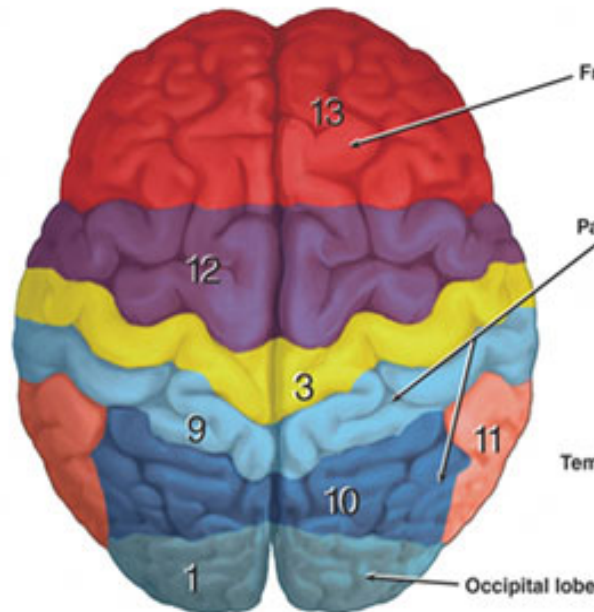
- 14 Motor Functions**
Coordination of movement
Balance and equilibrium
Posture



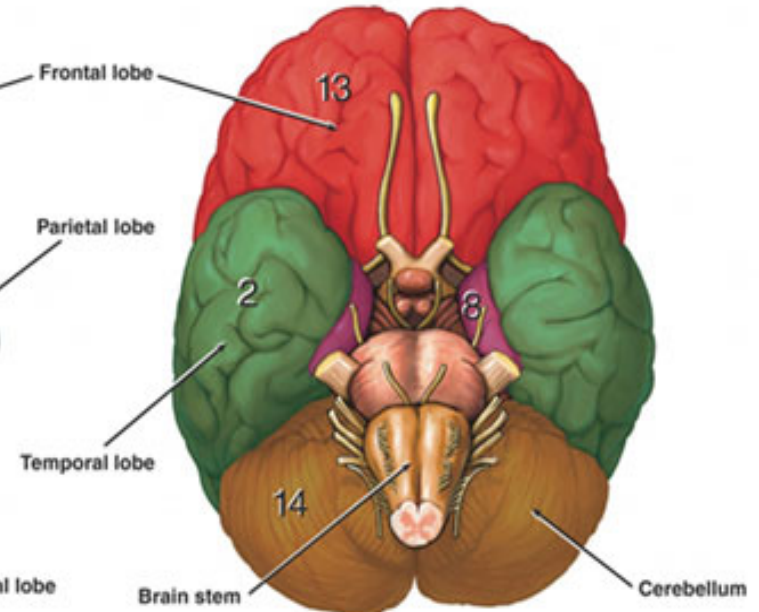
Lateral View



Sagittal View



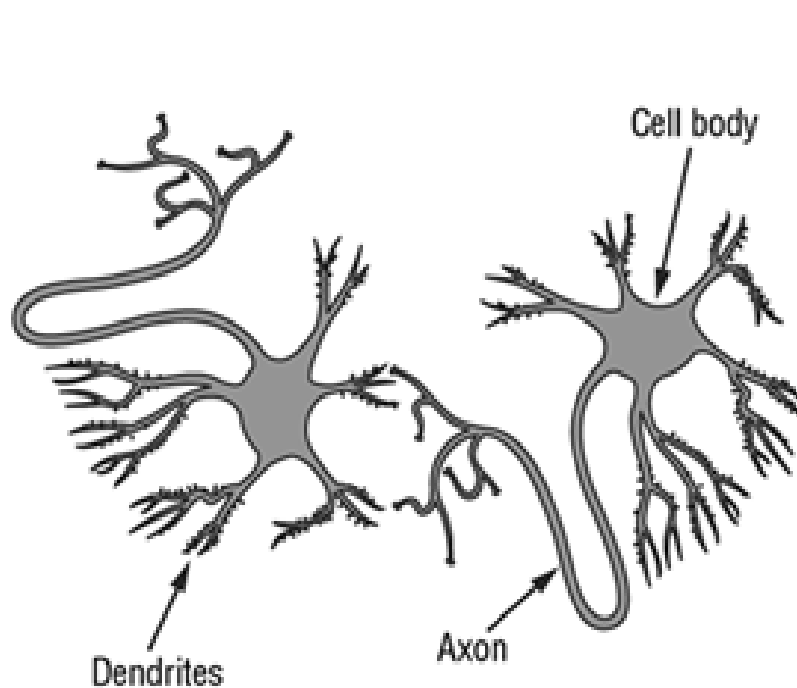
Superior View



Inferior View

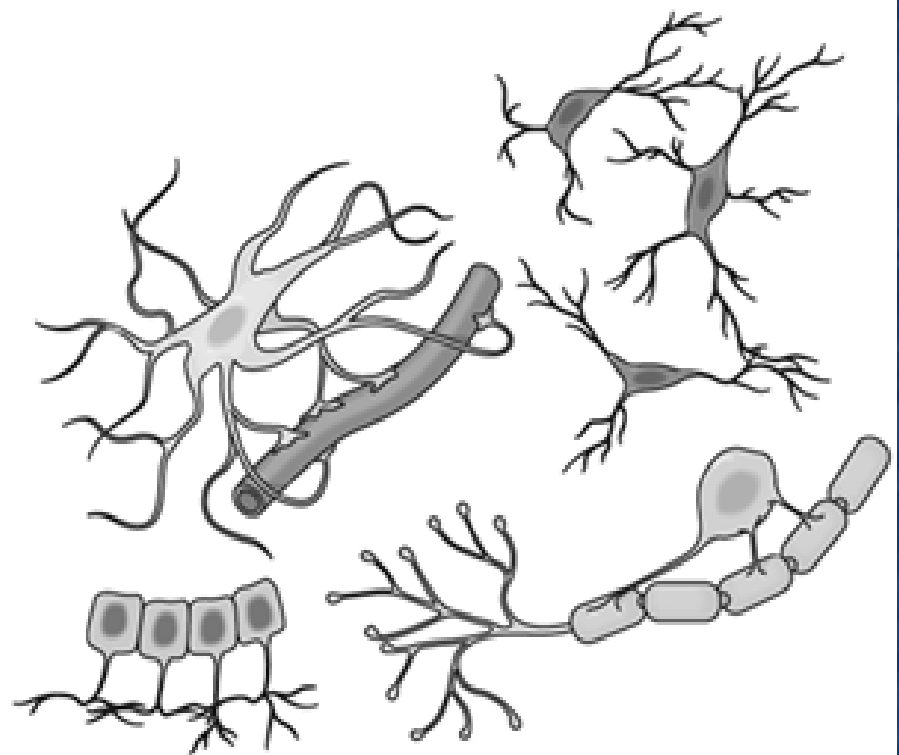
Injury

Both neurons and glial cells integrate neural outputs, release transmitters, have long-range signaling, can enwrap synaptic terminals, and are connected by gap junction.



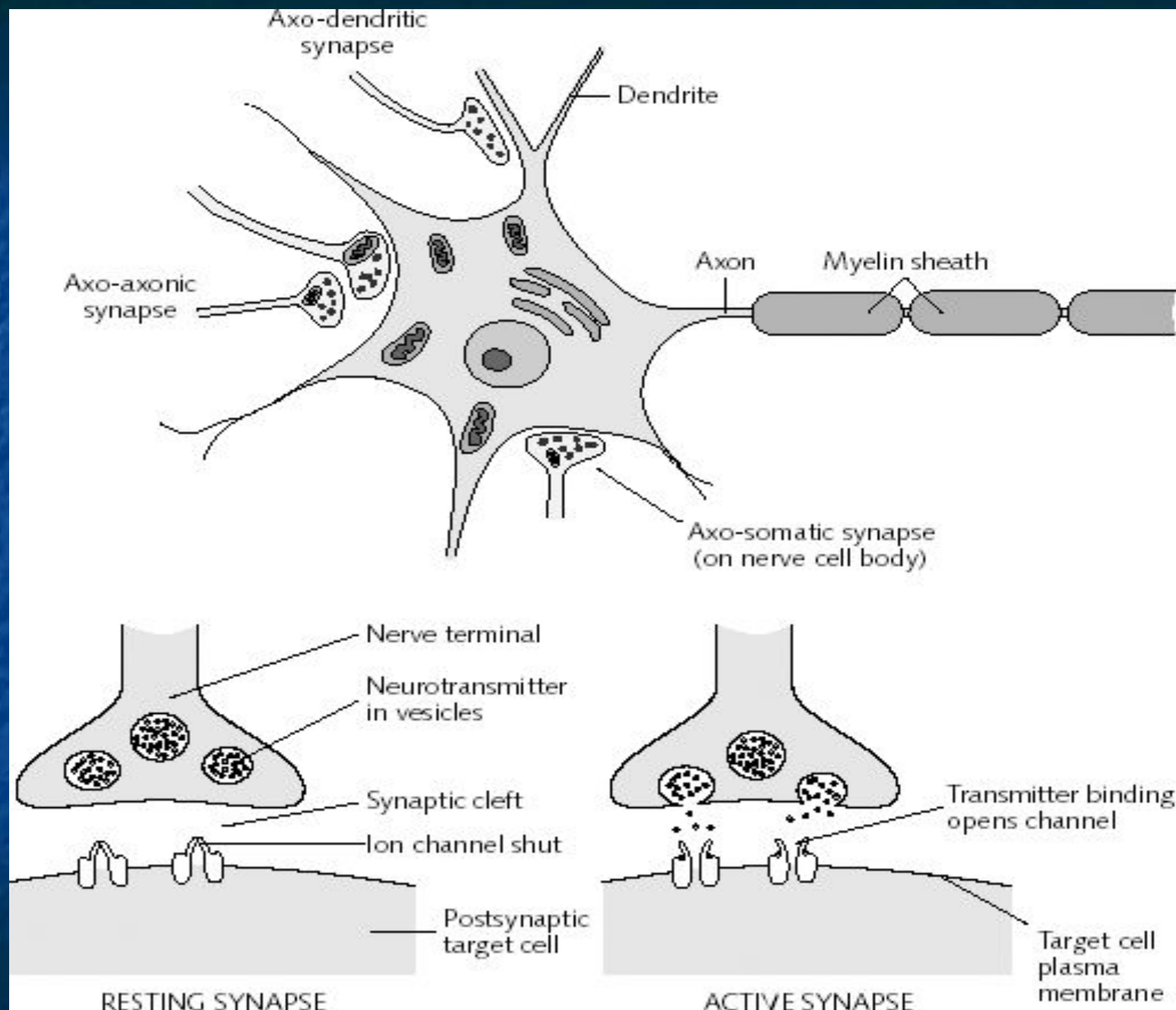
Typical neurons

Neurons receive stimulation from their branches, known as dendrites. They communicate with other neurons, creating a network with millions of other by firing a nerve impulse along an axon.



Various types of glial cells

Glia carry nutrients, speed repair, provide myelin for axons, support the blood-brain barrier, and may form their own communication network. They are also involved in neurogenesis.



Injury

Primary injuries/moment of insult--

- Tissue deformation (compression, stretching, shear).
- Nerve damage
- Hearing loss
- Vertigo
- Hematoma
- Contusion
- Laceration
- Intracranial hemorrhage
- Diffuse axonal injury
- Hypermetabolism
- Catabolism

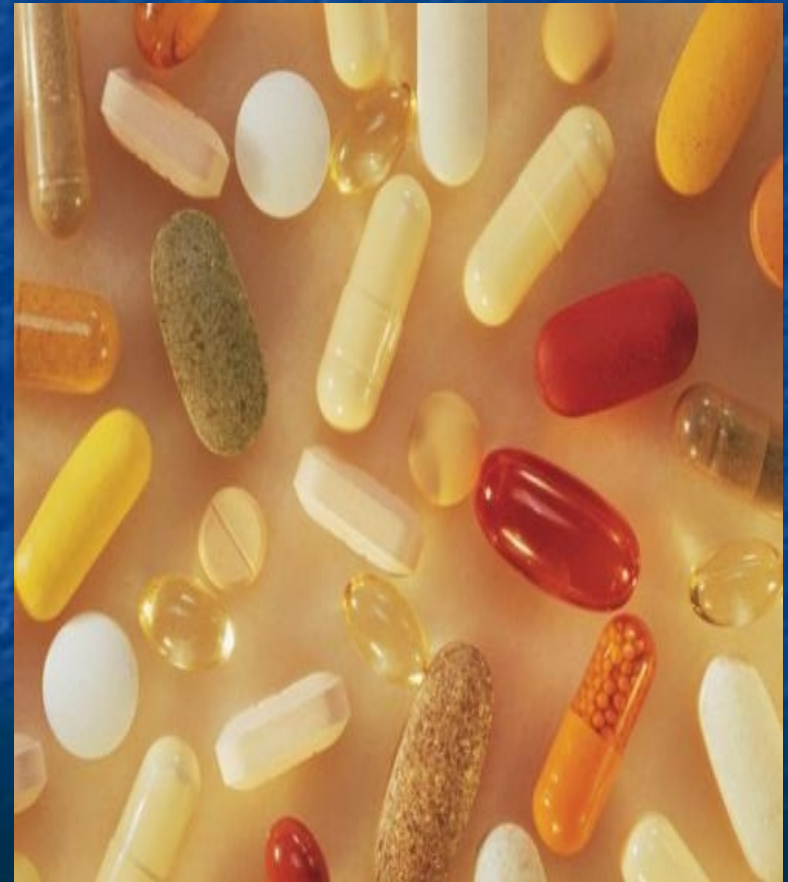
Injury

Secondary injuries/from effects of primary insult and consequences, hours or days after trauma--

- Neuronal & cerebral swelling/death
- Increased extracellular potassium
- Free-radical production
- Body temperature shifts
- Oxidative damage cascade
- Astrocyte swelling
- Increased brain metabolism
- Venous thromboembolism
- Respiratory & GI dysfunction
- Hypoxemia
- Seizures
- Muscular hypertonus
- Dysautonomy
- Increased glucose use
- Calcium influx leading to further brain injury
- Inflammation
- Increased ICP
- Disruption of the BBB
- Obstruction of the CSF
- Brain herniation
- Pituitary hormone deficiencies
- Immune compromise
- Hypercatabolic state

Interventions

Optimize Nutrition, Enhance Cognition,
Reduce Oxidative Damage,
Promote Oxygenation & Perfusion,
Reduce Inflammation & Seizure Potential



Interventions

Nutrients/Supplements

- Alpha-Lipoic Acid
- L-Arginine
- B Complex
- Branched-Chain AA's
- Citicoline/Choline
- Creatine
- DMAE
- Glutamine
- Medium Chain Triglycerides
- Omega-3 Fatty Acids
- Phosphatidyl Serine
- Probiotics
- SAMe
- Taurine
- Vitamin E
- Zinc

Herbs

- Bacopa
- Blue Vervain
- Blueberry
- Chinese polygala
- Curcumin/Tumeric
- Gastrodia
- Ginkgo
- Gotu Kola
- Holy Basil
- Lavender
- Lobelia
- Resveratrol/Japanese Knotweed
- Rosemary
- Scullcap
- White Peony

Optimize Nutrition



Optimize Nutrition: Rationale

- No standard enteral therapy for the treatment of TBI has been established in either acute or post-acute setting, despite clinical trials.
- Dietary factors can impact brain repair:
 - regulate neurotransmitter pathways
 - impact synaptic transmission
 - influence membrane fluidity & signal-transduction pathways
 - affect cognitive processes
 - modulate brain plasticity and function
 - act on emotional health
- Great opportunity to assimilate dietary and nutritional supplement studies to effect therapeutic benefit.

Optimize Nutrition: Form

- Liquid nutrients metabolized more efficiently, and can be put into feeding tubes.
- Enteral nutrition support (feeding tube to the stomach or small intestine) is effective and causes less complications than parenteral (bypasses digestive system) nutrition.
- Use unless GI tract non-functioning or access unobtainable/unsafe.
- Consider intervention with gastrostomy or J-tube at early stage when nutritional intake is expected to be inadequate, first weeks after injury.
- Parenteral associated with electrolyte imbalances, degeneration of organs in intestinal tract, blood clots, damage to blood vessels.
- Formulas individualized to general & specific needs.

Optimize Nutrition: Timing

- 2008 New York State analysis of 797 adult patients with severe TBI showed effect of timing and quantity of nutrition on death.
- Patients who were not fed within 5 & 7 days after TBI had a 2- and 4-fold increased likelihood of death, respectively.
- Every 10-kcal/kg decrease in caloric intake was associated with a 30–40% increase in mortality.
- Even after controlling for known mortality factors, including arterial hypotension, age, pupillary status, initial GCS score, and CT scan findings.
- Nutrition is a significant predictor of death in TBI.
- One of the therapeutic interventions that can directly affect TBI outcome.

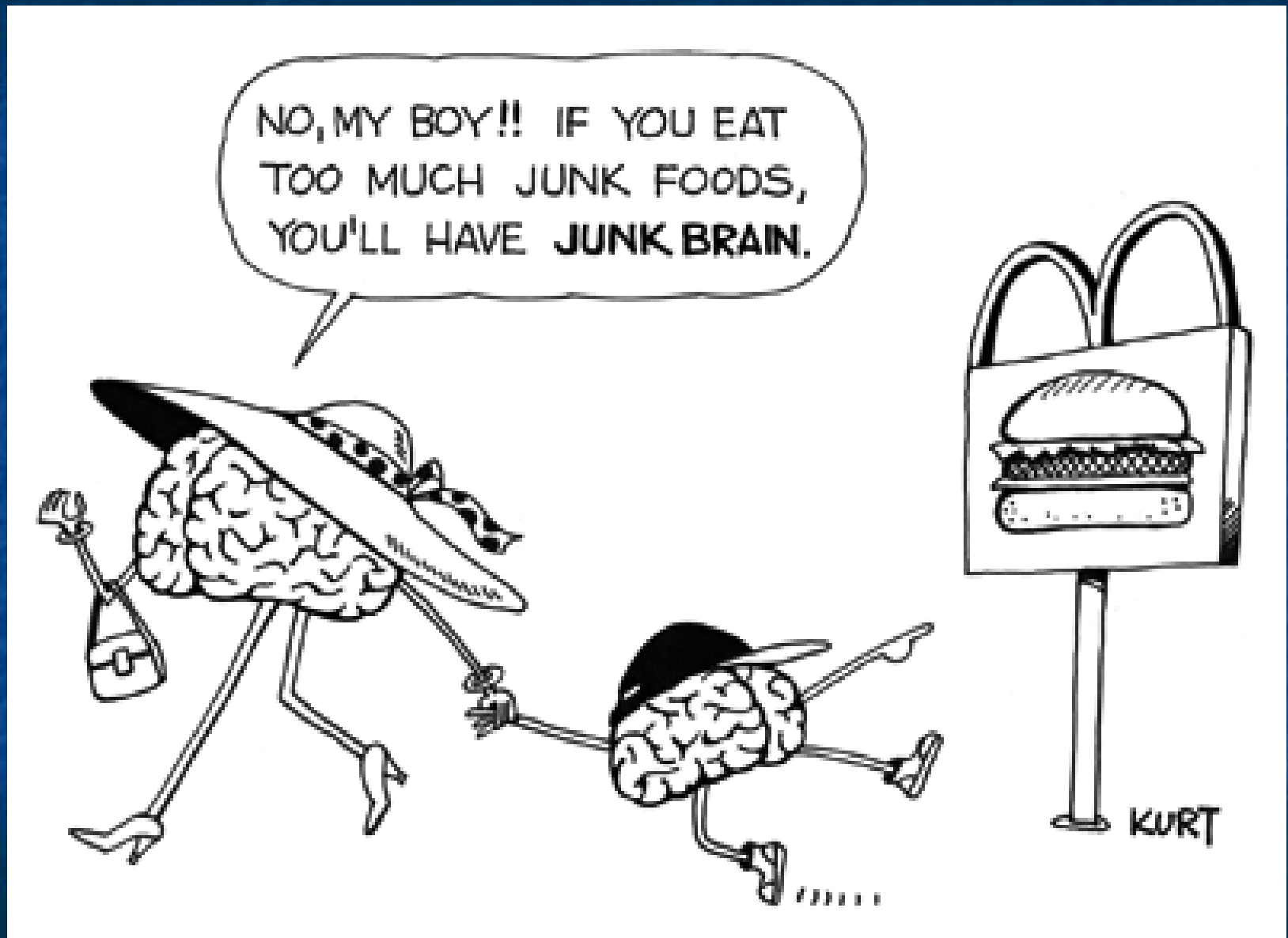
Optimize Nutrition: Needs

- The brain consumes an immense amount of energy relative to the rest of the body.
- TBI results in a hypermetabolic state that increases cerebral *and* systemic energy needs.
- Brain injury patients have higher **energy** and **protein** expenditures and are prone to infections.
- Non-supplemented TBI patients can lose 10% or more of lean body mass a week.

Optimize Nutrition: Needs

- Calories: Needs assessed via indirect calorimetry.
- Best outcomes for TBI patients were observed when patients received a minimum of 25 kcal/kg each day (1,700 calories), or at 40-70% above basal needs (35-40 kcal/kg/d 2,720 calories).
- In temperature fluctuations, the metabolic rate may vary as much as 25%.
- Fever & sepsis increase calorie needs by 7.2% for every degree F above normal.
- Seizures and posturing increase calories 20– 30% to a maximum of 3500 – 4000 total calories.
- If on sedatives, barbiturates, musculo-skeletal blocking agents, or if no brain activity, have 14% lower energy expenditure.

Optimize Nutrition: Needs



Optimize Nutrition: Needs

- Early hyperglycemia is associated with poor outcomes for severe TBI patients.
- Tight control of serum glucose (without reducing nutritional support) may improve prognosis.
- Elevated insulin and glucose (and aging) can lead to the formation of advanced glycation end products/sugar-damaged proteins (AGEs).
- AGEs activate inflammatory compounds and free-radicals, promote neurodegeneration.
- Avoid trans fatty acids/trans fats in fast foods or anything with partially hydrogenated oil.
- Trans fats disrupt brain communication, interfere with metabolism of essential fatty acids, trigger insulin resistance.

Optimize Nutrition: Low Carb Pyramid



Optimize Nutrition: Needs

- Protein: 23 total, control most cellular processes.
- 9 *essential* amino acids (we don't make).
- Essential amino acids: Histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine.
- Protein needs in TBI estimated at 1.5 – 2.2 g/kg/d (if 68 kg/150 lbs. = 102 - 150 g protein/d).
- In TBI, can lose up to 30g/day, measured as nitrogen loss (fasting individual loses 3-5 g/d).
- Negative nitrogen loss persists for 2-3 weeks, peaks @ 10th day, regardless of protein given.
- Protein loss correlates with injury severity.
- Immobility, steroids, increase nitrogen loss.

Optimize Nutrition: Needs

- 14 Non-essential: Alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, serine, glutamine, glycine, ornithine, proline, taurine, tyrosine
- Glutamine: the most abundant human amino acid.
- Directly crosses the blood brain barrier & alternative source of brain fuel.
- Glutamine makes two crucial brain neurotransmitters: glutamic acid (excitatory) and gamma-aminobutyric acid/GABA (inhibitory).
- Helps stop stress-induced protein breakdown.
- 2008 animal study showed post-TBI glutamine supplementation reduced intestinal NF-kappaB activation and inflammatory cytokine expression.

Optimize Nutrition: Needs

- Branched-chain amino acids/BCAAs: refers to structure of leucine, isoleucine, valine (essential).
- Play role in protein synthesis, brain insulin availability.
- Brain insulin governs higher cognitive processes of learning, memory and attention.
- BCAAs increase brain energy production, help synthesize, secrete and transport neurotransmitters, aid brain repair & circuitry remodeling.
- 2008 study of 41 TBI vegetative or minimally conscious patients, 22 received i.v. BCAA (19.6 g/d), 19 placebo, for 15 days.
- Those with BCAAs had significantly improved scores on the disability rating scale.
- 68% of the BCAA group *exited* the vegetative or minimally conscious state, continued to improve after end of treatment.

Optimize Nutrition: Needs

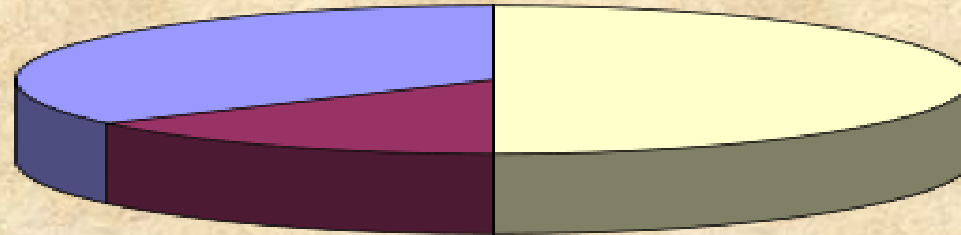
- Lipids: Calories to be 30-40% lipids, to minimize hyperglycemia.
- Source lipids with 50-60% medium-chain triglycerides (MCTs) & omega 3 ratio of 2:1 – 8:1.
- MCT fats have unique chemical structure that allows direct absorption, faster use, more ketogenic.
- First used in the mid-1900s with ketogenic diet to reduce seizures.
- Naturally in milk fat, palm oil, and coconut oil.
- 2006 review indicates the ketogenic diet could have beneficial effects in TBI and many brain disorders characterized by the death of neurons.

Gasior M, Rogawski MA, Hartman AL, Neuroprotective and disease-modifying effects of the ketogenic diet, (2006) *Behavioural Pharmacology*, 17 (5-6), 431-439.

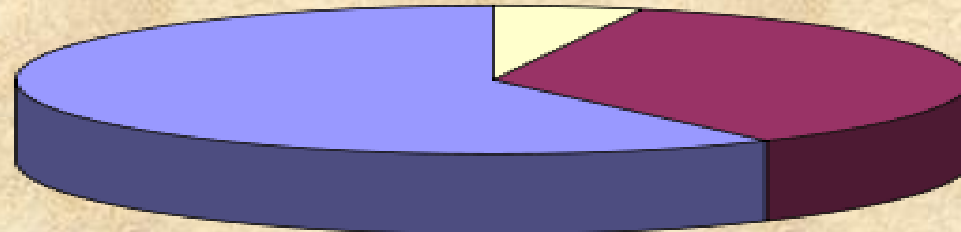
Optimize Nutrition: Modified Ketogenic

- Ketogenic diet is a high fat, adequate protein, low carb diet in clinical use for 80+ years for epilepsy.
- The diet mimics starvation by forcing the body to burn fat rather than carbohydrate.
- Liver breaks down fat into fatty acids and ketone bodies, which pass into the brain replacing glucose as an energy source.
- Ketone bodies are a more efficient fuel than glucose, can remain stable in the face of increased energy demand, and may have a neuroprotective effect.
- Suggesting a blend of Atkins-MCT-ketogenic diet, (higher protein).

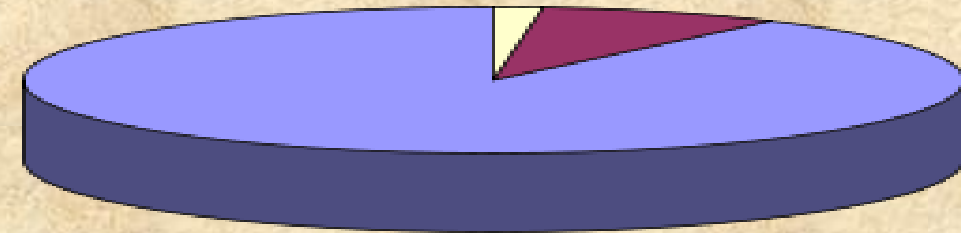
Typical American diet



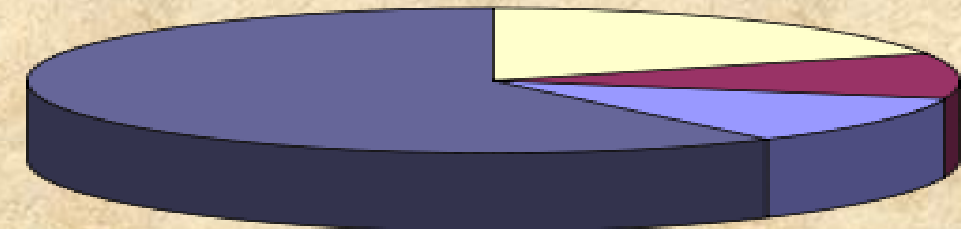
Atkins (induction phase)



Classic ketogenic diet 4:1



MCT ketogenic diet



□ Carbohydrate ■ Protein ■ Fat LCT ■ Fat MCT

Optimize Nutrition: Needs

- **Omega-3/DHA:** An essential fatty acid from fatty fish, and the most abundant essential fatty acid in the brain (and retina).
- DHA composes 50% of the brain cell plasma membranes, and is involved in protein transport.
- Deficiency linked with cognitive decline, increased brain cell death.
- Studies show supplementation of omega-3 fatty acids in the diet of TBI animal models counteracted all of the studied negative effects.
- In TBI animals, omega-3 improved levels of anti-inflammatory brain compounds, reduced oxidative damage, counteracted learning disability.
- **Concluded omega-3 enriched diet can provide protection against reduced plasticity and impaired learning ability after TBI.**

Optimize Nutrition: Needs

- Vitamins & minerals: Plasma levels of vitamins B & C, and other vitamins and minerals, are low in TBI.
- Vitamin B Complex: 8 water-soluble vitamins, related compounds.
- All play critical role in brain function, from neurotransmitter manufacture to regulating energy release in brain cells to maintaining mental agility.
- B1/thiamine plays a role in brain functions related to memory & cognition. Deficiency over-excites the neurons, hampers the brains ability to use glucose.
- B3/niacin vital to formation of nerve tissue.
- Given 15 minutes & 24 hours to animals after TBI. Showed significantly improved behavior, reduced size of lesion, reduced expression of GFAP protein (increased in infection or neurodegeneration).

Optimize Nutrition: Needs

- B6/pyridoxine needed to make myelin sheath to speed nerve signals, and make neuro-transmitters *norepinephrine, serotonin, dopamine*.
Low levels may provoke seizures, if prone.
- B12/cobalamin helps form myelin sheath.
- B9/folic acid helps maintain normal levels of *serotonin*.
Depression, schizophrenia if low levels.
- Choline critical to learning, mental alertness, cell membrane and makes neurotransmitter *acetylcholine*, which affects memory.
- Inositol part of cell membrane, helps make *serotonin* and *acetylcholine*.
- B6, B12, folic acid, choline & other nutrients can lower homocysteine, which damages the brain in excess, and is predictive of AD and dementia.

Optimize Nutrition: Needs

- **Zinc:** Essential metallic mineral for normal brain function, nerve impulse transmission and repair.
- High levels in hippocampus (short term memory).
- TBI, seizure and ischemic brain injury result in the release of cellular zinc.
- Post TBI, high risk for zinc depletion, especially if severe injury, immobility.
- Albumin a major transport protein for zinc, frequently low in severe head injury, leading to further zinc deficiency.
- **Moderate zinc deficiency after TBI significantly increased neuronal cell death.**

Optimize Nutrition: Needs

- In study of 68 TBI adults, randomized to adequate or supplemental zinc (12 mg/d zinc sulfate within 72 hours x 15 days, then 22 mg zinc gluconate x @21 more days).
- Supplemental zinc treatment group showed improved protein synthesis, improved scores on the Glasgow Coma Scale, and continuous improvements throughout the study over the patients in the adequate zinc group. No changes in serum or CSF zinc concentration.
- Balance type and amount of zinc to give protection without toxicity. Up to 30 mg/d well-tolerated.

Optimize Nutrition: Needs

- **Probiotics:** dietary supplements containing beneficial bacteria or yeasts.
- Somewhere between 300 and 1000 different species live in the gut, estimates at about 500.
- Strains of the genera *Lactobacillus* and *Bifidobacterium* most widely used bacteria.
- Many useful functions--ferment unused energy substrates, train the immune system, prevent growth of harmful species, produce biotin, folic acid vitamin K, make hormones to direct fat storage.
- One 2004 study to investigate effects in TBI— 10 received standard diet, 10 received enriched with **glutamine** and *L. johnsonii* fermented milk.
- **Control group had 100% infections, 3 sepsis. Supplement group 50%, no sepsis, shorter icu stay.**

Optimize Nutrition



Optimize Nutrition: Ideal Blend

- 25-40 kCal/kg/d
- Low carb, low sugar (no HFCS)
- High quality fats, 60% lipids (30% as MCT) ketogenic (no trans, hydrogenated fats)
- High quality protein (non-GMO, non-soy) with 19 g/d as BCAAs

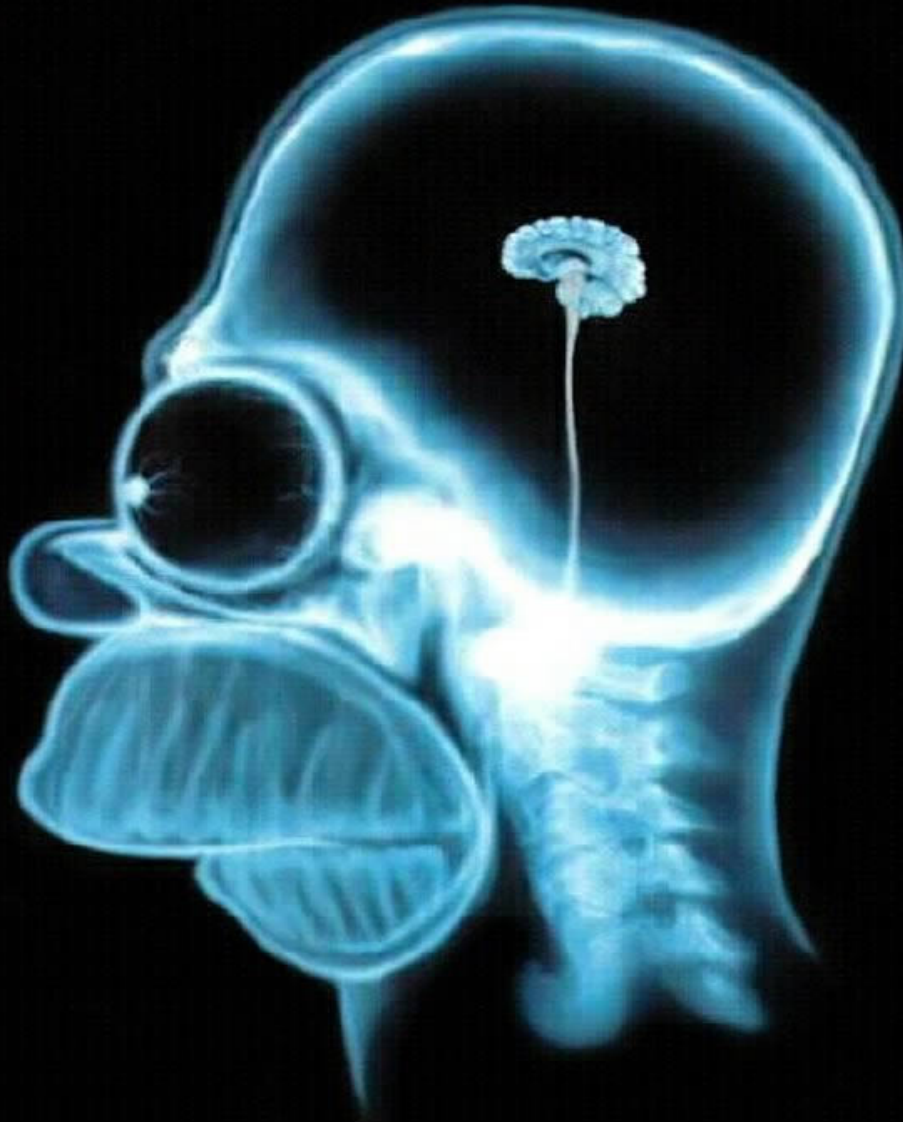
Modified Atkins-

1.5-2.2 g/kg/d,

With:

- L-Arginine
- B-complex
- Cocoa powder, unsweetened
- Citicoline
- Creatine
- Curcumin
- Glutamine
- Mixed antioxidant berry, spice & vegetable concentrates
- Omega-3 DHA (& EPA) oils
- Probiotics
- Taurine
- Vitamin E
- Zinc

Enhance Cognition



Enhance Cognition

- Diets high in trans fats, saturated fat and sucrose reduce molecular structures that support cognitive processing.
- Increase the risk of neurological dysfunction in humans and animals.
- This is our western diet, and may increase the *susceptibility* of the brain to insults.
- After 3 weeks on junk food diet, rodents showed a loss of synaptic plasticity in the hippocampus.
- The diet worsened the neurological effect associated with experimental brain injury.
- Curcumin and vitamin E counteracted these.
- Several dietary components have been identified as having effects on cognitive abilities.

Nutrient	Effects on cognition and emotion	Food sources
Omega-3 fatty acids (for example, docosahexaenoic acid)	Amelioration of cognitive decline in the elderly ¹⁴⁸ ; basis for treatment in patients with mood disorders ⁸⁰ ; improvement of cognition in traumatic brain injury in rodents ⁸¹ ; amelioration of cognitive decay in mouse model of Alzheimer's disease ^{149,150}	Fish (salmon), flax seeds, krill, chia, kiwi fruit, butternuts, walnuts
Curcumin	Amelioration of cognitive decay in mouse model of Alzheimer's disease ¹²³ ; amelioration of cognitive decay in traumatic brain injury in rodents ⁸⁹	Turmeric (curry spice)
Flavonoids	Cognitive enhancement in combination with exercise in rodents ⁹² ; improvement of cognitive function in the elderly ¹⁵¹	Cocoa, green tea, Ginkgo tree, citrus fruits, wine (higher in red wine), dark chocolate
Saturated fat	Promotion of cognitive decline in adult rodents ⁴ ; aggravation of cognitive impairment after brain trauma in rodents ⁸⁸ ; exacerbation of cognitive decline in aging humans ³	Butter, ghee, suet, lard, coconut oil, cottonseed oil, palm kernel oil, dairy products (cream, cheese), meat
B vitamins	Supplementation with vitamin B6, vitamin B12 or folate has positive effects on memory performance in women of various ages ¹⁵² ; vitamin B12 improves cognitive impairment in rats fed a choline-deficient diet ¹⁵³	Various natural sources. Vitamin B12 is not available from plant products
Vitamin D	Important for preserving cognition in the elderly ¹⁵⁴	Fish liver, fatty fish, mushrooms, fortified products, milk, soy milk, cereal grains
Vitamin E	Amelioration of cognitive impairment after brain trauma in rodents ¹⁰² ; reduces cognitive decay in the elderly ¹¹⁹	Asparagus, avocado, nuts, peanuts, olives, red palm oil, seeds, spinach, vegetable oils, wheatgerm
Choline	Reduction of seizure-induced memory impairment in rodents ¹⁵⁵ ; a review of the literature reveals evidence for a causal relationship between dietary choline and cognition in humans and rats ¹⁵⁶	Egg yolks, soy beef, chicken, veal, turkey liver, lettuce
Combination of vitamins (C, E, carotene)	Antioxidant vitamin intake delays cognitive decline in the elderly ¹⁵⁷	Vitamin C: citrus fruits, several plants and vegetables, calf and beef liver. Vitamin E: see above
Calcium, zinc, selenium	High serum calcium is associated with faster cognitive decline in the elderly ¹⁵⁸ ; reduction of zinc in diet helps to reduce cognitive decay in the elderly ¹⁵⁹ ; lifelong low selenium level associated with lower cognitive function in humans ¹⁶⁰	Calcium: milk, coral. Zinc: oysters, a small amount in beans, nuts, almonds, whole grains, sunflower seeds. Selenium: nuts, cereals, meat, fish, eggs
Copper	Cognitive decline in patients with Alzheimer's disease correlates with low plasma concentrations of copper ¹⁶¹	Oysters, beef/lamb liver, Brazil nuts, blackstrap molasses, cocoa, black pepper
Iron	Iron treatment normalizes cognitive function in young women ¹⁶²	Red meat, fish, poultry, lentils, beans

Enhance Cognition

- TBI impairs cognitive function and synaptic plasticity, resulting in cumulative free-radical oxygen species.
- 2004 another animal study showed free-radical formation associated with eating high saturated fat diet **worsened the outcome of TBI on cognition & neuroplasticity.**
- Tumeric and ginger offered effective protection followed by ginkgo, polygonatum sp., Chinese cinnamon, Korean rhubarb, **Gastrodia elata** and Chinese scullcap.

Enhance Cognition

- Vitamin E: is the collective name for a set of 8 fat soluble related tocopherols and tocotrienols.
- Low levels associated with poor memory in humans.
- Vitamin E prevented accumulation of beta-amyloid peptides, reduced behavioral deficits in TBI mice.
- TBI mice had lowered levels of compounds which maintain brain function & repair DNA in the hippocampus (short term memory) and cerebral cortex (memory, attention, thought, language, consciousness).
- Vitamin E normalized these areas in TBI mice.
- Rodents on a regular diet, vit. E significantly raised hippocampal repair levels, lowered oxidized proteins.

Enhance Cognition

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WELL I DON'T KNOW IF THE FISH OILS HAVE
HELPED HIS CONCENTRATION, BUT THEY'VE
CERTAINLY KEPT THE FLY POPULATION DOWN

Enhance Cognition

- Omega-3/DHA: Human body is inefficient in synthesizing DHA, reliant on dietary sources.
- Crucial for maintaining cell membrane integrity, ionic permeability.
- Activates energy-generating pathways associated with learning & memory.
- Helps modulate receptor function, synaptic transmission and plasticity, support cognitive function.
- Dietary DHA supplementation found to raise levels of brain-derived neurotrophic factor (BDNF) in the hippocampus, enhance cognitive function, stimulate neuronal plasticity in rodent TBI models.

Enhance Cognition

- High oxidative stress of TBI can reduce the production of a compound helpful in brain protection, fatty acid and glucose metabolism (silent information regulator 2/ Sir2).
- After TBI in rodent studies, omega-3 fatty acids raised levels of Sir2, and other compounds (MtCK and AMPK and p-AMPK), important markers of the brain's cellular energy.

Enhance Cognition

- Vitamin B Complex: Folate or folic acid
Adequate levels essential for cognitive health.
- Folate supplementation, either alone or in conjunction with other B vitamins, shown to be effective in preventing cognitive decline and dementia in aging (and help anti-depressants).

Enhance Cognition



Citicoline 500mg tabs/2ml-4ml Inj.

Prevents neuronal dysfunction



Enhance Cognition

- Citicoline: A form of choline (vitamin B complex), citicoline sodium form used in clinical trials.
- Helps make *acetylcholine* and neuronal cell membrane, contributes to methylation.
- Increases brain levels of neurotransmitters *norepinephrine, dopamine*.
- Readily absorbed in GI tract, easily crosses BBB.
- Improves the structural integrity and function of the neuronal membrane to assist in membrane protection and repair.
- Protects against neuronal membrane damage caused by ischemia—reduces arachidonic acid release, decreases BBB dysfunction, less edema, protects hippocampal neurons.

Enhance Cognition

- Improved memory retention, motor performance, & reversed cerebral ischemia and edema in animal models.
- In study of TBI patients, those receiving i.v. citicholine showed greater cognitive and motor symptom improvements than the control.
- Other studies show citicoline facilitates memory rehabilitation by restoring blood flow to the lesion.
- In 2000 animal study, intraperitoneal citicoline significantly reduced brain edema, the volume of ischemic area surrounding the injury, and the BBB breakdown in cortex and hippocampus.

Enhance Cognition

- Human trials 272 stroke patients, 133 received 1,000mg/d i.v. in acute stage of moderate-severe infarct, mild-moderate disturbances of consciousness x 4 days. LOC improved significantly in the CDPC group, with 54% improved compared to 29% of placebo.
- Citicoline has also been investigated as a therapy in stroke patients.
- Improvements in muscle strength, neurological function, ambulation, cognition post-stroke.
- Initiating treatment within first 24 hours after stroke onset “increases the probability of complete recovery at three months.” *Stroke* 2002; 33:2850-2857.

Enhance Cognition

- Much research shown positive findings for post-stroke treatment, TBI, memory loss in aging.
- Reduced size of cerebral infarct when combined with rtPA in animal embolic stroke models.
- Other stroke studies inconclusive, with no significant effect over placebo.
- Very low toxicity profile, negligible side-effects, excellent clinical safety record.
- **Current trial:** Study of Citicoline for the Treatment of Traumatic Brain Injury (COBRIT), Study NCT00545662, a randomized, double-blind, placebo controlled, multi-center trial of the effects of 90 days of citicoline on functional outcome in patients with complicated mild, moderate and severe traumatic brain injury.

Enhance Cognition

- Alpha-lipoic acid: Powerful antioxidant micronutrient in the body, shown to reduce cognitive decay in Alzheimer's, improve memory deficits in animals.
- Nootropics are category of compounds which improve impaired human cognitive abilities—
- Enhance memory, slow/prevent cognitive decline, reduce brain oxidative damage, improve mood.
- The term covers a broad range of substances including drugs, nutrients and herbs that have purported cognitive enhancing effects.
- Include: **Bacopa** (*Bacopa monniera*), Bhringaraj (*Eclipta alba*), **Ginkgo**, Gotu kola (*Centella asiatica*), Lavender, Rosemary, White peony (*Paeonia lactiflora*), Yuan zhi (*Polygala tenuifolia*).

Enhance Cognition



Enhance Cognition

- Bacopa monniera: Known in Ayurvedic Medicine as useful treatment of cognitive impairment.
- In Alzheimer's mouse model, Bacopa/Brahmi reduced beta-amyloid levels, scavenged free radicals, reduced divalent metals, inhibited lipoxygenase activity and reduced the formation of inflammatory lipid peroxides.
- Bacopa 300mg/d given continuously for 12 weeks in *healthy* subjects improved higher cognitive function--early information processing, verbal learning and memory consolidation.
- In RDBCT study, Bacopa given to *healthy* adults, results show significant effect on retention and decreased rate of forgetting new info.

Reduce Oxidative Damage



Reduce Oxidative Damage

- Brain is very susceptible to oxidative damage due to its high metabolic load and abundance of oxidizable material.
- Fatty membrane covering all brain cells susceptible to oxidative damage from trauma, environmental pollutants, normal metabolic processes, fried foods, trans fats, nutrient deficiencies, aging, genetics.
- After TBI, via several different mechanisms, a cascade of injurious events worsens cell death, creating *more* antioxidants and free radicals.
- Protective systems and antioxidant stores are depleted, surrounding cells die, contributing to *further* oxidative stress and cell death.

Reduce Oxidative Damage

- Start antioxidant therapies at the earliest possible time post-injury, to delay/inhibit oxidation, prevent neuronal death, improve survival and reducing morbidity.
- Also reduces the risk of developing AD.
- Fish oil: DHA Essential fatty acid stimulates glucose utilization and mitochondrial function, reducing oxidative stress.
- Animals fed 8% fish oil diet after TBI significantly increased antioxidant Sir2a levels by reducing oxidative stress.
- Levels of beneficial Sir2a can be manipulated by dietary factors, including omega-3, resveratrol.

Reduce Oxidative Damage

- Vitamin B complex: Niacin acts as a potent antioxidant in brain cells.
- Studies suggest that reducing homocysteine levels may be neuroprotective.
- Folic acid supplementation may be beneficial to reduce homocysteine and improve the neuron's ability to protect against oxidative stress.
- Glutathione deficiency contributes to oxidative stress.
- Glutamine is the precursor and can raise glutathione levels/synthesis in the liver.
- Adequate protein nutrition is crucial to maintain glutathione balance.

Reduce Oxidative Damage

- Antioxidants from natural products, as well as long-term dietary alterations, may be effective scavengers of reactive oxygen species (ROS) and reactive nitrogen species (RNS).
- For specific brain health, anthocyanins appear to offer the *best benefit* against the effects of oxidative stress in the aging and ischemic brain, and the best penetration of the BBB.
- Several studies of rats with stroke fed high antioxidant blueberries showed reduced hippocampal damage, likely due to anthocyanins.
- Blueberry compounds activate genes involved in neuroprotection, which reduce the release of inflammatory mediators, increase glutathione, lower oxidative stress.

Reduce Oxidative Damage

Anthocyanin Content: mg per 100g food

- Eggplant 750
- Black Currant 130-400
- Blackberry 83-326
- Blueberry 25-497
- Cherry 350-400
- Chokeberry 200-1,000
- Cranberry 60-200
- Elderberry 450
- Raspberry 10-60
- Red Grape 30-750
- Strawberry 15-35

Reduce Oxidative Damage

Many antioxidant-rich culinary spices & foods,
oxygen radical absorbance capacity (ORAC) list:

- Clove 314,000
- Cinnamon 267,500
- Unsweetened cocoa powder 180,900
- Turmeric 159,000
- Cumin 76,800
- Basil 67,500
- Ginger 28,800
- Goji berry 20,200
- Pomegranate 10,500
- Blueberry 6,600 *(25x more anthocyanins than strawberries and raspberries)*
- Kale 1,800
- Broccoli 900

Reduce Oxidative Damage



Reduce Oxidative Damage

- Curcumin: yellow-pigmented component of tumeric, many beneficial functions.
- Easily passes through cell membranes & BBB.
- Immuno-stimulating, it stops formation and expression of free radicals in the brain, protects neurons from oxidative damage.
- Inhibits COX-2 and other inflammatory markers linked to neuronal death.
- In rats, curcumin treatment counteracted the effects of combined applications of high fat diet and brain injury in all experimental conditions.
- In another rat study, tumeric reduced oxidative damage, facilitated synaptic transmission, and counteracted cognitive impairment caused by TBI.

Reduce Oxidative Damage

- Based on study, curcumin supplement may provide neuroprotection and protection against cognitive impairment after TBI.
- In AD patients, tumeric decreased beta-amyloid plaques, delayed neuron degradation, improved overall memory and cognition.
- Indian citizens in 70's four times *less likely* to have AD than Americans in their 70's. Correlated w/ tumeric/curry intake.
- Poor absorption, co-supplement with piperine/pepper to increase bioavailability.
- C/I in biliary obstruction—stimulates bile secretion.

Reduce Oxidative Damage



Ginkgo Reduce Oxidative Damage

- Ginkgo: Leaf extract EGb 761 used for brain health.
- Ginkgo induces neuroprotective antioxidant compounds, needed against free radical damage.
- Ginkgo may also act to modulate signal transduction pathways involved in cell death, inhibit nitric oxide-induced toxicity, and reduce platelet-activating factor properties.
- 2000 review concluded Ginkgo shows promise in treating some of the neurologic sequelae associated with TBI, Alzheimer's, stroke, normal aging, edema, tinnitus and macular degeneration.
- May be effective in treating inflammation, and free-radical toxicity associated with TBI.

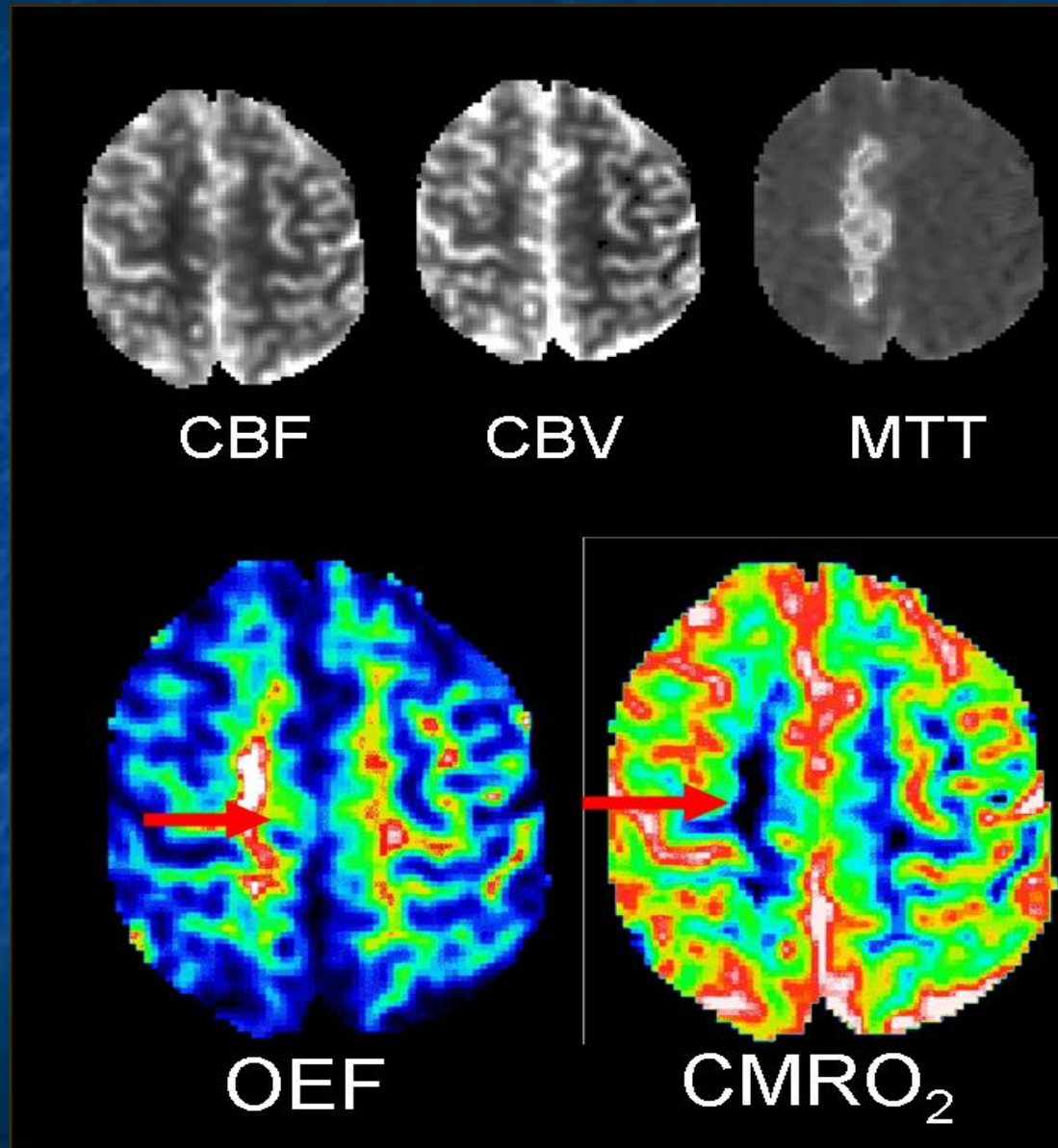
Reduce Oxidative Damage

- October 2008, Johns Hopkins researchers demonstrated that **daily doses of ginkgo (EGb761) in mice can prevent or reduce brain damage after an induced stroke.**
- Ginkgo treated mice had less neurological dysfunction and significantly smaller volumes of brain damage than untreated mice.
- Ginkgo is safe, caution in blood thinners.
- 2005 *British Journal of Clinical Pharmacology* showed ginkgo and ginger at recommended doses *did not* significantly affect clotting status, pharmacodynamics or pharmacokinetics of warfarin in healthy subjects.

Reduce Oxidative Damage

- Antioxidant effects of Gastrodia elata rhizome, known in Chinese medicine for its anti-convulsive effect.
- Its main constituents may have potential in the treatment of lipid peroxidation-associated neurological disease.

Promote Oxygenation & Perfusion



Promote Oxygenation & Perfusion

- Bring sufficient blood and oxygen to the tissues.
- L-arginine: An amino acid used to make the nitric oxide, a compound that relaxes blood vessels.
- In rat models of TBI, L-arginine helps restore cerebral blood flow and improve neurological outcome without increasing ICP.
- L-arginine prevents TBI-induced increases in cell inflammatory compounds in rat studies.
- L-arginine but not D-arginine prevented post-injury cerebral hypoperfusion.
- In TBI patients, citicoline helped memory rehabilitation by restoring blood flow to the lesion.
- Inadequate B12 or folic acid can *reduce* amounts of oxygen-carrying red blood cells to the brain.

Reduce Inflammation & Seizure Potential



Reduce Inflammation & Seizure Potential

- There is a proven link between chronic brain inflammation, increased cytokine formation, and neurodegeneration.
- Brain inflammatory processes may be a predisposing factor contributing to epilepsy and neuronal injury in seizures.
- In TBI, iron and hemoglobin released from injury are associated with generating compounds (ROS, RNS), involved in the animal model of seizures.
- Recent data suggest inflammation related to neurodegeneration is directly affected by nutrition.
- Intake of omega-3 fatty acids and levels of inflammation are inversely related.
- Add omega-3 fats, anti-inflammatory foods.

Reduce Inflammation & Seizure Potential

- **Choline:** Part of the Vitamin B complex, helps make up cell membranes and the neurotransmitter *acetylcholine*.
- In study of cognitive impairment following brain injury, rats were exposed to choline-supplemented diets or control for 2 weeks prior to induced TBI and throughout the recovery phase.
- **Choline supplement resulted in significant cortical tissue sparing, reduced brain inflammation.**
- Also a modest degree of gain in spatial memory.
- **Citicoline:** inhibits release of inflammatory arachadonic acid, may counteract the deposition of beta-amyloid.

Reduce Inflammation & Seizure Potential

- **Taurine**: A component of bile salts, involved in the development of the brain and retina.
- Crosses the BBB. In times of physical stress, body may not produce enough
- **Taurine is inhibitory neurotransmitter, helps prevent epileptic seizures, supports GABA function, and stabilizes membranes.**
- Taurine and can act as an antioxidant, important during ischemic reperfusion injury, inflammation, and brain swelling.
- In many models of oxidant-induced injury, taurine was shown to be tissue-protective and non-toxic.

Reduce Inflammation & Seizure Potential

- Creatine: A naturally-occurring organic acid, helps to supply energy to nerve and muscle cells.
- Pretreatment with alpha-lipoic acid or creatine showed neuroprotective or reduced seizure activity in animals.
- *Avoid alcohol* after TBI, or in seizure disorders, as it lowers the seizure threshold.

Reduce Inflammation & Seizure Potential



Reduce Inflammation & Seizure Potential

- Gastrodia elata was able to reduce seizures, oxygen free radicals, microglia activation, and apoptosis in induced epilepsy in rats.
- Antioxidants vitamin E/a-tocopherol, EGCG, Gastrodia elata shown to ravage ROS, RNS and prophylactic in epilepsy.
- Bacopa monniera treatment to epileptic rats significantly increased the anticonvulsive protein metabotropic glutamate-8 receptor (mGluR8) expression in the cerebellum, low during epilepsy, to near control rate.

Summary

Optimize Nutrition	Enhance Cognition	Reduce Oxidative Damage	Promote Oxygenation & Perfusion	Reduce Inflammation & Seizures
Low Carb Calories ASAP	Curcumin/Tumeric	O-3: DHA	L-Arginine	O-3: DHA & EPA
Balance BS/Insulin	Vitamin E	Resveratrol	Citicoline	Choline
Protein & BCAAs	O-3: DHA	Vitamin B Complex	Vitamin B Complex	Citicoline
Glutamine	Vitamin B Complex	Glutamine & Protein		Taurine
Lipids & MCTs	Citicholine	Blueberries		Creatine
O-3: DHA	Alpha-Lipoic Acid	Antioxidant Spices, Foods		Alpha-Lipoic Acid
Vitamin B Complex	Nootropics: Bacopa	Curcumin/Tumeric		Vitamin E
Probiotics	Gastrodia	Ginkgo/EGb 761		Gastrodia
Zinc	Ginkgo/EGb 761	Gastrodia		Bacopa

Future Food For Thought

- DMAE
- Galantamine/Galantbus nivalus
- Glisodin
- Huperzine A/Huperzia serrata
- Idebenone
- Phosphatidylserine/PS
- Picamilon
- Pyroglutamate
- Racetams
- Rhodiola
- S-Adenosylmethionine/SAMe
- Vinpocetine

“The human brain is a wonderful organ.
It starts to work as soon as you are born, and
doesn't stop until you get up to deliver a speech.”

George Jessel

Thank You!

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