Nutritional Medicine and the Nervous System: Part 2

Neuropathies, Concussion, Nervous System Toxicity, and Autism

Nutritional Medicine in Neuropathies

What Is Neuropathy?

- Neuropathy refers to general diseases or malfunctions of the nerves. Neuropathy is often classified according to the types or location of nerves that are affected or according to the disease causing it. (i.e. diabetic neuropathy).

Types of Neuropathy

- **Peripheral neuropathy:** Peripheral neuropathy is when the nerve problem affects the nerves outside of the brain and spinal cord, affects the nerves of the extremities- the toes, feet, legs, fingers, hands, and arms.
- **Cranial neuropathy:** Cranial neuropathy occurs when any of the twelve cranial nerves (nerves that exit from the brain directly) are damaged. Two common types of cranial neuropathy are optic neuropathy and auditory neuropathy.
- **Autonomic neuropathy:** Autonomic neuropathy is damage to the nerves that control the heart and circulation digestion, bowel and bladder function, the sexual response, and perspiration.

Causes of Neuropathy

Nerve damage may be caused by a number of different diseases, injuries, infections, and even vitamin deficiency states.

Diabetes: Diabetes is the condition most commonly associated with neuropathy. The risk of having diabetic neuropathy rises with age and duration of diabetes. Neuropathy is most common in diabetes who have had difficulty controlling their diabetes, or those who are overweight or have elevated blood lipids and high blood pressure. Forty to sixty percent of diabetics who have had the disease for 25 plus years, develops peripheral neuropathy. It is the most common peripheral neuropathy seen in clinical practice.

Diabetic Neuropathy

Etiology:

- Persistent hyperglycemia is thought to increase the polyol pathway, which results in accumulation of fructose and sorbitol that damage nerves. Advanced glycosylated end-products also contribute to inflammation and crystal deposits within the microcirculation that provides blood to peripheral nerves.

- Immunologic mechanisms also play a role in diabetic peripheral neuropathy due to **anti-neural antibodies** found in some diabetic patients. **Antiphospholipid antibodies** may also be present which damage the nerve cell membrane.

- Endoneural vascular insufficiency, due to decreased nitric oxide production (endothelial dysfunction) also contributes to diabetic peripheral neuropathy, with associated decrease ATP production affecting the sodium-potassium pumps, and often hyperhomocysteinemia (which also damages blood vessels and nerve fibers).

- Thickening of the blood vessel wall ultimately leads to compromised endoneurial blood flow. In addition to **high blood sugar, the ingestion of alcohol, smoking and exposure to heavy metals** can exacerbate diabetic peripheral neuropathy, as can certain genetic factors.

Signs and Symptoms: usually presents with stocking-and-glove distribution with sensory loss, dysesthesia (abnormal sensation to touch), and painful paraesthesia, most commonly in the lower extremities.

Common symptoms Include: tingling, prickling, or numbness, burning or freezing pain, sharp, stabbing or electric pain, extreme sensitivity to touch, muscle weakness and loss of balance and coordination.

Note: Hyperglycemia-induced ischemic and Auto-oxidative lipid peroxidation are suggested to play a key role in producing diabetic neuropathy

More Detailed Look at Interrelated Pathogenic Mechanisms In Diabetic Neuropathy:

- Hyperglycemia inhibits nitric oxide synthesis, resulting in impaired microvascular tone, reduced nerve blood flow, and endoneurial hypoxia. Endoneurial hypoxia is secondary to a reduction in nerve blood flow and increased endoneurial vascular resistance. **Much of the endoneurial microvascular damage and hypoxia is due to nitric oxide inactivation.**

- The hypoxic nerve can continue to function on glucose alone under anoxic circumstances via anaerobic glycolysis. Hyperglycemia increases nerve cell glycolysis and leads to increased flux of the polyol pathway, mediated by **aldose reductase** and **sorbitol dehydrogenase,** leading to accumulation of sorbitol and depletion of *myo*-inositol. Nevertheless, sorbitol *per se* is non-toxic and it seems likely that mechanisms other than nerve sorbitol accumulation cause neuropathy.

- Reduction of myo-inositol is associated with reduced Na^+-K^+-ATPase activity. **Myo-inositol is a key plasma membrane phospholipid**, signaling agent and preserves the function of Na^+-K^+-ATPase activity. Reduced Na^+-K^+-ATPase activity is shown to decrease amino acid uptake by cells, which impairs protein synthesis required to renew important neuronal structures (e.g. microtubules) as well as peptides and neurotransmitters. It also reduces intracellular potassium and may increase intracellular sodium, which have detrimental effects on cell function.

- Hyperglycemia also activates protein kinase (PKC), which promotes synthesis of diacylglycerol (DAG). The increased activity of PKC may impair endoneural blood flow.

- The increased availability of glucose in diabetes induces enhanced production of AGEs. This process is defined as auto-oxidative glycosylation and is considered the major cause of increased ROS production among diabetic subjects.

- Accumulation of advanced glycation end products (AGEs) that exert their damaging effects by binding to specific receptors on the surface of neurons. Binding of AGEs to their receptors causes oxidative stress and activates nuclear factor-κB (NF-κB). Hyperglycemia-induced oxidative stress induces programmed cell death of nerves, which contributes to the pathology of diabetic neuropathy. **Note that specific antioxidants and over expression of antioxidant enzymes can inhibit NF-κB activation**

- As diabetes has been associated with increased production and/or decreased clearance of ROS, oxidative stress has been suggested to contribute to defective nerve blood supply and endoneural oxidative damage.

- Increased nerve lipid peroxidation *in vivo*. The most reliable index of increased oxidative stress is reduction in GSH – a common finding in diabetic and other types of nerve damage.

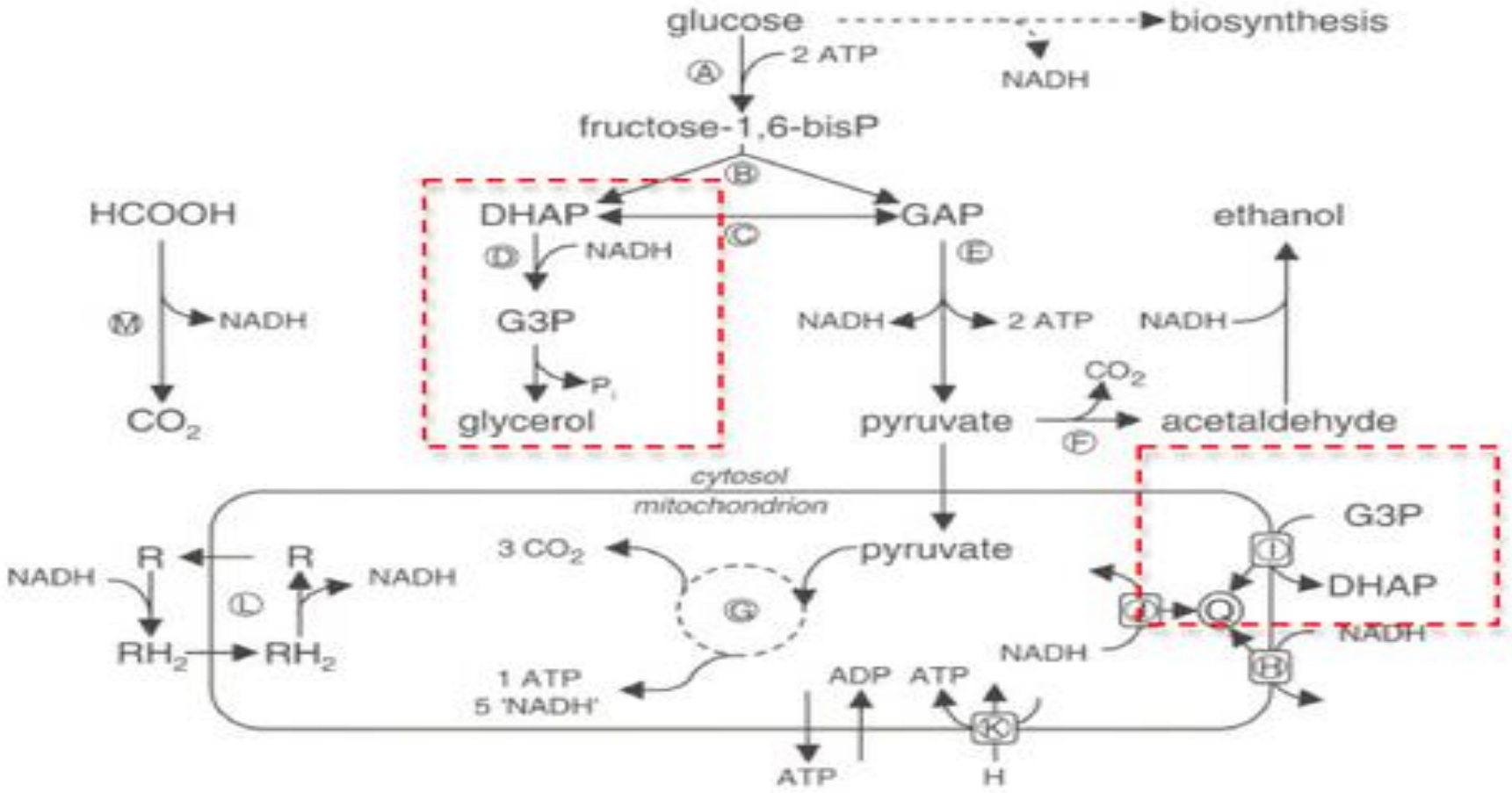
- Alterations in mitogen-activated protein kinases (MAPKs) results in a signaling cascade involved in the pathogenesis of peripheral diabetic neuropathy.

- Abnormal Ca^{2+} homeostasis and signaling

Reference:

- Vallianou, N, Evangelopoulos and Koutalas. Alpha-lipoic Acid and diabetic neuropathy. Rev Diabet Stud. 2009 Winter; 6(4): 230–236. Published online 2010 February 10. 10.1900/RDS.2009.6.230

Hyperglycolysis in Nerves increases Free Radical Formation in Cytosol from DHAP to Glycerol-3-Phospate (glycerol-3-phosphate dehydrogenase) and Conversion of Pyruvate to Acetyl-CoA (pyruvate dehydrogenase). Insulin not required for glucose to enter nerve cells.



Non-Supplement, Natural Treatments for Diabetic Neuropathy

- **Strict glycemic control** may reduce incidence of diabetic neuropathy by to 64%. Multiple studies have shown that following a whole food, low-fat, high fiber, plant-based diet, along with exercise alone can decrease type 1 diabetic medications by up to 40% or eliminate them for type 2 diabetics. Daily walks for 30-60 minutes should be a core aspect of diabetes management if the patient is unwilling to do more vigorous types of exercise. (Pritikin N – showed this in the 1970's)

- **Yoga** has been shown to help improve various diabetic biomarkers and improve nerve conduction velocity in patient with neuropathy, sometimes in as little as 9-10 days (2-3 times per wk for 30-90 minutes). Daily practice is most beneficial. However **heated yoga should be avoided in diabetics with known heart or retinopathy problems. (High correlation - neuropathy and retinopathy)**

- **Tai Chi** – has also improved nerve conduction velocity as well as coordination, sensation and balance in diabetic neuropathies, and has improved other biomarkers (HbA1c).

- **Biofeedback and Progressive Relaxation** – have been shown to improve blood circulation to extremities and reduce pain in diabetic peripheral neuropathy.

Reference:

Integrative Medicine (Third Edition) David Rakel M.D. Elsevier Saunders (2012) P. 104-105

Other Causes of Neuropathy

- **Vitamin deficiencies:** Deficiencies of vitamins B12 and folate, as well as other B-vitamins can cause damage to nerves.
- **Vitamin B6 Toxicity –** neurotoxicity, including neuropathy
- **Autoimmune neuropathy:** Autoimmune diseases such as rheumatoid arthritis, systemic lupus, and Guillain-Barre syndrome can cause neuropathies.
- **Infection:** Some infections, including HIV/AIDS, Lyme disease, leprosy, and syphilis, can damage nerves.
- **Post-herpetic neuralgia:** Post-herpetic neuralgia, a complication of shingles (varicella-zoster virus infection) is a form of neuropathy.

- **Alcoholic Neuropathy:** Alcoholism is often associated with peripheral neuropathy. Although the exact reasons for the nerve damage are unclear, it probably arises from a combination of damage to the nerves by alcohol itself along with the poor nutrition and associated vitamin deficiencies (i.e. vitamin B1) that are common in alcoholics.

- **Genetic or inherited disorders:** Genetic or inherited disorders can affect the nerves and are responsible for some cases of neuropathy. Examples include Friedreich's ataxia and Charcot-Marie-Tooth disease.

- **Amyloidosis:** Amyloidosis is a condition in which abnormal protein fibers are deposited in tissues and organs. These protein deposits can lead to varying degrees of organ damage and may be a cause of neuropathy.

- **Uremia:** Uremia (a high concentration of waste products in the blood due to kidney failure) can lead to neuropathy.

- **Toxins and poisons can damage nerves.** Examples include, gold compounds, lead, arsenic, mercury, some industrial solvents, nitrous oxide, and organophosphate pesticides.

- **Drugs or medication:** Certain drugs and medications can cause nerve damage. Examples include cancer therapy drugs such as vincristine (Oncovin, Vincasar), and antibiotics such as metronidazole (Flagyl), and isoniazid (Nydrazid, Laniazid).

- **Trauma/Injury:** Trauma or injury to nerves, including prolonged pressure on a nerve or group of nerves, is a common cause of neuropathy. Decreased blood flow (ischemia) to the nerves can also lead to long-term damage. **Oxidative stress has also been shown to play a role pressure-induced neuropathy and animal studies demonstrate that N-acetylcysteine can elevate nerve cell glutathione levels and thereby reduce pain associated with pressure or impingement neuropathies -** http://onlinelibrary.wiley.com/doi/10.1016/j.ejpain.2005.08.006/full

- **Tumors:** Benign or malignant tumors of the nerves or nearby structures may damage the nerves directly, by invading the nerves, or cause neuropathy due to pressure on the nerves.

- **Idiopathic:** Idiopathic neuropathy is neuropathy for which no cause has been established. The term idiopathic is used in medicine to denote the fact that no cause is known.

References: Neuropathies

- Integrative Medicine (Third Edition) David Rakel. Elsevier Saunders (2012) P. 104-105
- https://www.emedicinehealth.com/neuropathy/article_em.htm#types_of_neuropathy

Supplements in Neuropathy Treatment

Alpha-Lipoic acid

Dosage: 600 mg, 1-3X daily (Human Clinical Studies). Start with 600 mg/d and increase slowly over next two weeks

Mechanisms : Approved treatment for diabetic neuropathy in Germany since 1959. Helps repair nerve damage and supports nerve function in 2 important ways:

1. **Nerve Energy Production** – **via Pyruvate Dehydrogenase (PD)**– Acetyl -CoA synthesis to initiate Krebs cycle. PD also requires CoA (Pantothenic acid), TDP (thiamine), FAD (riboflavin) and NAD (niacin).

   Nerve cells normally highly dependent on **oxidative phosphorylation of glucose** for energy production, thus optimal function of PD is essential for function and nerve repair

2. **Water and Fat Soluble Antioxidant** – enters nerve cell membrane, protects mitochondria and nerve cell membrane from free radical damage and inflammation. Halting mitochondrial damage, enables mitochondrial DNA to repair mitochondrial damage, which ultimately improves ATP synthesis required for nerve repair mechanisms to be effective in reversing pathology.

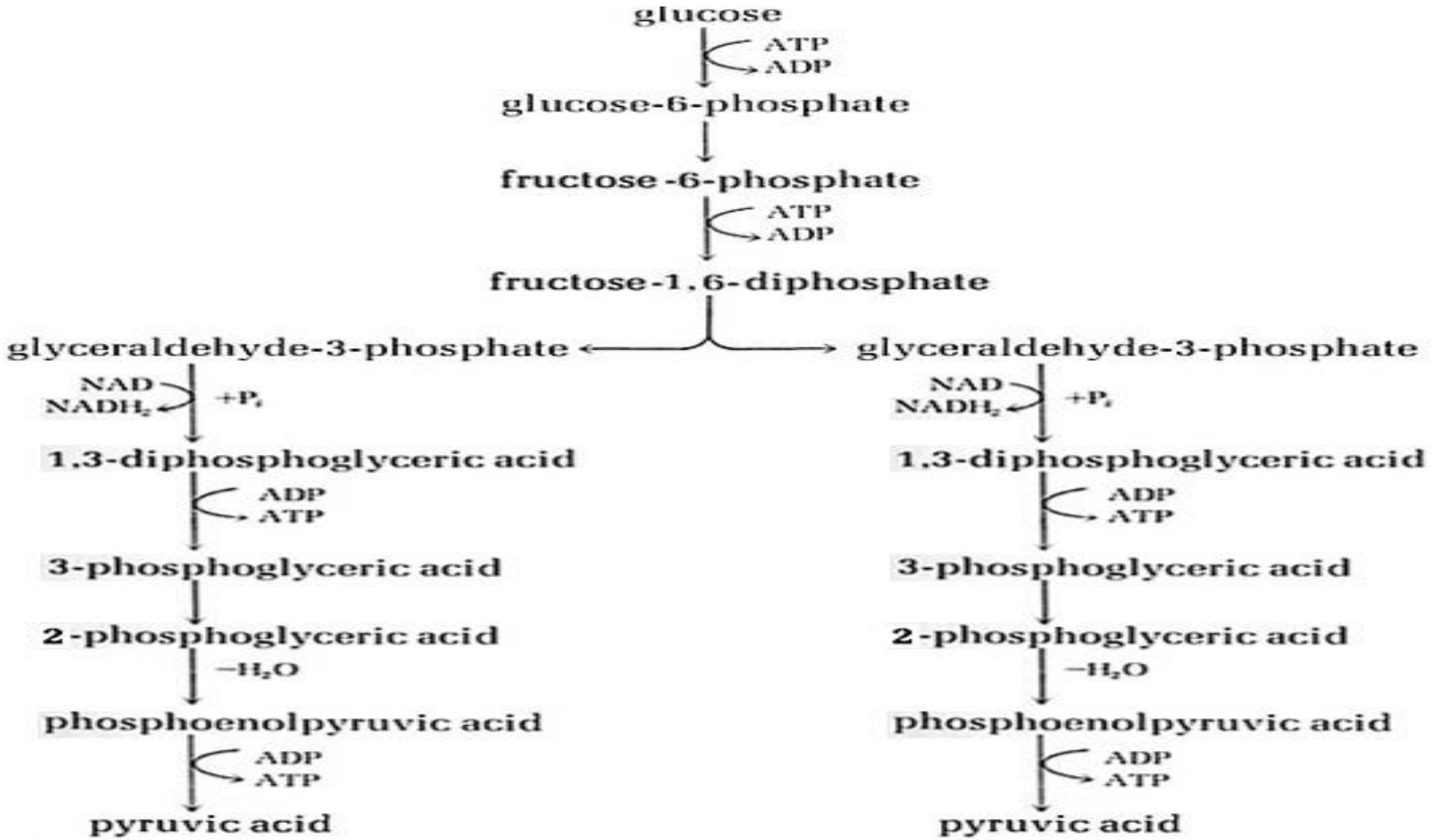
Energy Production in Nerves Relies Heavily on Pyruvate Dehydrogenase and Its 5 Coenzymes

- The additional energy required by nerve cells to repair internal nerve damage is highly dependent upon the ability of nerve cells to convert pyruvate to acetyl-coA within the mitochondria of the cell. Unlike many peripheral cells, nerve cells are almost exclusively dependent upon glucose for energy (although they can switch to ketones to a large degree in a low blood sugar or uncontrolled diabetic state).
- Within nerve cells, glucose first undergoes glycolysis to form pyruvate (generating a minimal amount of ATP energy for nerve cell function and repair). In turn, pyruvate passes from the cytosol into the mitochondria where it is converted to acetyl-coA by the enzyme pyruvate dehydrogenase (PD). This is an important step as acetyl-CoA then reacts with oxaloacetate to from citrate, enabling the Krebs cycle to generate a significant amount of ATP energy via oxidative phosphorylation. What often gets overlooked is the fact that pyruvate dehydrogenase (PD) requires the presence of five coenzymes in order to catalyze this vital reaction in nerve energy production. The five coenzymes required by PD include four B-vitamins and alpha lipoic acid:

- Vitamin B1 (thiamine) - in the form of thiamine diphosphate or TDP – previously known as TPP
- Vitamin B2 (riboflavin) – in the form of FAD (flavin adenine dinucleotide)
- Vitamin B3 (niacin) – in the form of NAD (nicotinamide adenine dinucleotide)
- Pantothenic Acid – in the form of coenzyme A (CoA)
- Alpha Lipoic Acid

Reference: http://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/krebs.htm

Glycolysis


glucose
ATP
ADP
glucose-6-phosphate
fructose-6-phosphate
ATP
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fructose-1,6-diphosphate
glyceraldehyde-3-phosphate
glyceraldehyde-3-phosphate
NAD
NADH2
+Pi
1,3-diphosphoglyceric acid
ADP
ATP
3-phosphoglyceric acid
2-phosphoglyceric acid
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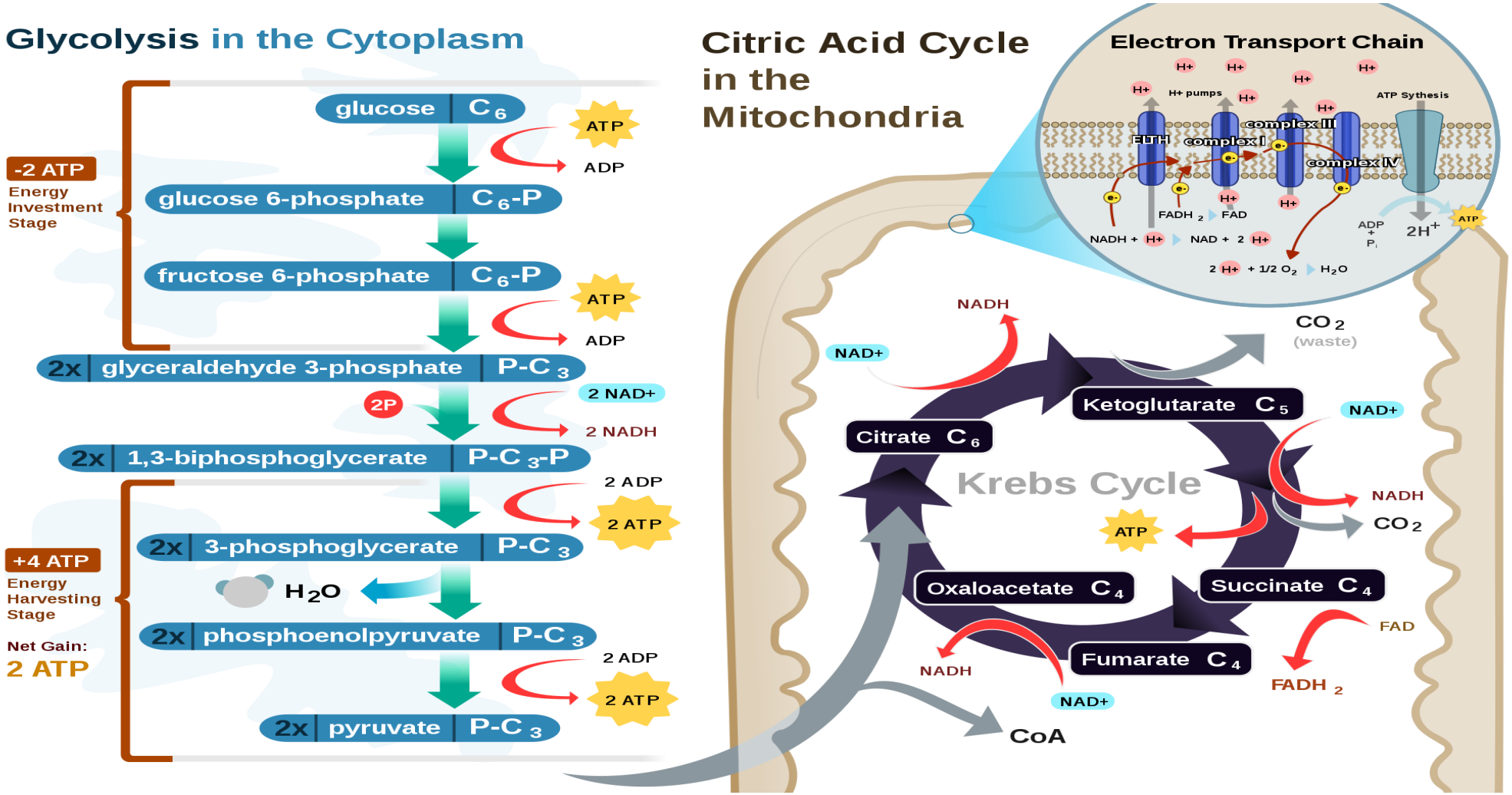
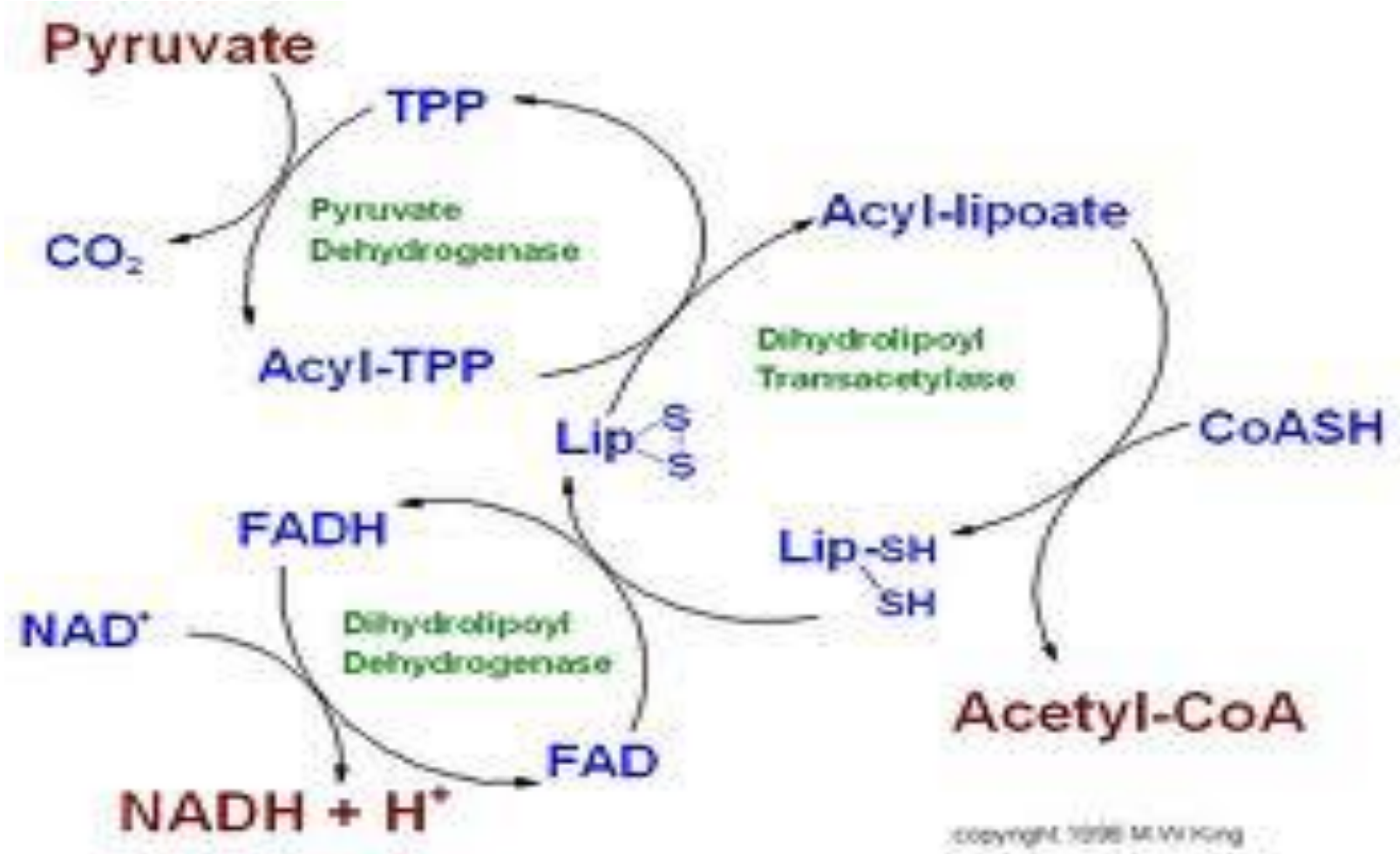
phosphoenolpyruvic acid
ADP
ATP
pyruvic acid

Pyruvate Enters Krebs cycle and Converted to Acetyl-CoA by Pyruvate Dehydrogenase (PD)



Pyruvate Dehydrogenase and Coenzymes



Oral Treatment with Alpha-lipoic Acid Studies:

- Five week study showed improved neuropathic symptoms and deficits in 187 patients with **diabetic symmetrical polyneuropathy.** An oral dose of 600 mg once daily seems to provide the optimum risk-to-benefit ratio in the SYDNEY 2 trial. The adverse effects (mainly nausea) with the 1,200 mg dose daily occurred in 21% of patients, somewhat higher than that observed in the ALADIN I (15%) and ALADIN II study (7%), with the same dose of alpha-lipoic acid.

- In the seven-month ALADIN III trial, 509 subjects received either 600 mg of alpha-lipoic acid or placebo. While no significant difference was noted in subjective symptom evaluation among the groups, treatment with alpha-lipoic acid was associated with **improved nerve function.**

- In the ISLAND Study, 300 mg of alpha-lipoic acid was applied as monotherapy and in combination with 150 mg imbesartan daily. There was a significant increase in endothelium-dependent flow-mediated vasodilation of the brachial artery, by 44% and 75% respectively, compared with placebo treatment after four weeks. This effect was accompanied by reductions in plasma levels of interleukin-6 and plasminogen activator-1, **suggesting that alpha-lipoic acid may improve endothelial dysfunction via anti-inflammatory and antithrombotic mechanisms**

- Other studies have reported good results in diabetic neuropathy using a daily dosage of 600 mg, three times daily

- Alpha-lipoic acid has also been shown to down-regulate the expression of cell-adhesion molecules ICAM-1 and VCAM-1 in a dose-dependent manner. These observations might be of preventive and/or therapeutic benefit in arteriosclerosis and other inflammatory disorders.

- Clinical and post-marketing surveillance studies have revealed a highly favorable safety profile of the alpha-lipoic acid.

Reference: Vallianou, N, Evangelopoulos and Koutalas. Alpha-lipoic Aaid and diabetic neuropathy. Rev Diabet Stud. 2009 Winter; 6(4): 230–236. Published online 2010 February 10. 10.1900/RDS.2009.6.230

Alpha-Lipoic Acid (ALA): Other Considerations

- Decreased synthesis with age – allows increased free radical damage to neuronal mitochondria and decreased ATP synthesis. **Mitochondrial dysfunction is a common finding in Diabetes**

- Supplementation with Alpha-Lipoic acid shown to **improve insulin sensitivity** and glucose control in several human studies.

- ALA – also **recycles other antioxidants** (vitamin C, Glutathione, vitamin E and Coenzyme Q10) and may increase cell levels of catalase and superoxide dismutase in peripheral nerves.

- ALA – also chelates transition metals (iron, copper) and heavy metals, decreasing heavy metal nerve toxicity and free radical generation.

- By decreasing oxidative stress, it improves endoneurial blood flow and nerve conduction velocity.

- Has improved autonomic neuropathy, diabetic polyneuropathy and other peripheral neuropathies and cranial neuropathies.

- Most patients see improvement within first 2-3 weeks.

Reference: Integrative Medicine (Third Edition) David Rakel. Elsevier Saunders (2012) P. 107

Vitamin B12

Vitamin B12 is well known for its role in myelin synthesis and repair. Vitamin B12 is a coenzyme for methylmalonyl-CoA mutase (MUT) required in myelin synthesis.

Vitamin B12 converts methylmalonyl-CoA to succinyl Co A. Excessive methylmalonyl-CoA prevents normal fatty acid synthesis, required to form the myelin sheath around the nerve cells.

As such, some impressive research shows that vitamin B12 supplementation has been helpful in treating certain neuropathies and improving some of the symptoms of multiple sclerosis (a demyelinating disease).

Vitamin B12

Dosage: 500 mcg, 3-4X daily (Human Clinical Studies). Along with B-50 Complex. Best results using **Methylcobalamin** form of vitamin B12

Mechanism:

- **Myelin Synthesis and Repair** - vitamin B_{12} is coenzyme for methylmalonyl-CoA mutase (MUT) required in myelin synthesis, **converting methylmalonyl-CoA to succinyl-Co A.**

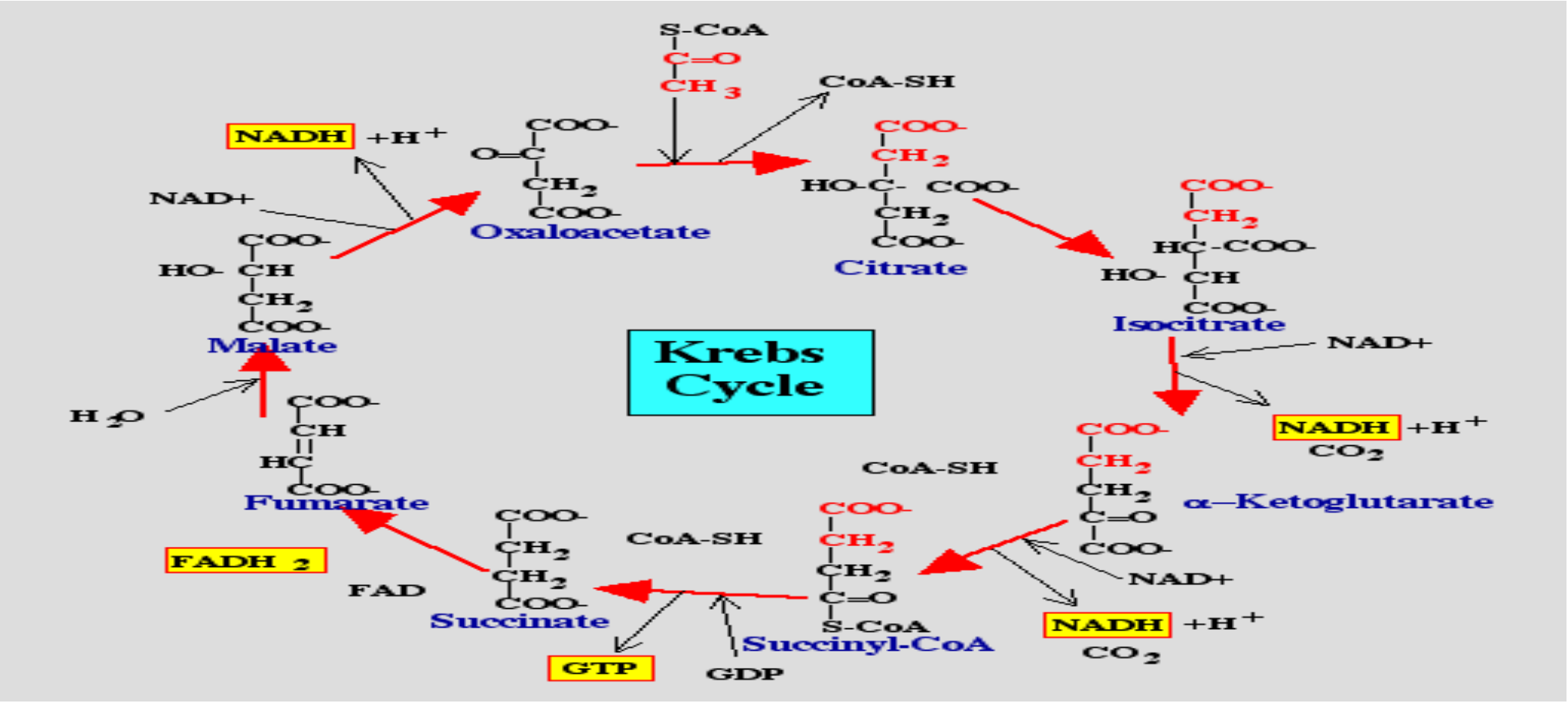
  Excessive methylmalonyl-CoA prevents normal fatty acid synthesis, required to form the myelin sheath around the nerve cells.

B12 Deficiency well known to cause neuropathies via decreased myelin synthesis.

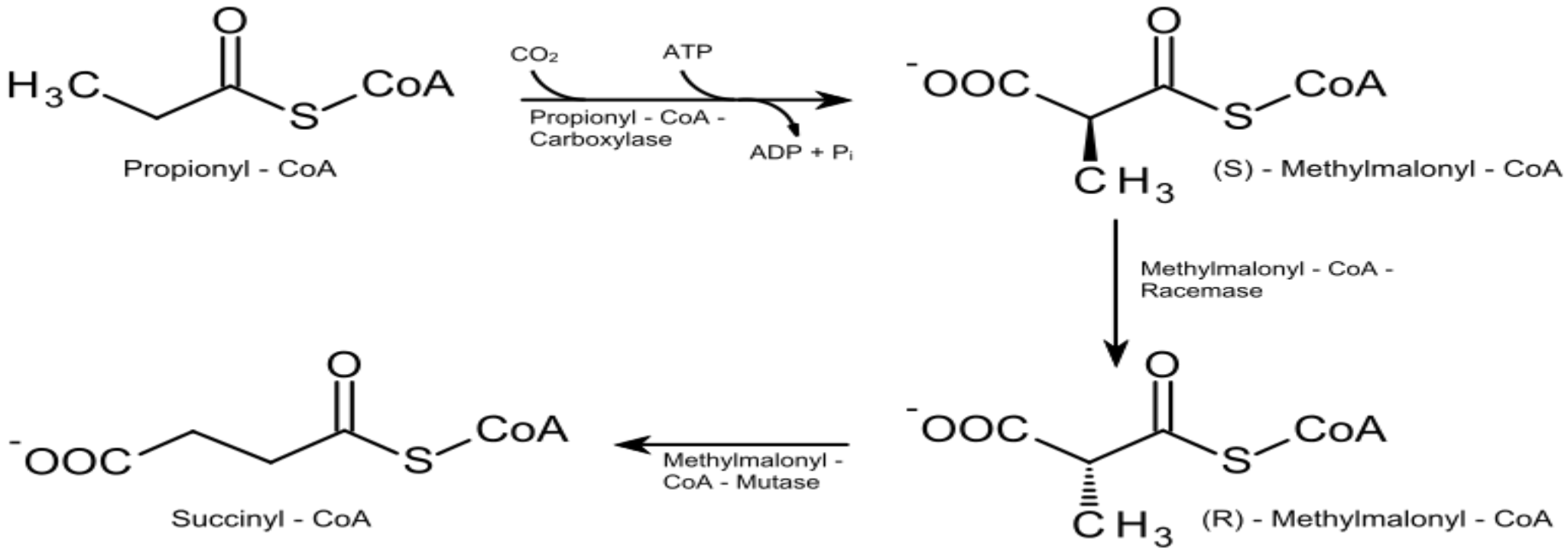
References: Vitamin B12:

1. Integrative Medicine (Third Edition) David Rakel. Elsevier Saunders (2012) P. 108
2. Kira J, Tobimatsu S, GotoI. Vitamin B_{12} metabolism and massive-dose methyl vitamin B_{12} therapy in Japanese patients with multiple sclerosis. Int Med 1994;33:82-6.
3. Modern Nutrition in Health and Disease – 10th edition. Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ (publisher Lippincott Williams & Wilkins – 2006) pages: 485-490
4. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2995210/
5. http://www.ncbi.nlm.nih.gov/pubmed/15896807
6. http://www.anaturalhealingcenter.com/documents/Thorne/articles/multiple_sclerosis.pdf

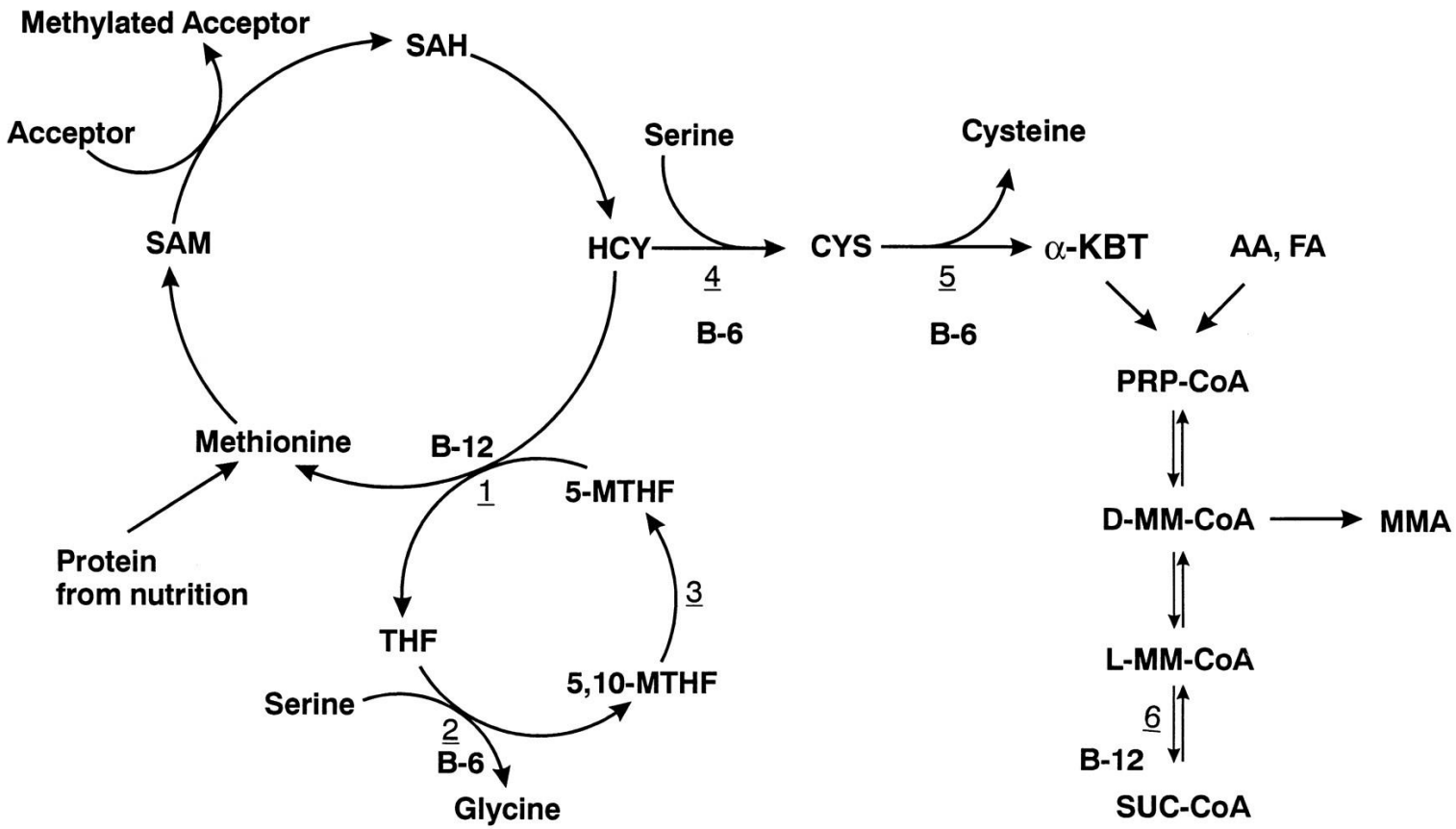
Note Krebs cycle Intermediates – some Succinyl-CoA dependent on B12, Pantothenic Acid for synthesis



Conversion of Methylmalonyl-CoA to Succinyl-CoA requires vitamin B12



Note Vitamin B12 – Methylmalonyl-CoA to Succinyl-CoA (also FA, B6 in other rxns)



Pantothenic acid

Dosage: 100- 500 mg per day (Human Clinical Studies)

Mechanisms (CoA-dependent reactions):

1. Nerve Energy Metabolism:

- **Pyruvate dehydrogenase** – forming acetyl CoA
- Conversion of **alpha-ketoglutarate** to **succinyl CoA** – **Krebs cycle** and **myelin synthesis**
- Oxidative degradation of certain amino acids also requires CoA to **transform AA into Acetyl-CoA**, as substrates for the Krebs cycle and energy production

2. Myelin synthesis - **Acyl-coenzyme A (CoA) synthetase** present in myelin, suggesting capacity to integrate free fatty acids into myelin lipids

3. Acetylcholine Synthesis – important neuro-muscular junction neurotransmitter for muscle contraction

Reference: http://www.lef.org/prod_hp/abstracts/php-ab415.html#1

Benfotiamine – **Fat Soluble Vitamin B1 (Thiamine)**

- Absorbed up to 3.6- 5x times greater than vitamin B1, and associated with a 120-fold greater increase in levels of metabolically active TDP (thiamine diphosphate)

- Its lipid solubility enables it to penetrate nerve membranes more efficiently than ThTP (thiamine triphosphate).

- Shown to reduce peripheral neuropathy symptoms and increase nerve conduction in various studies.

Dosage: 150-300 mg/d, 2X daily (Human Clinical Studies)

Mechanisms and Other Conditions:

1. **Pyruvate Dehydrogenase** – Energy production (Krebs cycle)
2. **ThTP** – required for nerve conduction in non-coenzyme role
3. **Suppresses activation of NF-kb** (anti-inflammatory and inhibits inflammatory cytokine release) – used successfully to **treat uveitis** (10-15% of all blindness) in this capacity.
4. **Diabetic Retinopathy** – human studies show improvement

Reference: Yadav UCS, Subramanyan S, Ramana KV. Prevention of endotoxin-induced uveitis in rats by benfotiamine, a lipophilic analogue of vitamin B1. Investigative Opthalmology & Visual Science. 2009. 50(5): 2276-2282.

- In certain jurisdictions Benfotiamine is a supplement and in other jurisdictions it is a drug, requiring a prescription.

References: Benfotiamine

1. Stracke H, Lindemann A, Federlin K. "A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy." Exp Clin Endocrinol Diabetes. 1996;104(4):311-6.
2. Winkler G, Pál B, Nagybéganyi E, Ory I, Porochnavec M, Kempler P. "Effectiveness of different benfotiamine dosage regimens in the treatment of painful diabetic neuropathy." Arzneimittelforschung. 1999 Mar;49(3):220-4.
3. Integrative Medicine 3rd edition. Rakel D (published by Elsevier Saunders – 2012) page: 108

Acetyl-L Carnitine (ALC)

- Supplementation with acetyl-L carnitine has been shown to increase nerve membrane phospholipid synthesis and to increase synthesis of the neurotransmitter acetylcholine. For muscle contraction to occur motor nerves must synthesize and release acetylcholine. The binding of acetylcholine to the muscle membrane allows for the initiation of an action potential, which initiates muscle contraction. Human studies using acetyl-L carnitine to treat various neuropathies have used a dosage of 500 – 1000 mg, three times daily.

- ALC is the ester acetylated form of the amino acid L-carnitine. L-carnitine transports fatty acids across the mitochondrial membrane to allow beta-oxidation to occur, which generates ATP energy aerobically. As such, the final step in the synthesis of ALC takes place in the mitochondrial matrix by the enzyme acetyl-L-transferase, which uses the substrates carnitine and acetyl-CoA.

- As an integral compound in mitochondrial function, ALC is widely distributed throughout tissues, with the highest concentrations found in cardiac and skeletal muscle. The brain also has high levels, and ALC has been shown to influence neurotransmitters, including **acetylcholine and dopamine.**

- ALC may also prevent neural degeneration related to aging in the brain through the preservation of the neurotrophin, nerve growth factor (NGF). These actions of ALC have been known for decades and account for the popular use of ALC as an anti-aging or memory-supportive nutrient.

Acetyl-L-Carnitine and Acetylcholine Synthesis

- Acetyl-L-carnitine absorbed from food is broken down in plasma by esterases, to become L-carnitine. Richest source is red meat and dairy products, but many foods contain some L-carnitine or acetyl-l-carnitine

- The body also synthesizes L-carnitine from L-lysine and methionine.

- L-carnitine shuttles fatty acids from the cytosol into the mitochondria for oxidation and energy production.

- **Acetyl-L- carnitine is synthesized in mitochondria from L-carnitine and unused acetyl-CoA by carnitine O-acetyltransferase**

- **Acetyl-L-carnitine provides a way to carry these acetyl groups through the mitochondrial membranes back out into the cytosol.**

- In brain and other nerve tissues, this acetyl group export by acetyl-L-carnitine out of the mitochondria into the cytosol is important in maintaining normal levels of acetyl groups for the **production of acetylcholine and other acetylated neurotransmitters, that are so crucial for normal brain and nerve function**

- In the early 1990s the positive influence on neurotransmitter synthesis was proposed as the mechanism of ALC's anti-nociceptive effect (reducing sensitivity to painful stimuli).

- More recently it has been discovered that ALC's anti-nociceptive effects also involve direct actions at the dorsal root ganglia or peripheral axonal synapses.

- In addition to reducing the perception of pain, there is also evidence suggesting that ALC acts as a neuro-protectant and neuro-regenerative agent. This dual action of both blocking pain perception and protecting the nerve from further damage suggested that ALC would be an ideal candidate to include in the treatment of peripheral neuropathy.

A number of clinical trials have shown positive effects when ALC has been used to treat various forms of peripheral neuropathy. ALC has reduced pain and improved nerve function in clinical trial involving patients suffering from:

1. **Chemotherapy-Induced Peripheral Neuropathies** (CIPN) – countering the impact of various combinations of chemotherapy drugs on nerve damage.
2. **Human Immunodeficiency Virus (HIV)–**Associated Peripheral Neuropathy - caused by nucleoside reverse transcriptase inhibitor drugs used in treatment of HIV.
3. **Diabetic Peripheral Neuropathy**
4. **Compression-Induced Peripheral Neuropathy**

In summary ALC demonstrates multi-modal effects in the treatment of peripheral neuropathies. Some of these mechanisms of action of including positive effects on circulating neurotrophins, mitochondrial function (including anti-apoptotic effects), and synaptic transmission influencing both nerve structure/ function and patient perception of neuropathic symptoms.

- Clinical trials of several prominent causes of peripheral neuropathy suggest oral doses from 1,000 mg daily to 3,000 mg daily are effective for symptom relief in a majority of patients. Electrophysiological testing and skin biopsies substantiate the regenerative capacity of ALC on nerve innervation. Tolerance to ALC appears to be excellent with mild, infrequent side effects, including insomnia and gastric irritation.

Reference: Kaczor T. The therapeutic effects of Acetyl-L-Carnitine on peripheral neuropathy: A review of the literature. Natural Medicine Journal. 8/1/2010. http://www.naturalmedicinejournal.com/article_content.asp?edition=1&section=2&article=77

Acetyl-L-Carnitine

Dosage – 500-1000 mg, 3X daily (Human Clinical Studies)

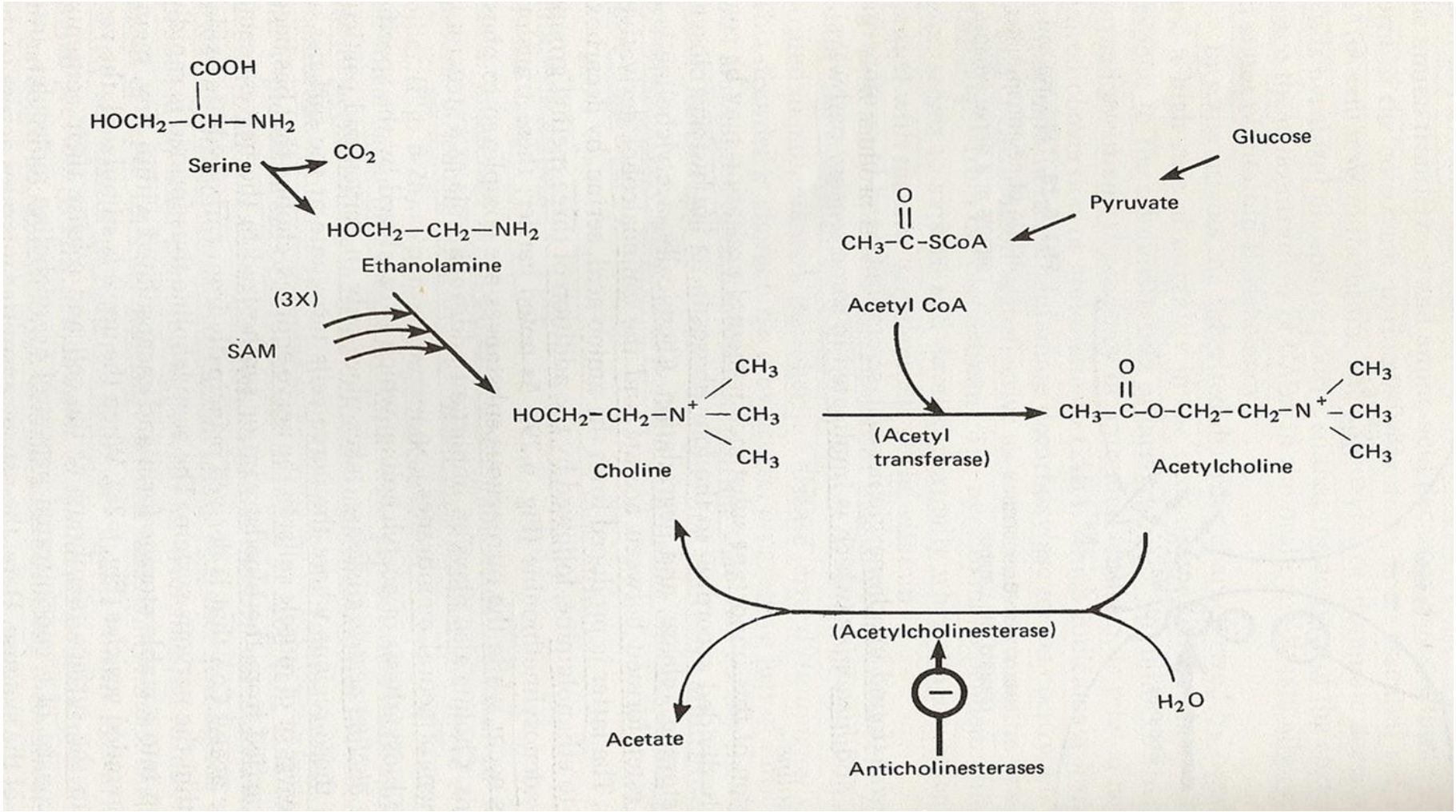
Basic Mechanisms:

1. Synthesis of Nerve Cell Phospholipids – nerve conduction

2. Increases Acetylcholine Synthesis

- **Note**: acetylated form required to cross blood-brain barrier, but L-Carnitine is sufficient to enter most other cells in body.

Acetylcholine: most people experience a decrease in acetylcholine after 55 due to decreased brain synthesis of choline.



Other Functions of Acetyl-L-Carnitine

- Antioxidant, protecting the nerve membrane from oxidative damage
- Other nerve membrane protective properties.
- Animal studies indicate that acetyl-L-carnitine preserves normal levels of nerve growth factor in brain tissue during aging.
- Human studies indicate that acetyl-L-carnitine increases cerebral blood flow

Reference: http://www.douglaslabs.ca/pdf/pds/82730.PDF

Curcumin

- Curcumin is principal curcuminoid found in the spice turmeric, and has recently been studied for its role in the treatment of various central nervous system disorders. Curcumin demonstrates neuroprotective action in Alzheimer's disease, tardive dyskinesia, major depression, epilepsy, and other related neurodegenerative and neuropsychiatric disorders.

- In regard to peripheral neuropathy curcumin has been shown to possess anti-inflammatory properties which include its inhibitory effect on the production of inflammatory interleukin-8 (IL-8), interleukin-1β (IL-1β) and TNF-α levels.

- Animal studies using diabetic peripheral neuropathy models have shown that supplementation with curcumin attenuated many of the peripheral neuropathy symptoms typically associated with diabetic neuropathy. Some researchers have concluded that curcumin is a novel anti-nociceptive agent and can be used as a therapeutic option in the treatment of neuropathic pain associated with diabetes mellitus

- Other experimental studies using curcumin in the treatment of diabetic neuropathy showed that curcumin supplementation also enhanced the glucose lowering effect of insulin and protects against the onset of diabetic neuropathy.

Reference: Kulkarni SK and Dhir A. An overview of curcumin in neurological disorders. Indian J Pharm Sci. 2010 Mar-Apr; 72(2): 149–154. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929771/

Curcumin (from Turmeric)

Dosage: 500 – 1000 mg, 3X daily (Human Clinical Study)

Basic Mechanisms

Natural Anti-inflammatory via prostaglandins, and inhibits NF-kb, and inflammatory cytokines

- Shown to help to attenuate diabetic neuropathy

Reference: https://www.ncbi.nlm.nih.gov/pubmed/24315931

Curcumin in Animal Models of Diabetic Neuropathy

- Diabetic neuropathic pain, the common complication of diabetes, is one of the most difficult types of pain to treat.

- Approximately 50% of people with diabetes will eventually develop nerve damage in some stage of life.

- This pain arises due to damaging nerves as a result of high blood sugar levels (hyperglycemia) and related deposition of advanced glycosylated end-products (AGE-proteins) in the microcirculatory blood vessels – causing inflammation and microvascular damage, as well as other pathophysiological events described previously.

- The fact that curcumin possesses anti-inflammatory properties which included its inhibitory effect on the production of interleukin-8 (IL-8), interleukin-1β (IL-1β) and TNF-α levels prompted assessment of curcumin evaluation in animal models of diabetic neuropathy.

- In theses studies, chronic administration of curcumin reversed an increase in TNF-alpha levels in diabetic rats. Moreover, curcumin also reversed an increase in nitrite concentration induced due to streptozotocin. Streptozotocin (STZ) is a compound that has a preferential toxicity toward pancreatic β cells.

- In a similar study, curcumin in association with insulin significantly attenuated thermal hyperalgesia and the hot-plate latencies.

References:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929771/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857752/

Vitamin E

- Some small trials have shown that vitamin E supplementation was able to attenuate or prevent peripheral neuropathy caused by chemotherapy drugs (six courses of cumulative cisplatin, paclitaxel, or their combination), when given **prophylactically during chemotherapy and 3 months after its cessation**.

- It is known that vitamin E deficiency causes neuropathy and that vitamin E protects nerve cell membranes and mitochondria from oxidative damage.

- Chemotherapy-induced peripheral neuropathy (CIPN) is a major side effect of many commonly used chemotherapeutic agents, including platinum drugs, taxanes, epothilonesand vinca alkaloids, and also newer agents such as bortezomib and lenolidamide. Vinca alkaloids, cisplatin, and taxanes are the drugs that commonly cause chemotherapy-induced peripheral neuropathy, **with incidences of CIPN from these agents ranging from 30% to 40%.**

- Some evidence strongly suggests that **intravenous calcium and magnesium** therapy can attenuate the development of oxaliplatin-induced CIPN, without reducing treatment response. Some studies show that vitamin E may also attenuate the development of CIPN.

- The daily dosage of vitamin E used in these studies was 400-600 IU per day.

References:

- Modern Nutrition in Health and Disease – 10th edition. Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ (publisher Lippincott Williams & Wilkins – 2006) pages: 403-405
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- http://ac.els-cdn.com/S1543291213601691/1-s2.0-S1543291213601691-main.pdf?_tid=4d2b8a68-2c60-11e3-83c8-00000aab0f6c&acdnat=1380827967_3d9576d76872750a867e00d96fef08bc
- http://ac.els-cdn.com/S1543291213601691/1-s2.0-S1543291213601691-main.pdf?_tid=4d2b8a68-2c60-11e3-83c8-00000aab0f6c&acdnat=1380827967_3d9576d76872750a867e00d96fef08bc
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3329941

Vitamin E

Dosage – Typically use 600 IU per day (Human Clinical Studies)

- Shown to protect against chemotherapy-induced peripheral nerve damage

http://www.neurology.org/content/64/1/26.short

Primary Mechanisms:

1. Vitamin E deficiency causes neuropathy
2. Vitamin E protects nerve cell membrane from oxidative damage
3. Vitamin E protects mitochondria membrane from oxidative damage

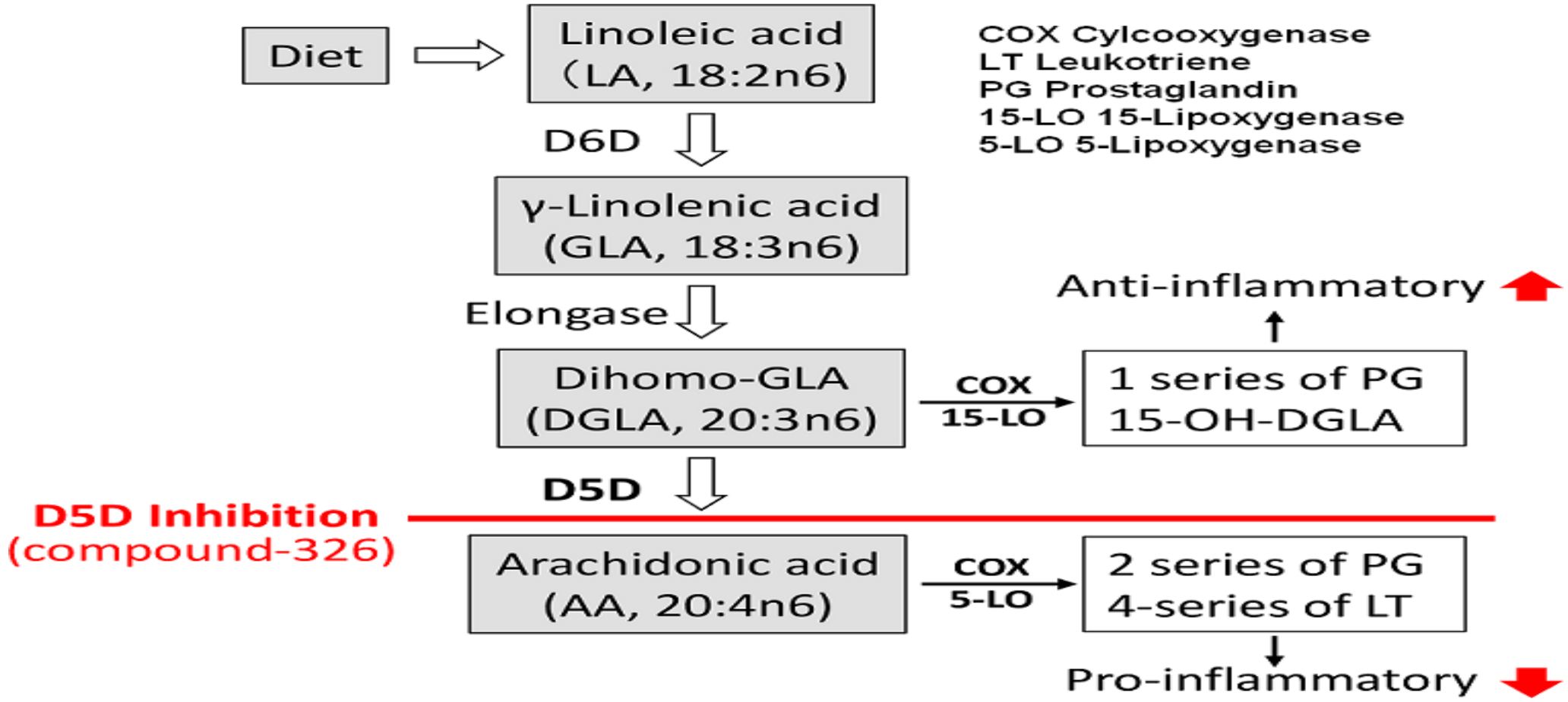
Gamma Linolenic Acid (GLA)

- Studies confirm that the first step in the conversion of the essential fatty acid (EFA) linoleic acid to gamma-linolenic acid (GLA) is impaired in diabetics. This results from a deficit of the enzyme delta-6-desaturase.

- In more severe cases essential fatty acid metabolism is impaired in two places, which is caused by a production deficit of the delta 5-desaturase enzyme, further down the conversion chain.

- The result of this broken process is shortage of GLA and its metabolites; prostacyclin and PG-1 prostaglandins. **Diabetic neuropathy is a progressive disease that is strongly associated with chronic deficiency of prostacyclin and prostaglandin-series 1 synthesis.** This is central to the pathogenesis of diabetic neuropathy.

Note: Delta-6 Desaturase Enzyme



- In addition to consequences on the nerve cell membrane, the very low levels of prostacyclin/prostaglandins PG-1 among diabetics also results in the membranes of red blood corpuscles of diabetics to become brittle and unable to be deformed.

- The consequence is that the oxygen-carrying corpuscles are less able to squeeze into the small capillary vessels, including those of the endoneurium.

- As such, nerve cells become hypoxic, which further contributes to the pathology in diabetic neuropathy. A 1990 study showed that endoneurial capillary density increased by 22 % with the supplementation of a high GLA-yielding essential fatty acid supplement. Results were enhanced with concomitant supplementation with vitamin C.

- Human studies have confirmed that GLA supplementation can be an effective agent in the adjunctive treatment of **distal diabetic polyneuropathy**. In a double-blind study involving 22 patients, the treatment group received either 360 mg gamma-linolenic acid (12 patients for 6 months).

- Compared to the placebo group the results showed that patients using gamma-linolenic acid supplementation showed statistically significant improvement in neuropathy symptom scores, median nerve motor conduction velocity and compound muscle action potential amplitude, peroneal nerve motor conduction velocity and compound muscle action potential amplitude, median and sural sensory nerve action and potential amplitude, and ankle heat threshold, and cold threshold values.

- Other human trials have shown similar results. For example, a double-blind study followed 111 people with diabetes for a period of 1 year. The results showed an improvement in subjective symptoms of peripheral neuropathy, such as pain and numbness, as well as objective signs of nerve injury. People with good blood sugar control improved the most.

- Other experimental studies have shown that GLA supplementation can protect nerves from diabetes-induced injury. The therapeutic dosage to consider is 330 - 440 mg per day. Essential oils with high GLA concentrations include borage seed oil (22%), black currant oil (22%) and evening primrose oil (9%).

- As omega-3 fatty acids have also been shown to reduce inflammation and improve the lipid profile in diabetic patients, according to human clinical studies, some experts suggest that an essential fatty acid supplement for diabetics should include a combination of fish, flaxseed and borage seed oils.

- If each 1200 capsule contains 400 mg of each of these oils, then a daily dosage of 4-6 capsules would be an appropriate therapeutic dosage for the diabetic patient.

References: GLA

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- Stevens EJ, Lockett MJ, Carrington AL, et al. Essential fatty acid treatment prevents nerve ischaemia and associated conduction anomalies in rats with experimental diabetes mellitus. *Diabetologia.* 1993;36:397-401.
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- De Caterina R, Modonna R, Bertolotto A, Schmidt EB. N-3 fatty acids in the treatment of diabetic patients: Biological rationale and clinical data. Diabetes Care April 2007 vol. 30 no. 4 1012-1026. http://care.diabetesjournals.org/content/30/4/1012.full

Gamma-Linolenic Acid (GLA)

Dosage: 330-460 mg per day (e.g. borage seed oil – 21-22% GLA)

Human Clinical Trials – Diabetic Neuropathy

Primary Mechanisms:

1. Conversion to anti-inflammatory prostaglandin series-1

2. Nerve Cell membrane EFA

Omega-3 fats may also be helpful in treating peripheral neuropathy for similar reasons (DHA is primary nerve cell membrane EFA in brain and most nerve cells)

Reference: Integrative Medicine (Third Edition) David Rakel. Elsevier Saunders (2012) P. 106

Coenzyme Q10

Dosage: 100 mg per day (Anecdotal)

- **Experimental:** Study involving **diabetic rats,** supplementation with coenzyme Q10 restored conduction velocities to that of healthy control rats which were slowed down as a result of diabetes.

- The authors state, "In addition to its effects on mitochondrial alterations (**ATP energy),** these positive effects of CoQ10 on diabetic neuropathy can be attributed to its **antioxidant activity.“**

- CoQ10 protects mitochondria in antioxidant role, enabling mitochondrial DNA to repair damage and increase ATP energy required to reverse pathology

Reference: Coenzyme Q(10) and alpha-lipoic acid supplementation in diabetic rats: conduction velocity distributions," Ayaz M, Tuncer S, et al, Methods Find Exp Clin Pharmacol, 2008; 30(5): 367-74

Charcot-Marie-Tooth (CMT) Peripheral Neuropathy

- Hereditary neuropathy refers to a group of disorders characterized by a chronic motor and sensory polyneuropathy. The affected individual typically has distal muscle weakness and atrophy often associated with mild to moderate sensory loss, depressed tendon reflexes, and high-arched feet.

- EMG/NCV testing, and occasionally sural nerve biopsy. More than 40 different genes/loci are associated with CMT. Molecular genetic testing is possible for some types of CMT.

- Individuals with CMT experience symmetric, slowly progressive distal motor neuropathy of the arms and legs usually beginning in the first to third decade and resulting in weakness and atrophy of the muscles in the feet and/or hands. Pes cavus foot deformity is common.

- Progressive weakness of the distal muscles in the feet and/or hands is evident on medical history.

- Individuals with typical CMT have high-arched feet, weak ankle dorsiflexion, thin distal muscles, depressed tendon reflexes, and distal sensory loss.

- Electrophysiologic studies (electromyography [EMG] and nerve conduction velocity [NCV]), when carefully done, are almost always abnormal.

Reference: https://www.ncbi.nlm.nih.gov/books/NBK1358/

Management MCT

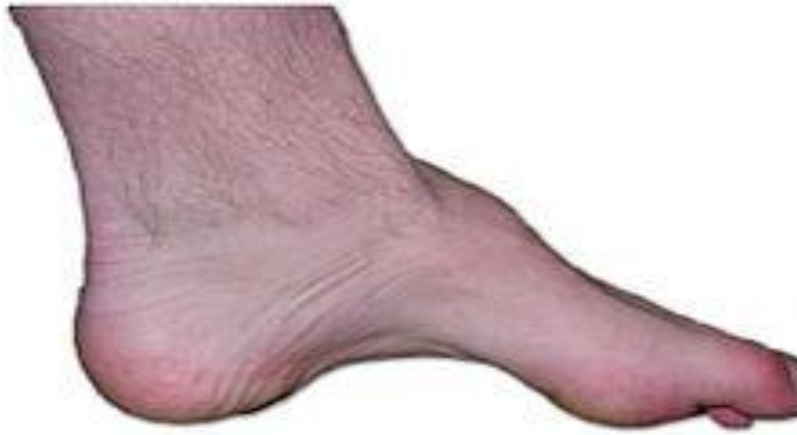
- Often the most important goal for patients with CMT is to maintain movement, muscle strength, and flexibility. Therefore, an inter-professional team approach with occupational therapy, physical therapy, podiatrist and or orthopedic surgeon is recommended.

Reference: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Charcot-Marie-Tooth-Disease-Fact-Sheet

Marie-Charcot –Tooth Disease

1 in 2,500 people

Involves - hereditary motor and sensory neuropathy and peroneal muscular atrophy



Early sign = Foot Drop

Later: Loss of touch sensation in the feet, ankles and legs

Pain: Sometimes Peripheral Neuropathy Pain

Can progress to affect upper limbs, swallowing, hearing etc

The lack of muscle, a high arch, and claw toes are signs of this genetic disease.

A Dentist Reports Improvement With Charcot-Marie-Tooth PN Using Following Supplement Regiment:

- Alpha-Lipoic Acid --- 300mg/day, 2X daily on an empty stomach
- L-Carnitine 500 mg -- 500 mg once a day on an empty stomach
- Vitamin B12 1000mcg -- this is in the liquid form he takes twice a day placing the drops under his tongue
- Turmeric 400-600 mg -- 3 times a day with food
- CoQ10 - 100mg -- once a day with food
- http://www.cmtausa.org/index.php?option=com_content&view=article&id=607&Itemid=78

He may also consider **Hyperbaric Oxygen Therapy** for patients with various neuropathies and other neurodegenerative conditions (e.g. MCI ,chemo-induced neuropathy, diabetic neuropathy, autism etc.)

http://www.spectrumhealthcenter.com/pdfs/Neuropathy/HBOT-for-Neuropathy.pdf

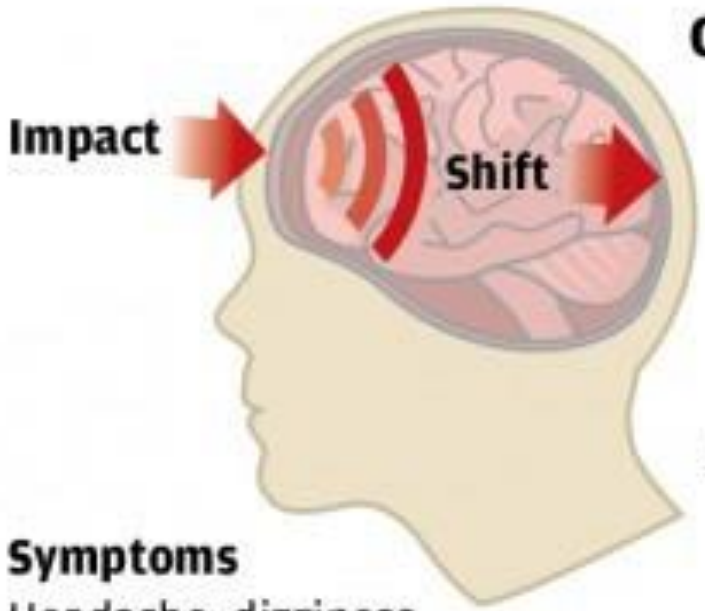
Supplement Hierarchy Considerations in Neuropathy

1. High Potency Multi-Vitamin (antioxidants, B-50 complex, vitamin D 1000 IU, A-zinc formula)
2. Essential Fatty Acids – (Fish, Flaxseed and Borage Seed oil – 400 mg each per capsules (4 caps/day)
3. Alpha-lipoic acid – 600 mg/d (increasing to 1800mg if necessary in divided doses)
4. Acetyl-L-Carnitine – 500 mg, 3X daily
5. Curcumin – 500 mg (3-4X daily) – diabetic neuropathy
6. Benfotiamine – 150-300 mg, 2X daily
7. Vitamin E – 1000-1600 IU per day – chemotherapy-induced neuropathy, although 400-600 IU has been used in clinical studies.
8. Pantothenic acid – 100 – 500 mg/d
9. Vitamin B12 – 500 mcg, 3X daily
10. Coenzyme Q10 – 100 mg

Nutritional Medicine and Concussion Management

Traumatic head injuries

A concussion occurs when a blow to the head results in the brain slamming against the skull.



Concussion

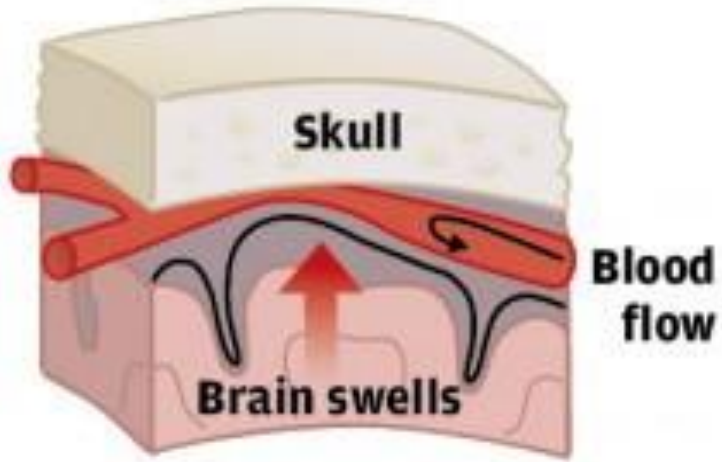
Brain collides with skull, which can cause bruising, torn tissues and swelling.

Symptoms

Headache, dizziness, confusion, nausea, difficulty hearing and seeing, lack of concentration

Second impact syndrome

When a player who is not fully recovered from a concussion suffers a second blow to the head, it can be fatal.



Massive swelling of brain

Cuts off flow of fresh blood to brain

SOURCE: American Academy of Neurology, U.S. Centers for Disease Control and Prevention, KRT

State Journal

References Cited on Following Slides

References

1. Petraglia AL, Winkler EA, and Bailes JE. Stuck at the bench: Potential natural neuroprotective compounds for concussion.Surg Neurol Int. 2011; 2: 146. Published online 2011 October 12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3205506/
2. Willer B, Leddy JL. Management of concussion and post-concussion syndrome. Current treatment options in Neurology. 2006, 8:415-426
3. Modern Nutrition in Health and Disease 10th edition (Editors Shils M, Shike M et al). Lippincott Williams & Wilkins Publishers. 2006. Page 532.
4. Levin HS. Treatment of postconcussion symptoms with CDP-choline. J Neurol Sci. 1991, 103 (supp): S39-S42
5. http://bvftd.blogspot.ca/2011/05/niacin-vitamin-b3-and-dementia.html (2011 update)

Neuronal Alterations Following Traumatic Brain Injury

Concussion and mild traumatic brain injury (mTBI) are the result of rapid deceleration of the brain with the skull that imparts shearing or torsional forces to neural tissue followed by metabolic and mechanical changes (2).

Overview of Pathophysiology in Concussion

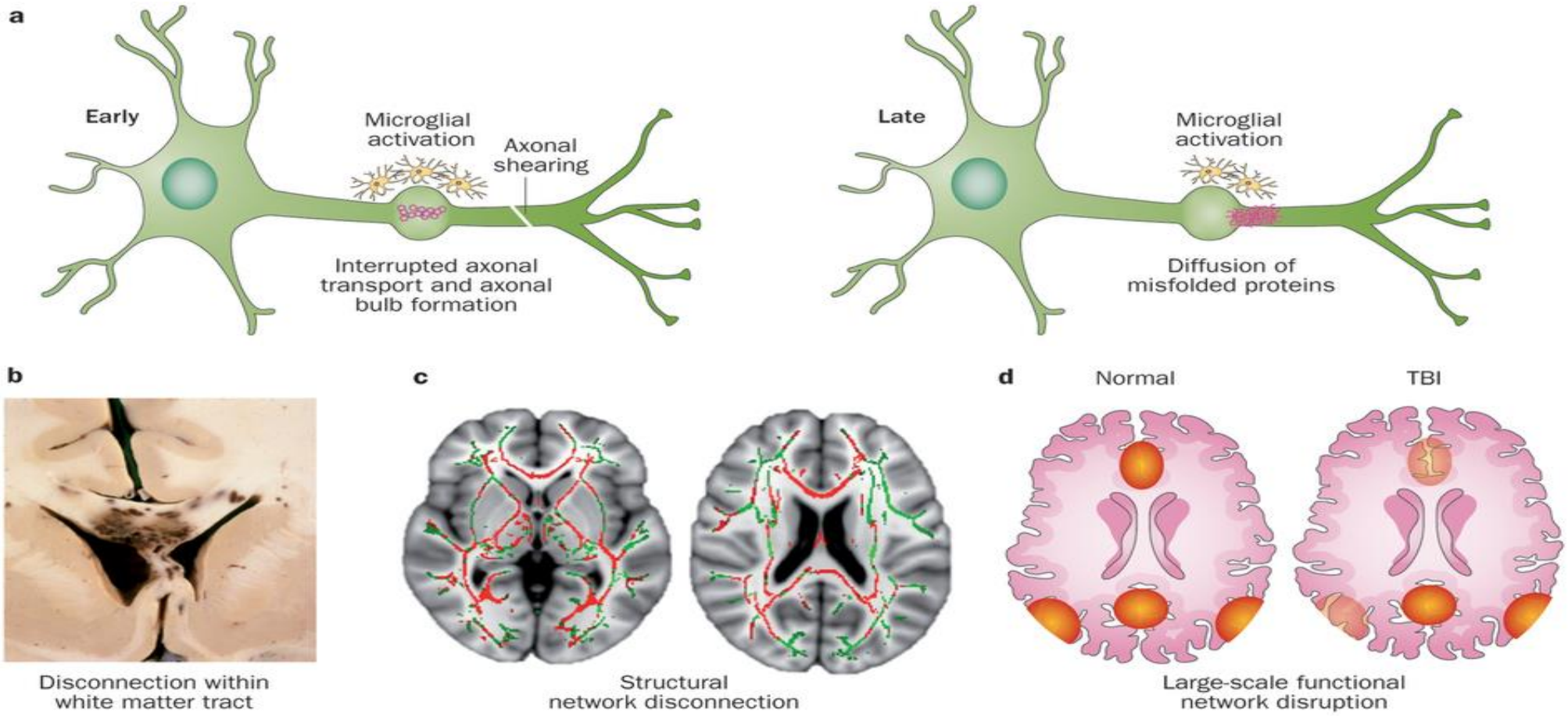
- **Diffuse axonal injury** is well documented and is sometimes visible on MRI because of eventual cell death. **Diffuse axonal injury** is considered instrumental in causing cognitive sequalae, such as **memory difficulties and concentration problems.**

- Changes involve **initial depolarization of neuronal membranes** and the release of excitatory amino acids, particularly **glutamate, which produces fluxes of calcium and potassium ions across neural and vascular tissue** resulting in a **hypermetabolic glycolytic state** as the neurons attempt to restore equilibrium:

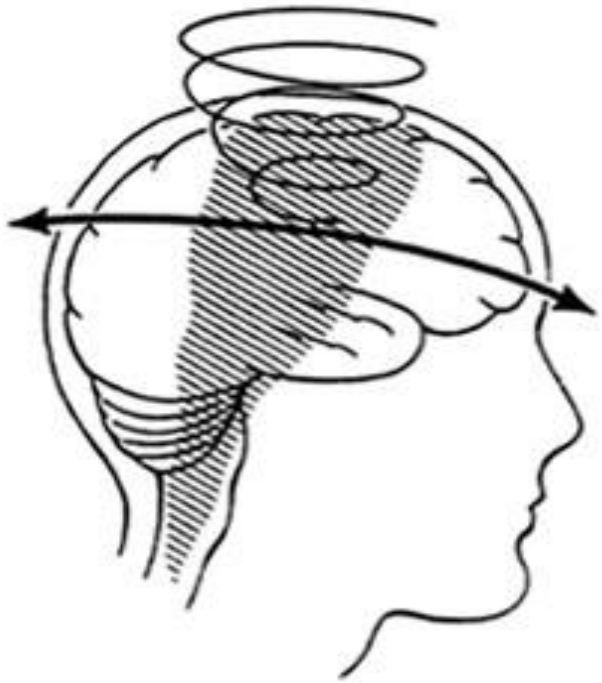
L-glutamate = excitatory NT; vs GABA= inhibitory NT. As L-glutamate is also toxic to nerve cells, Astrocytes play a major role in L-glutamate storage and recycling in the brain

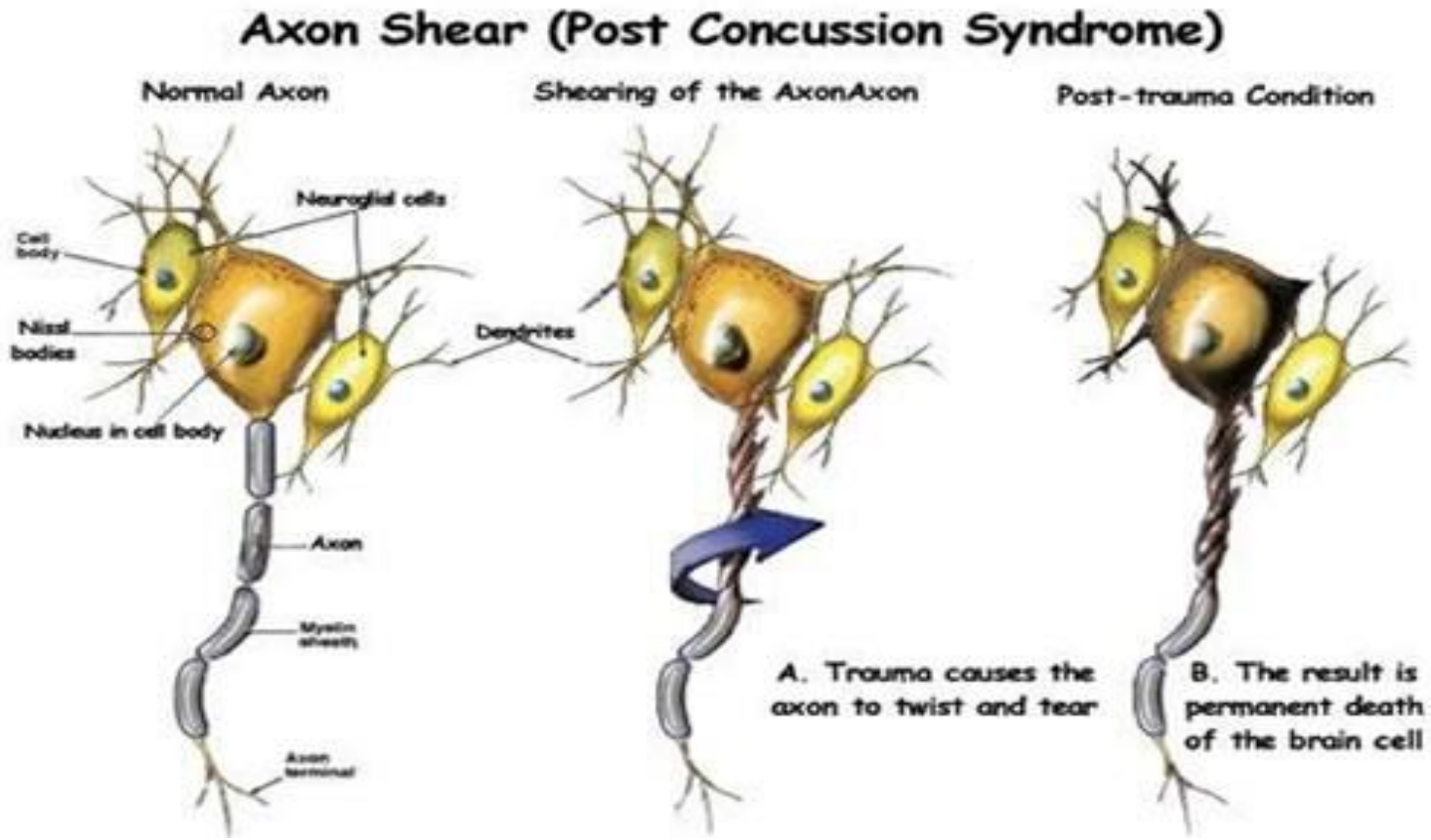
Increased hyperglycolytic state - as mitochondria damaged from concussion injury (glycolysis is less efficient energy source)

Axonal Injury – interrupted peptide transport.

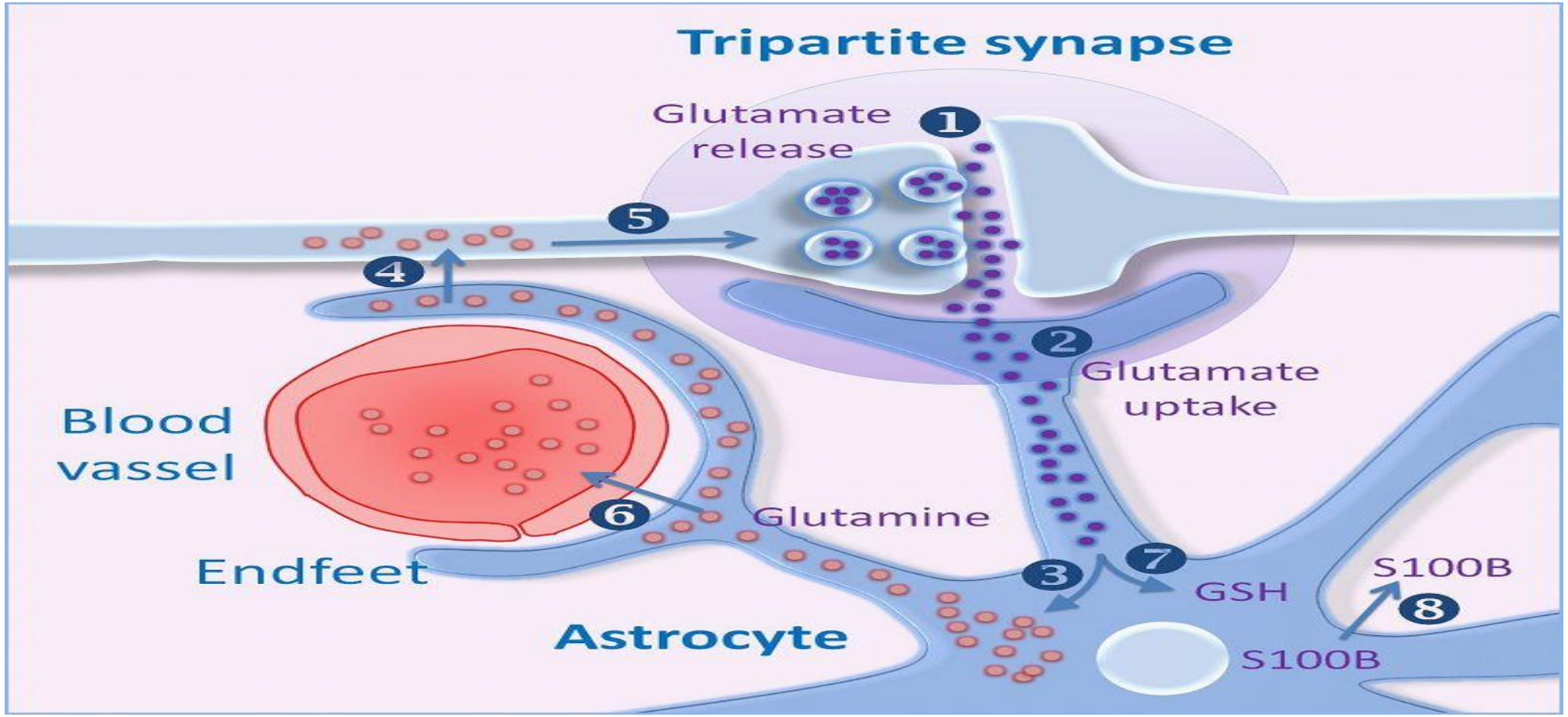


Severe Axonal Injury Can Result in Cell Death





Glutamate Normally Removed From Synaptic Cleft by Astrocytes to Prevent Toxic Build-Up and Neuronal Death



- **Vasoconstriction** - There follows a **calcium ion-induced vasoconstriction** that **reduces cerebral blood flow and glucose delivery** with a resultant metabolic depression (brain energy demand not adequately met, which may last for days).

- These changes appear to render neural tissue more susceptible to further injury: (2)

Biochemical and Morphological Neuronal Impact

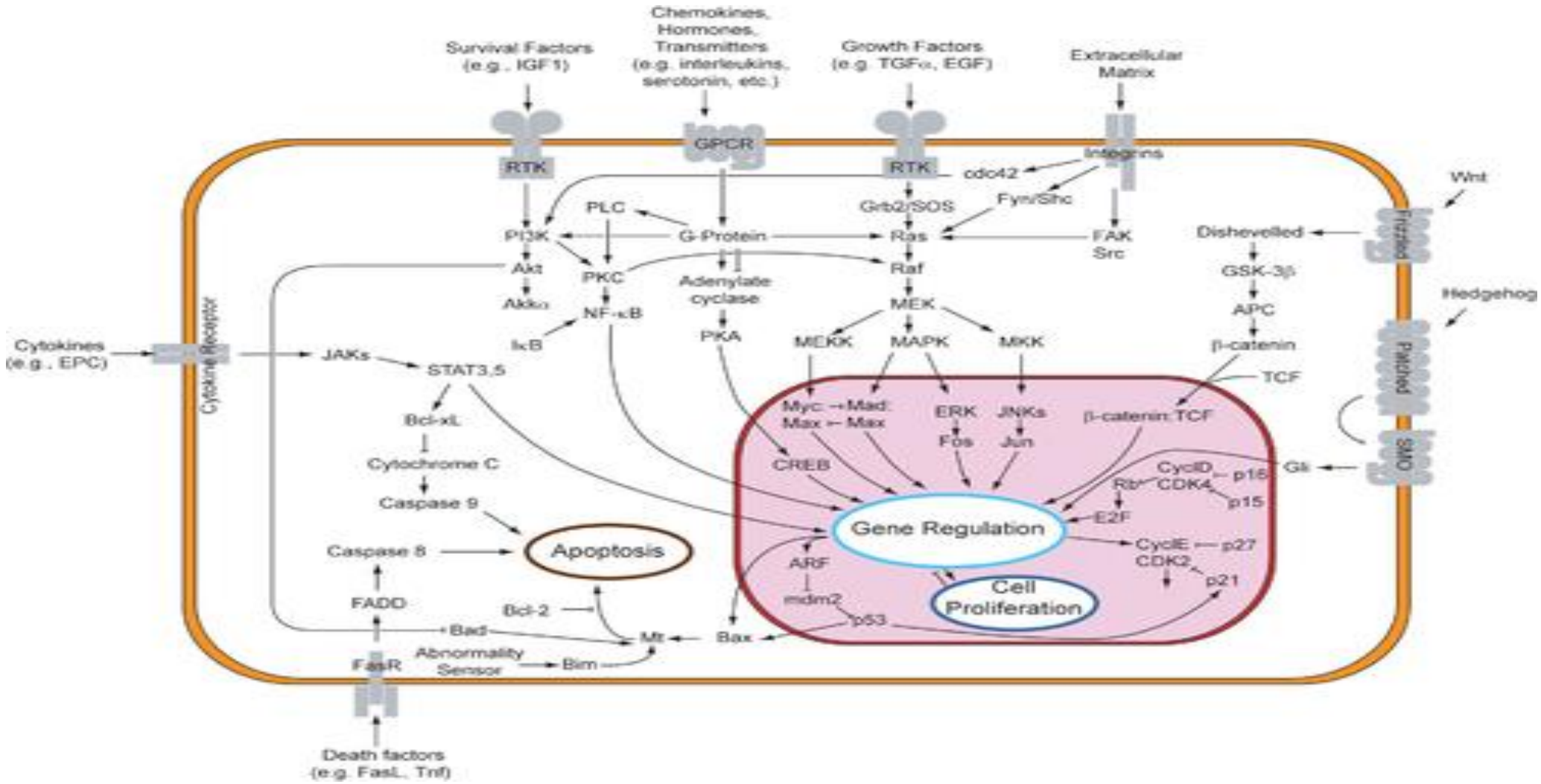
1. Initially - disruption of the neurofilaments and microtubules that provide a framework for axonal transport. This compromises anterograde and retrograde transport of molecular proteins to and from the cell body (somata).

2. Proteolysis - Axonal transport can also be affected by delayed, progressive injury secondary to proteolysis.

3. Neural Membrane Disruption and Inflammation - that leads to ionic shifts and an increase in intracellular glutamate and calcium. High intracellular glutamate is known to be toxic to brain cells.

Some cells may ultimately undergo **caspase-mediated apoptosis** as a result of these cellular changes. Inflammatory cascades also contribute significantly to further brain cell dysfunction.

Caspase – Induced Apoptosis



4. Two Major Glucose Metabolism Alterations - including hyperglycolysis and oxidative dysfunction with increase ROS.

5. Mitochondrial injury can also lead to failure in ATP generation and an **increase in reactive oxygen species**. Decreased ATP production is thought to hinder nerve cell repair ability. (CREATINE MONOHYDRATE CAN HELP)

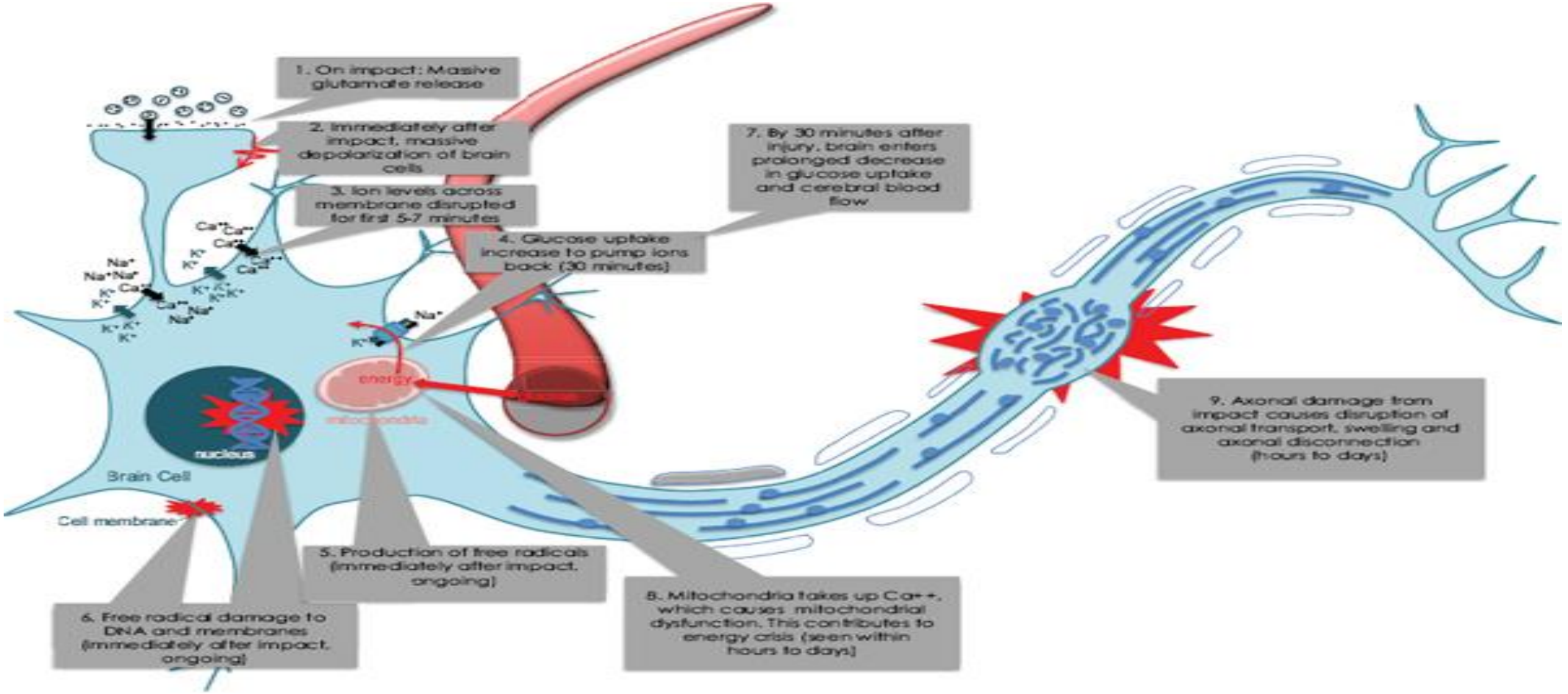
6. Reduced Cerebral Blood Flow – due to vasoconstriction (1)

References:

1. Petraglia AL, Winkler EA, and Bailes JE. Stuck at the bench: Potential natural neuroprotective compounds for concussion. Surg Neurol Int. 2011; 2: 146. Published online 2011 October 12

2. Willer B, Leddy JL. Management of concussion and post-concussion syndrome. Current treatment options in Neurology. 2006, 8:415-426

Review of Key Neuronal Events in Concussion



Goals of Supplementation in Concussion, mTBI and PCS

1. Decrease Inflammation
2. Increase ATP energy and Reverse Mitochondrial Dysfunction
3. Repair plasma membrane –stop leaking and allow phosphatidylcholine synthesis to resume – for acetylcholine synthesis
4. Increase and support acetylcholine synthesis (and possibly other neurotransmitters- dopamine, serotonin, norepineprhine)
5. Provide increased antioxidant protection to reduce ROS damage and decrease damage from L-glutamate (Huperzine A)
6. Improve cerebral blood flow- supply more oxygen and glucose
7. Stabilize and repair microtubules – axonal transport of key peptides

Best Available Evidence

Reducing Inflammation:

Omega-3 fats(EPA and DHA) – PG-3

Curcumin – blocking PG-2, TNF and NF-kappa-beta

Increasing ATP Synthesis and Reverse Mitochondrial Dysfunction

Creatine Monohydrate

Coenzyme Q10

Alpha-lipoic acid

Repairing Cell Membrane Phospholipids:

Choline (Lecithin)

CDP-Choline

Phosphatidylserine

DHA

Folic Acid, Vitamin B12

Increase Brain Acetylcholine, Dopamine, Serotonin, Norepinephrine:
CDP- choline

Choline – lecithin capsules

Phosphatidylserine, Bacopa monnieri, Huperzine A

Vitamin D

Reduce Reactive Oxygen Species and Defending Against L-glutamate Damage

Vitamin E – 400-800 IU

Vitamin C – 1,000 mg

Bacopa monnieri

Huperzine A – helps prevent damage from L-glutamate - https://nootropicsexpert.com/huperzine/

Improve Cerebral Blood Flow:

Omega-3 Fats

Stabilize Microtubules:

Nicotinamide (Vitamin B3)

Multi-Modal Effects of Magnesium

Reductions in Magnesium

- Intracellular magnesium levels are also immediately reduced after Traumatic Brain Injury (TBI) and remain low for up to 4 days.

- This reduction in magnesium has been correlated with post-injury neurologic deficits, and pre-treatment to restore magnesium levels results in improved motor performance in experimental animals.

- ATP Energy - Decreased magnesium levels may lead to neuronal dysfunction via multiple mechanisms. Both glycolytic and oxidative generation of ATP are impaired when magnesium levels are low.

- Membrane Potential - Magnesium is necessary for maintaining the cellular membrane potential and initiating protein synthesis. Finally, low levels of magnesium may effectively unblock the NMDA receptor channel more easily, leading to greater influx of Ca2+ and its potentially deleterious intracellular consequences.

Reference:

- Christopher C. Gizacorresponding author and David A. Hovda. “The Neurometabolic Cascade of Concussion” J Athl Train. 2001 Jul-Sep; 36(3): 228–235.

Bases for Pro-IV, which contains magnesium and zinc: The Pro-IV treatment is essentially a "cocktail" of substances that aim to rebalance those micronutrients, with some anti-inflammatories and non-opioid pain relievers mixed in to treat immediate symptoms. All of the individual ingredients are FDA approved (http://bleacherreport.com/articles/2728620-the-race-is-on-for-a-concussion-pill-as-new-nfl-season-begins)

Achieving Goals in Concussion Management

1. Reducing Inflammation

Omega-3 Fats

- Omega-3 polyunsaturated fatty acids are important structural components of all cell membranes modulating membrane fluidity, thickness, cell signaling, and mitochondrial function.

- EPA and DHA are highly enriched in neuronal synaptosomal plasma membranes and vesicles, with DHA being the predominant omega-3 fat in neuronal membranes.

- Neuronal DHA, in turn, influences the phospholipid content of the plasma membrane increasing phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine production and promoting neurite outgrowth during both development and adulthood

- Animal models show that fish oil effectively reduces post-traumatic elevations in protein oxidation resulting in stabilization of multiple molecular mediators of learning, memory, cellular energy homeostasis and mitochondrial calcium homeostasis as well as improving cognitive performance

- DHA has provided neuroprotection in experimental models of both focal and diffuse traumatic brain injury

- Studies in other models of neurologic injury have revealed a variety of potential mechanisms of neuroprotection, in addition to DHA and EPA's well-established anti-oxidant and anti-inflammatory properties.

- Some studies show DHA provided prophylactically may reduce extent of brain damage in traumatic brain injury models

Curcumin

- Curcumin is highly lipophilic and crosses the blood-brain barrier enabling it to exert a multitude of different established neuroprotective effects

- Animal models show that curcumin supplementation results in **significant reduction of neuroinflammation via inhibition of the pro-inflammatory molecules interleukin 1β and nuclear factor kappa B (NFκB)**. More importantly, the reduced neuroinflammatory response mitigated post-traumatic reactive astrogliosis and prevented upregulation of the water channel aquaporin 4, thus **reducing the magnitude of cellular edema.**

- Some studies show curcumin provided prophylactically may reduce extent of brain damage in traumatic brain injury models

- Animal studies demonstrate that curcumin is capable of significantly **reducing post-traumatic elevations in lipid peroxidation and protein oxidation, as well as disturbances in plasma membrane turnover and phospholipid metabolism.** Additionally, it has prevented reductions in proteins important for learning, memory, and synaptic transmission; and promoted cellular energy homeostasis. Post-traumatic administration of a curcumin supplement also improved injury-associated behavioral impairment, thereby suggesting that curcumin-induced normalization of multiple molecular systems **may help preserve neuronal structure and function during the post-injury period.**

2. Increase ATP Production

Creatine

- Mild TBI reduces brain creatine and phosphocreatine levels in rodent models, suggesting that resulting impairments in the maintenance of cellular energy may play a role in the evolution of secondary brain injury. Creatine is used to enhance ATP production. In the CNS, maintenance of cellular ATP levels is necessary for proper development and provides the cellular energy required to maintain the various cellular processes necessary for proper neuronal structure and function; including the maintenance of neuronal membrane potential, ion gradients underlying signal propagation, intracellular calcium homeostasis, neurotransmission, intracellular and intercellular signal transduction and neuritic transport.

- More recent evidence also suggests that creatine may serve as a neuronal co-transmitter augmenting post-synaptic GABA signal transduction.

- Studies of patients with CNS creatine deficiency and/or murine models with genetic ablation of creatine kinase have consistently demonstrated significant neurological impairment in the absence of proper creatine, phosphocreatine, or creatine kinase function; thus highlighting its functional importance.

- Preclinical studies in a variety of experimental models have suggested that dietary creatine may provide neuroprotection in animal models of chronic neurodegenerative disease, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The neuroprotective effects may also be conferred in acute neurological injuries, such as TBI

- In rodents, pre-traumatic dietary supplementation with creatine monohydrate significantly reduced the magnitude of cortical tissue damage and the concentration of two biomarkers of cellular injury, free fatty acids and lactic acid, following experimental injury.

- It was further elucidated that creatine-mediated neuroprotection is in part mediated by the maintenance of cellular ATP levels and improvements in mitochondrial bioenergetics; including increased mitochondrial membrane potential and reductions in mitochondrial permeability, reactive oxygen species, and calcium levels.

- In humans, studies utilizing nuclear magnetic spectroscopy have demonstrated that creatine supplementation does indeed increase cerebral creatine and phosphocreatine stores.

- Several studies have suggested that creatine supplementation may also reduce oxidative DNA damage and brain glutamate levels in Huntington disease patients.

- Another study highlighted that creatine supplementation marginally improved indices of mood and reduced the need for increased dopaminergic therapy in patients with Parkinson's disease. Together, these data suggest that dietary creatine supplementation may effectively increase CNS creatine/phosphocreatine stores and may modulate human neurological disease.

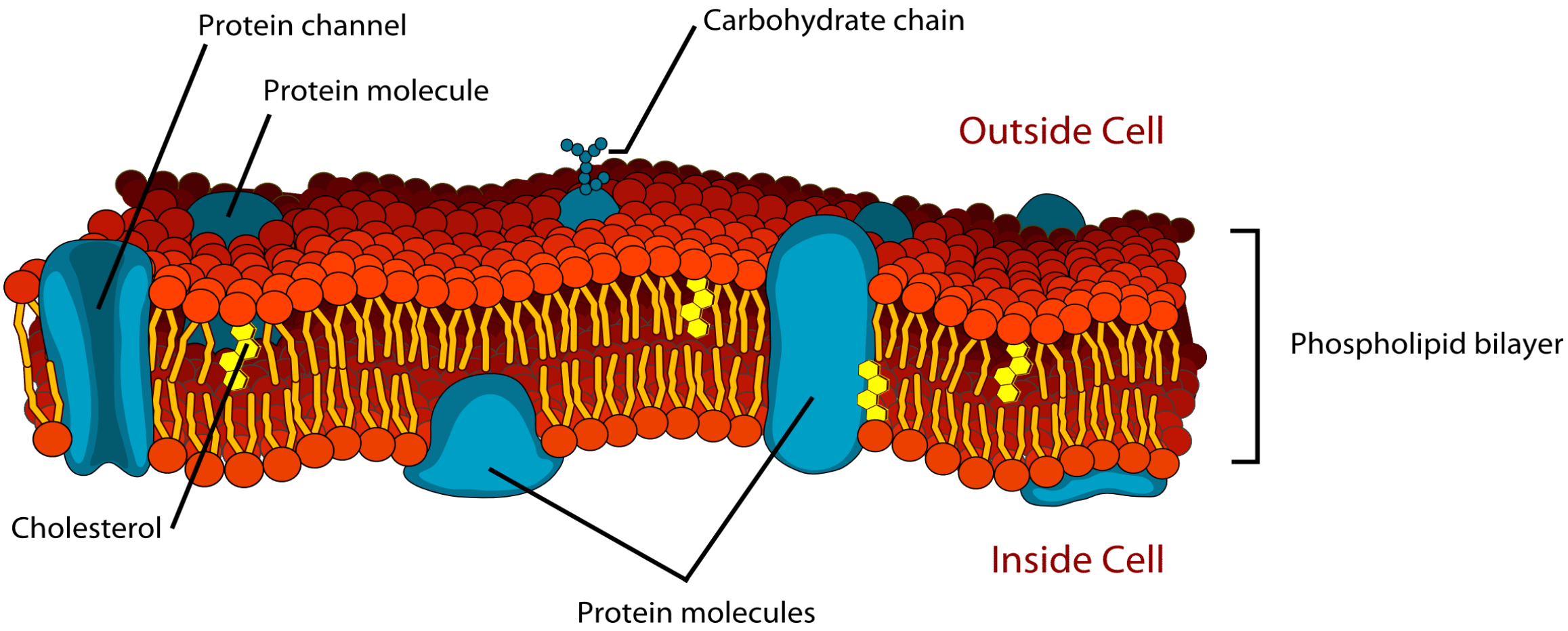
- Human Pediatric Evidence – Preliminary results obtained in a pediatric population have suggested that post-traumatic oral creatine administration (0.4 g/kg) given within four hours of traumatic brain injury and then daily thereafter, may improve both acute and long-term outcomes.

- Acutely, post-traumatic creatine administration seemed to reduce duration of post-traumatic amnesia, length of time spent in the intensive care unit, and duration of intubation. At three and six months post-injury, subjects in the creatine treatment group demonstrated improvement on indices of self care, communication abilities, locomotion, sociability, personality or behavior and cognitive function when compared to untreated controls.

- Further analysis of the same population, revealed that patients in the creatine-treatment group were less likely to experience headaches, dizziness and fatigue over six months of follow-up.

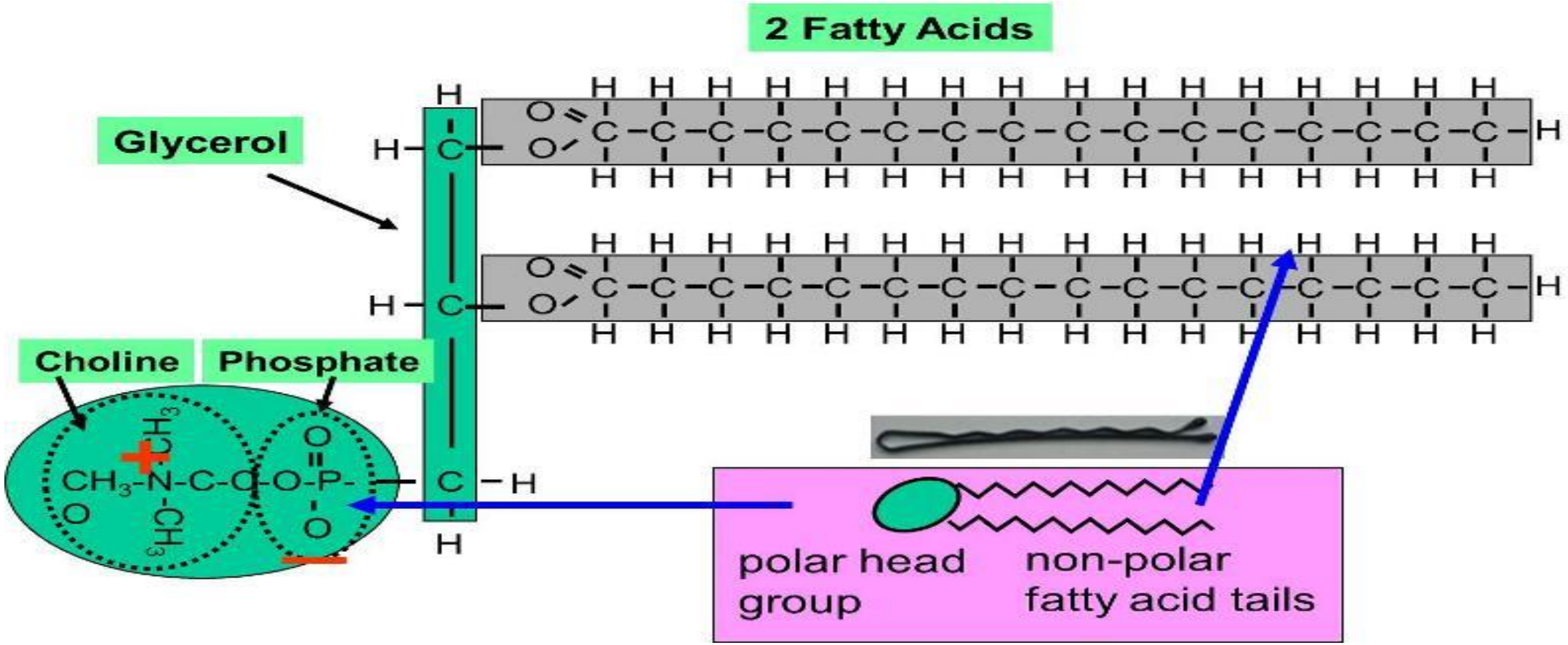
- Creatine treatment appeared to be well tolerated and there were no significant side effects reported; which was consistent with other human studies utilizing higher dosages.

3. Repairing Cell Membrane

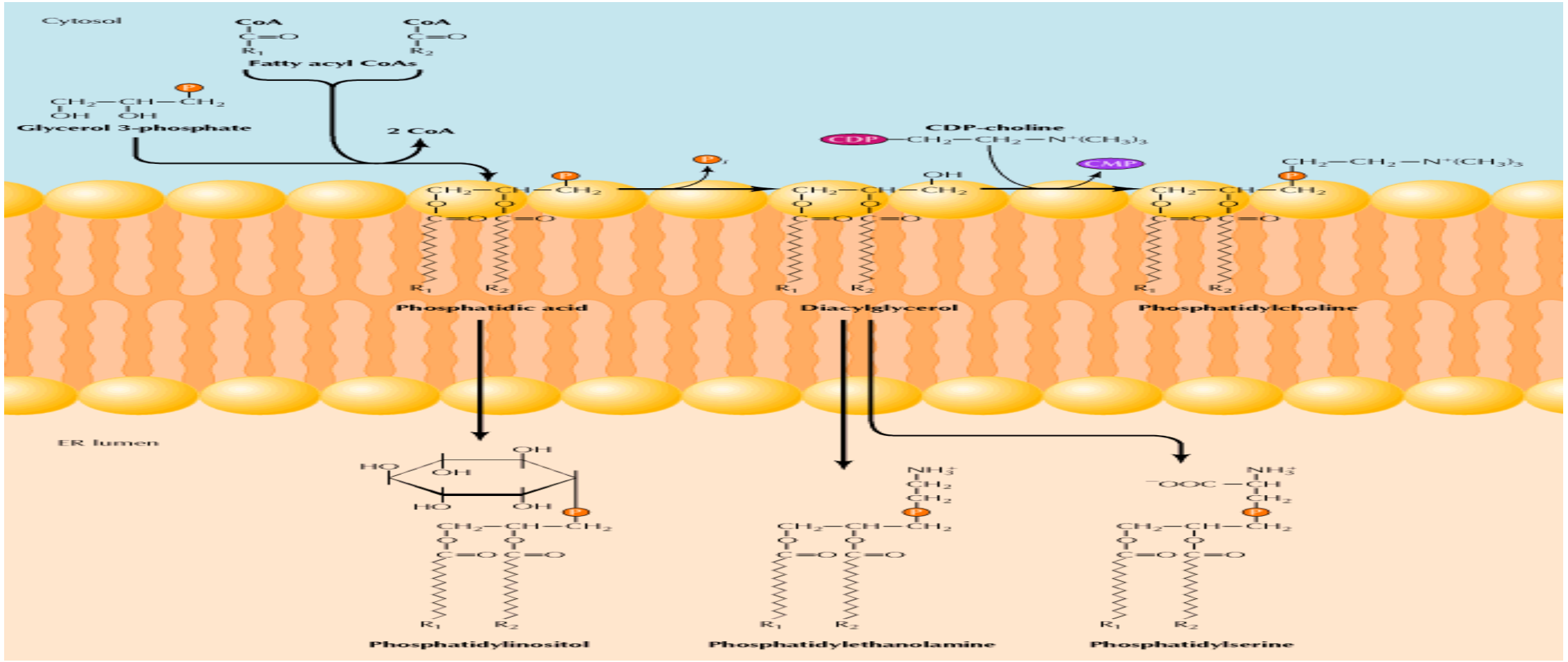


Phospholipid Structure. When R2 is DHA – get increased Phosphatidylcholine synthesis

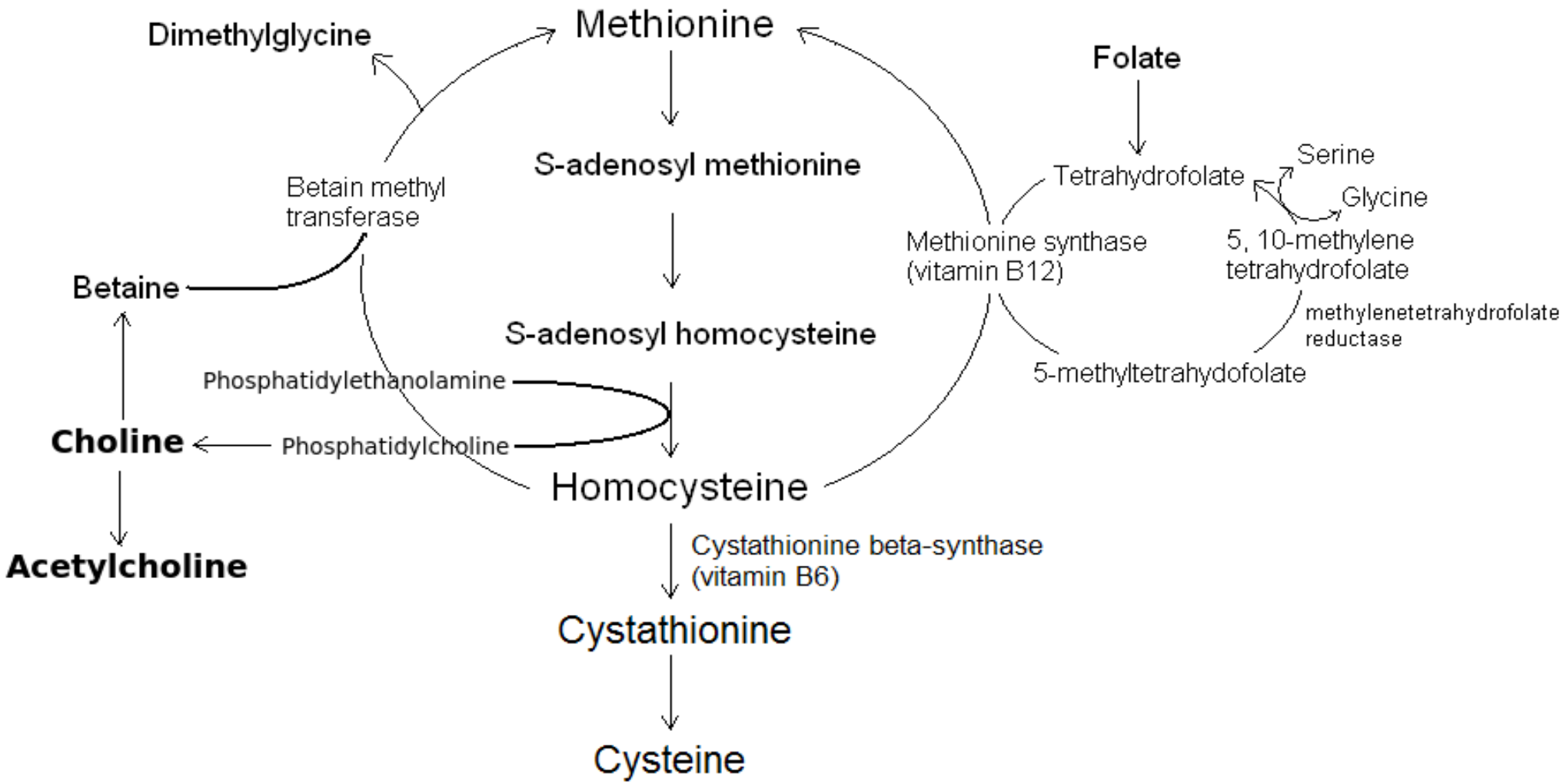
Reference: Choline and it's Products Acetylcholine and Phosphatidylcholine: Choline (Wurtman RJ, Cansev M, Ulus IH) Springer-Verlag-Berlin Heidelberg 2007):http://wurtmanlab.mit.edu/static/pdf/1020.pdf



Phospholipid Synthesis in Cell Membrane: Glycerol from Glycolysis; FFA from Fatty Acid Synthesis from Acetyl-CoA (Palmitic acid, Oleic Acid); Omega-3 fats, other PUFA from HDL and bound to Albumin after release from fat cell (unesterified fatty acid pool). ALA, DHA and EPA improve cell membrane fluidity, receptor function, signaling mechanisms and DHA increase synthesis of PC in presence of cytidine and choline.

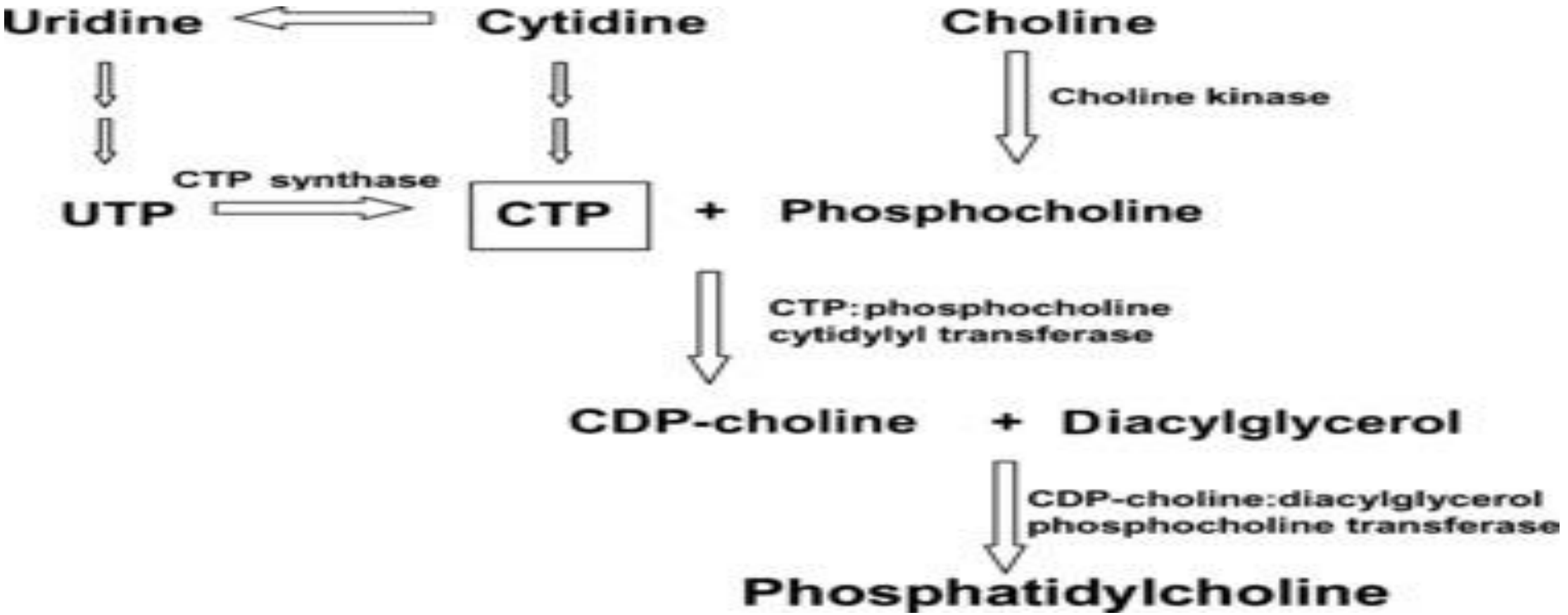


PE converted to PC via SAMe (folic acid, B12, choline)

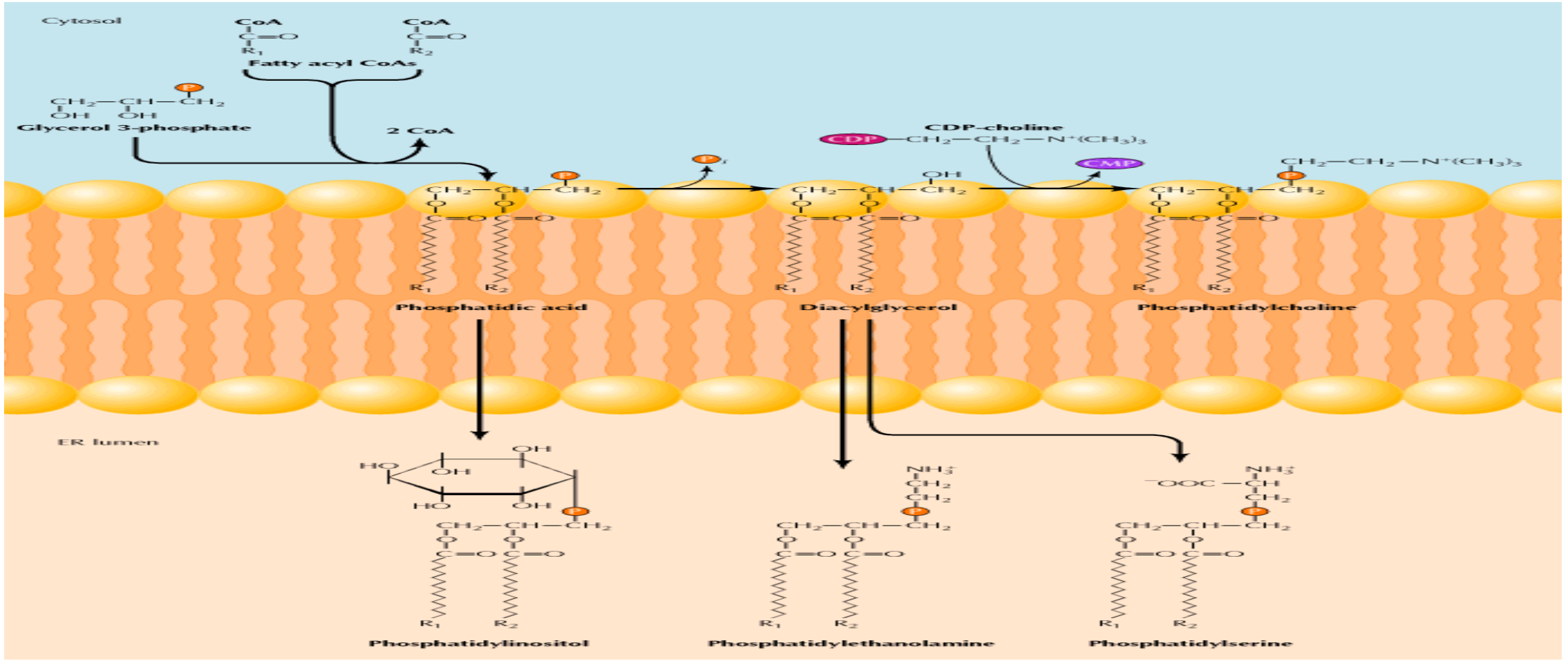


CDP Choline Supplementation- Repairs Cell Membrane:
Phosphatidylcholine is most dominant PL in Brain

Reference: Choline and it's Products Acetylcholine and Phosphatidylcholine: Choline (Wurtman RJ, Cansev M, Ulus IH) Springer-Verlag-Berlin Heidelberg 2007):http://wurtmanlab.mit.edu/static/pdf/1020.pdf

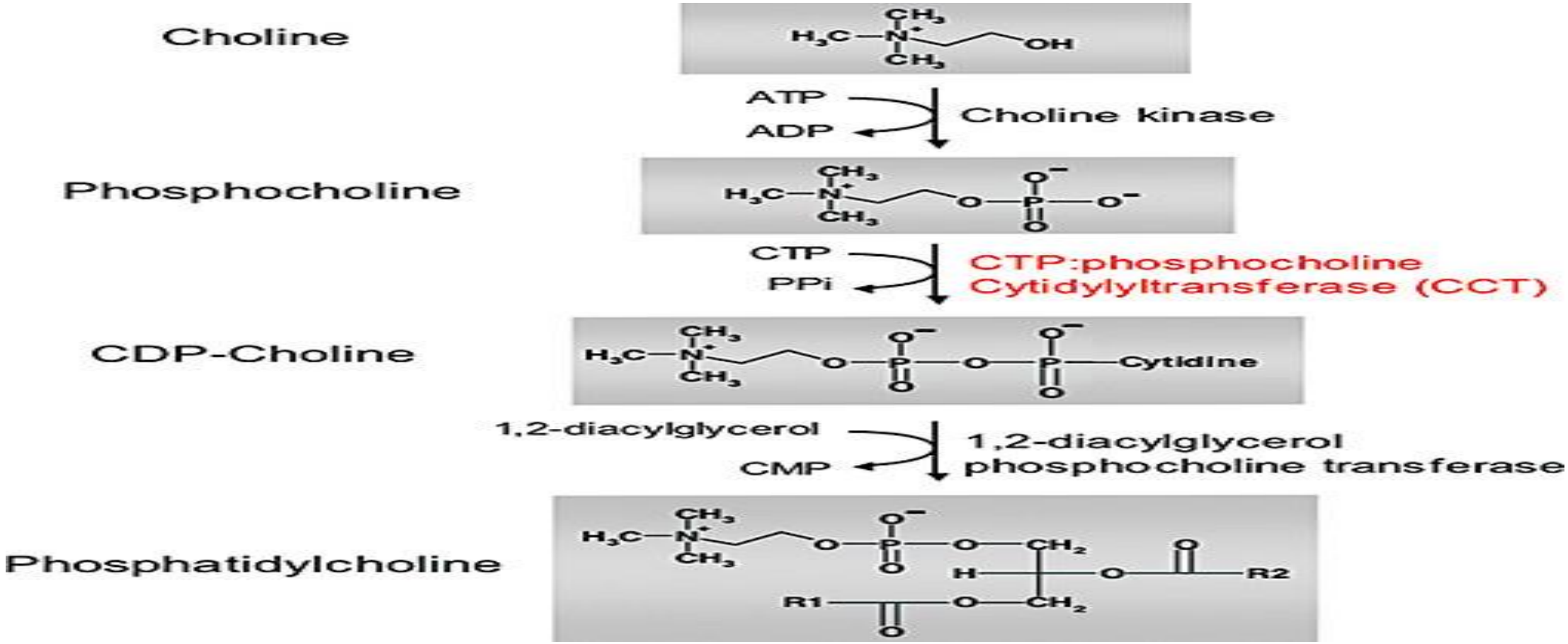


CDP-Choline becomes Phosphatidylcholine when attached to diacylglycerol in cell membrane. The key is to first enable brain to synthesize CDP-choline (CDP-choline supplementation has been shown to do this successfully) **In the presence DHA PC is synthesized even faster.**



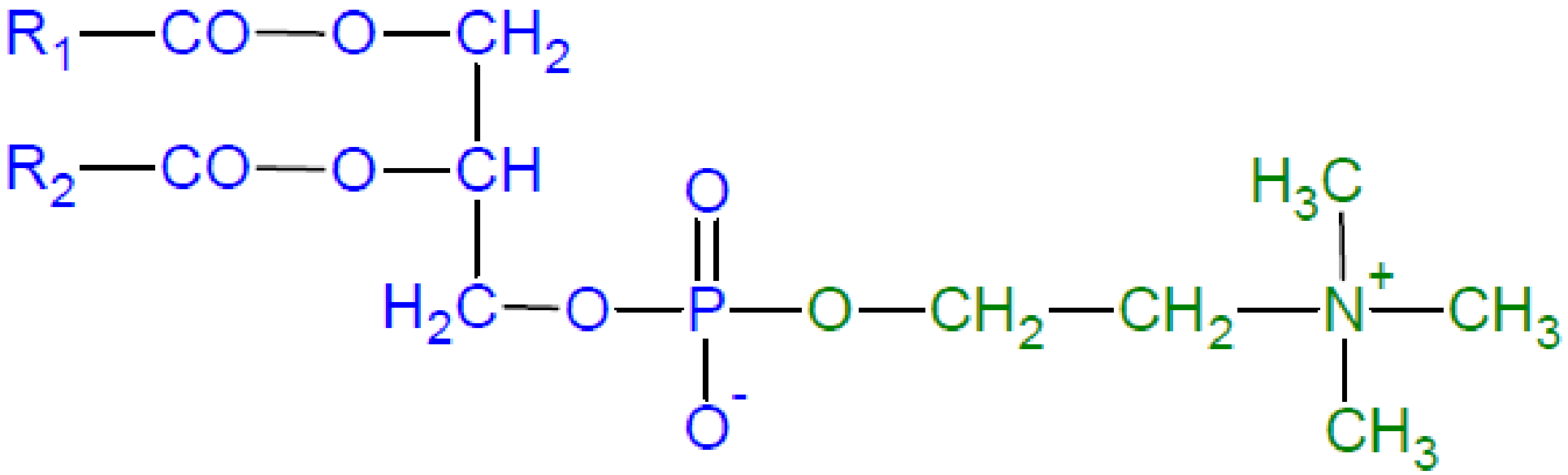
Some PC made in Liver in presence of cytidine and choline and transported to brain via HDL

https://www.researchgate.net/publication/274395019_High-Density_Lipoprotein_HDL_Phospholipid_Content_and_Cholesterol_Efflux_Capacity_Are_Reduced_in_Patients_With_Very_High_HDL_Cholesterol_and_Coronary_Disease



When R2 is DHA – increases synthesis of PC (in presence of choline and cytidine)

Reference: Choline and it's Products Acetylcholine and Phosphatidylcholine: Choline (Wurtman RJ, Cansev M, Ulus IH) Springer-Verlag-Berlin Heidelberg 2007): http://wurtmanlab.mit.edu/static/pdf/1020.pdf



Phosphatidylcholine

Other Benefits of CDP Choline

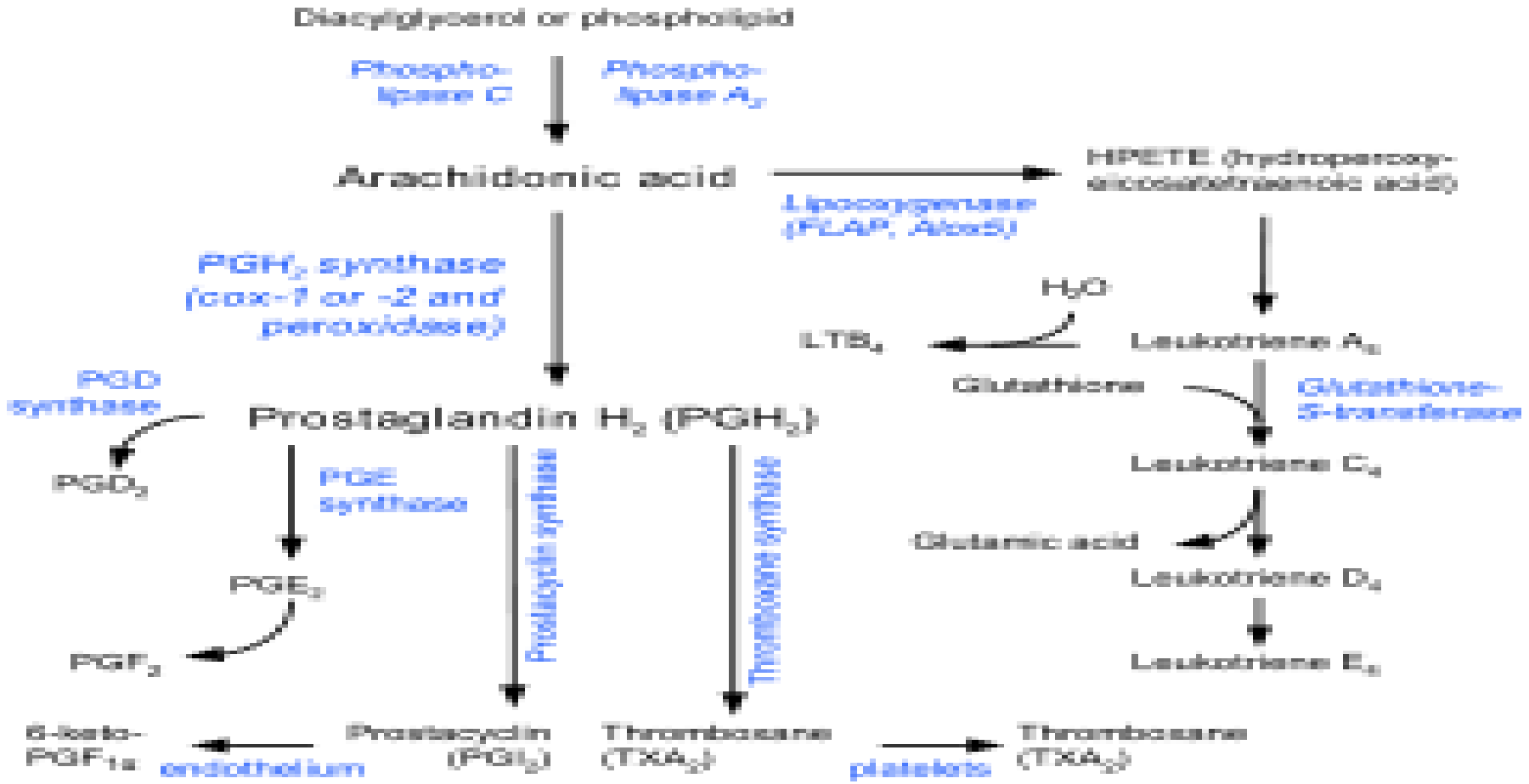
- Cytidine also reduces activity of phospholipase, thus decreases conversion of Arachidonic acid to PG-2 (reducing brain inflammation)

- Cytidine increases PC synthesis, glutathione synthesis, and uptake of glutamate by astrocytes to prevent further brain damage in injury and stroke

References CDP Choline

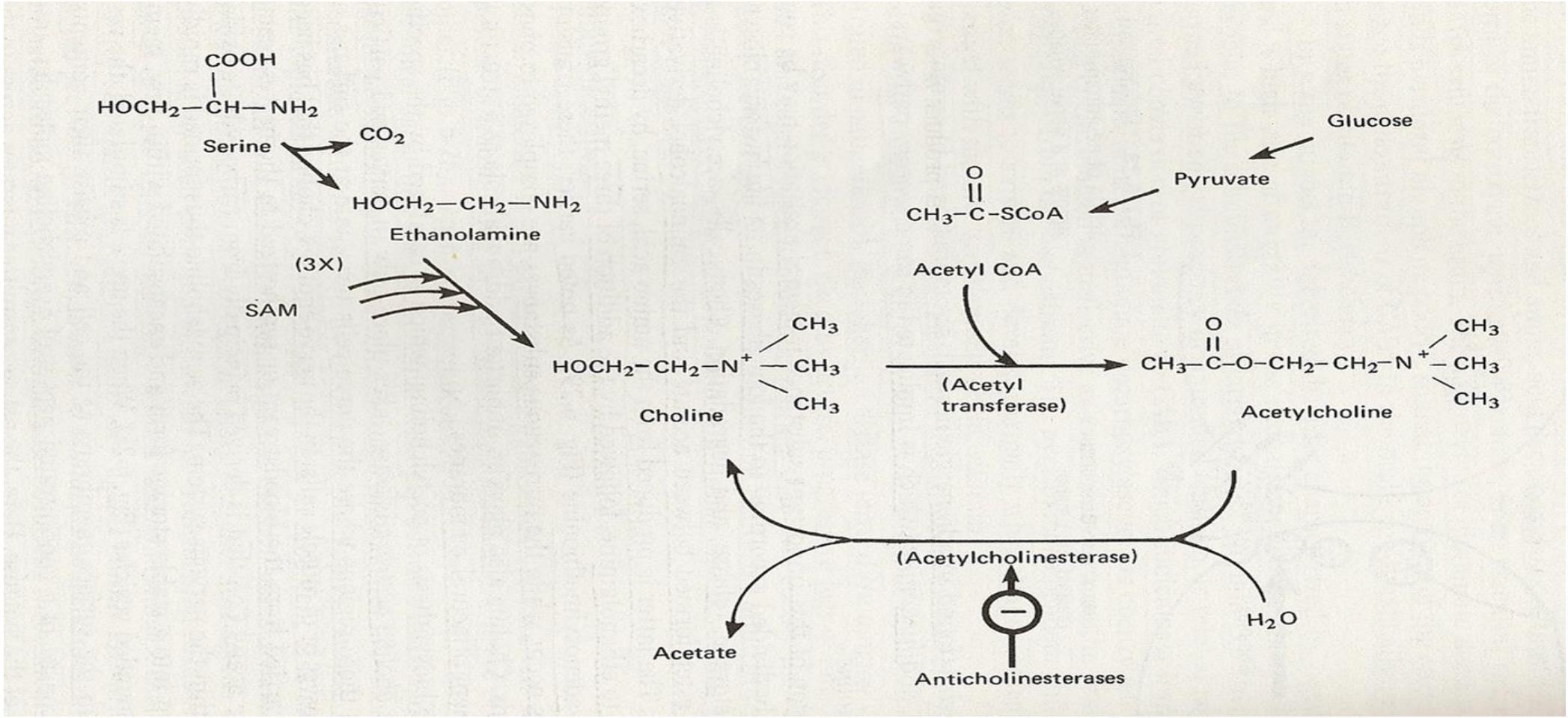
- Adibhatla RM, Hatcher JF, Dempsey RJ (Jan 2002). "Citicoline: neuroprotective mechanisms in cerebral ischemia". Journal of Neurochemistry. **80** (1): 12–23.
- López-Coviella I, Agut J, Savci V, Ortiz JA, Wurtman RJ (Aug 1995). "Evidence that 5'-cytidinediphosphocholine can affect brain phospholipid composition by increasing choline and cytidine plasma levels". Journal of Neurochemistry. **65** (2): 889–94.
- Conant R, Schauss AG (Mar 2004). "Therapeutic applications of citicoline for stroke and cognitive dysfunction in the elderly: a review of the literature". Alternative Medicine Review. **9** (1): 17–31.

Inflammatory PG-2 formed from AA released from cell membrane by Phospholipase A2 (CDP-choline inhibits this reaction, reducing brain inflammation)



Memory: Acetylcholine Synthesis for Phosphatidylcholine

Also - Slow breakdown with Acetylcholinesterase Inhibitors (Huperzine A)



4. Increase and support acetylcholine synthesis (and possibly other neurotransmitters- dopamine, serotonin, norepineprhine)

CDP Choline and Lecithin

- Cholinergic dysfunction is thought to underlie the memory impairment in patients with Alzheimer's disease, and thus, it is of interest that concussion patients show deficits in attention, and memory for new information (2).

- Human studies in young and older subjects demonstrate that supplementation with CDP-choline and/or lecithin increase brain levels of acetylcholine.

- Both CDP-choline and phosphatidylcholine (found in lecithin) cross the blood-brain barrier (facilitated by the choline transporter) and are subsequently incorporated into neuronal membranes as part of their phospholipid structure. The choline in brain phospholipids serves a choline pool for incorporation into acetylcholine synthesis.

- CDP-choline supplementation has been shown to activate the synthesis of structural phospholipids in the brain and other neuronal membranes, increase cerebral metabolism and acts on the levels of various neurotransmitters.

- Human trials reveal that it is effective in cases of senile cognitive impairment (e.g., Alzheimer's disease), slowing the evolution of the disease, and in the management of Parkinson's disease.

- Further, CDP-choline also has been shown experimentally to increase noradrenaline and dopamine levels in the central nervous system. Due to these pharmacological activities, CDP-choline has a neuroprotective effect in situations of hypoxia (oxygen starvation) and ischemia, as demonstrated that CDP-choline restores the activity of mitochondrial ATPase and of membrane sodium-potassium ATPase, inhibits the activation of phospholipase A^2, which otherwise triggers the formation of inflammatory prostaglandin-2 production.

- CDP-choline also has been shown to accelerate the resorption of cerebral edema in various experimental models. In studies carried out on the treatment of patients with head trauma, CDP-choline accelerated the recovery from post-traumatic coma and the recuperation of walking ability.

- Its use achieved a better final functional result and reduced the hospital stay of these patients, in addition to improving the cognitive and memory disturbances which are normally observed after head trauma of lesser severity and which constitute the disorder known as post-concussion syndrome.

- Of particular note is the fact that CDP-choline is well tolerated by patients and no serious side effects have occurred in any of the groups of patients treated with CDP-choline.

- Toxicology studies also indicate that it is a safe intervention and highlight the fact that it produces no adverse effects on the brain's cholinergic system (3,4). Moreover, there is accumulating evidence that cholinergic agents (natural ones include CDP-choline, Huperzine A, Phosphatidylserine) may alleviate some of the cognitive deficits suffered by head-injured patients (2).

5. Provide increased antioxidant protection to reduce ROS damage and decrease damage from L-glutamate (Huperzine A)

Vitamin E and Vitamin C

- Vitamin E is a potent, lipid-soluble, antioxidant that is present in high concentrations in the mammalian brain.

- In several animal models of brain injury such as ischemic stroke, subarachnoid hemorrhage and Alzheimer's disease, administration of alpha-tocopherol or its potent derivative alpha-tocotrienol has been shown to lessen oxidative stress and neuropathology.

- Other laboratory studies have demonstrated that pre-traumatic alpha-tocopherol supplementation reduces TBI-induced increases in lipid peroxidation and oxidative injury and impairments in spatial memory.

- Additional studies in transgenic mouse models of Alzheimer's disease have further demonstrated that pre- and post-traumatic vitamin E supplementation reduces lipid peroxidation, amyloidosis, and improves cognitive performance following repetitive concussive brain injury.

- One other point of consideration is that in neurodegenerative disease states like Alzheimer's disease and Parkinson's disease, where there are high levels of reactive oxygen species generation, vitamin E can tend to become oxidized itself. For maximal effectiveness and to maintain its antioxidant capacity, vitamin E must be given in conjunction with other anti-oxidants like vitamin C or flavonoids. These various factors might account for the null effects of alpha-tocopherol supplementation in patients with MCI and Alzheimer's disease in some studies.

- Human TBI – emerging evidence has suggested that daily intravenous administration of vitamin E following TBI significantly decreases mortality and improved patient outcomes when assessed at discharge and at two and six month follow-up time points. Importantly, no increase in adverse events was detected.

- This study also identified that high dose vitamin C administration following injury stabilized or reduced peri-lesional edema and infarction in the majority of patients receiving post-injury treatment. Like vitamin E, vitamin C, also known as ascorbic acid, is a potent antioxidant present in high concentrations in the CNS. Given these similarities in action, it has been speculated that combined vitamin C and E therapy may potentiate CNS antioxidation and act synergistically with regards to neuroprotection.

6. Improve cerebral blood flow- supply more oxygen and glucose

Omega-3 fats – PG-3 - vasodilation

7. Stabilize and repair microtubules – axonal transport of key peptides

Nicotinamide and Tau Protein Integrity

- Human Epidemiological Studies suggest that niacin intake is linked to reduced risk of Alzheimer's disease. Animal studies show that niacin supplementation reduces neurofibrillary tangle development in simulated Alzheimer's disease experiments.

- Nicotinamide administration led to an increase in tau proteins that strengthen microtubules.

- Nicotinamide slightly enhanced cognitive abilities in normal mice. "This suggests that not only is it good for Alzheimer's disease, but if normal people take it, some aspects of their memory might improve," said LaFerla, UCI neurobiology and behavior professor.
-

  Scientists also found that the nicotinamide-treated animals had dramatically lower levels of the tau protein that leads to the Alzheimer's tangle lesion.

- Human Equivalent Dosage: 1000 mg, three times daily (monitor liver enzymes as with nicotinic acid used to lower triglycerides and cholesterol) (5).

Other Nutrients of Interest

Vitamin D

- Research shows that cells in the brain not only possess the hydroxlase responsible for vitamin D activation, but that multiple regions in the brain abundantly express the nuclear vitamin D receptor. Binding of vitamin D to its nuclear receptor, in turn, leads to its association with other transcription factors, such as retinoic acid receptor.

- Subsequently this complex binds to vitamin-D response elements in genomic DNA, thus augmenting gene transcription. Vitamin D-induced alterations in gene transcription are now believed to **modulate a myriad of neuronal properties including proliferation, differentiation and maintenance of calcium homeostasis.**

- Population based studies have suggested that vitamin D deficiency in the elderly is indeed associated with an increased prevalence of Parkinson's disease dementia, Alzheimer's disease, increased stroke risk and a higher prevalence of MRI findings suggestive of primary cerebrovascular lesions. The association between vitamin D deficiency and elevated stroke risk or other cardiovascular disease has been confirmed in other studies. **Furthermore, a randomized controlled trial has suggested that post-ischemic administration of vitamin D may improve endothelial cell function.**

In vitro and *in vivo* studies have suggested that vitamin D supplementation with progesterone administration may significantly enhance neuroprotection.

Vitamin D deficiency may increase inflammatory damage and behavioral impairment following experimental injury and attenuate the protective effects of post-traumatic progesterone treatment.

Progesterone is one of the few agents to demonstrate significant reductions in mortality following TBI in human patients in preliminary trials and phase III multi-center trials currently in progress (1)

Green Tea

- Antioxidant Epigallocatechin-3-gallate (EGCG) is capable of crossing the blood-nerve and blood-brain barrier, and exerting neuroprotective benefits in animal models of peripheral nerve injury, spinal cord trauma, and ischemic stroke.

- Epigallocatechin-3-gallate also displays neuroprotective properties in animal models of chronic neurodegenerative diseases including amyotrophic lateral sclerosis, Parkinson's Disease, and Alzheimer's disease.

- Epigallocatechin-3-gallate's neuroprotection has largely been attributed to its potent antioxidant and anti-inflammatory properties; however, a number of studies have identified additional neuroprotective mechanisms.

Resveratrol

- Resveratrol shown to cross the blood-brain barrier and improve outcomes in animal models following multiple acute neurological insults including stroke, global cerebral ischemia, spinal cord injury, and traumatic brain injury (TBI).

- Resveratrol has also been demonstrated to slow the development of chronic neurodegenerative disease in animal models.

- Although many of resveratrol's therapeutic benefits are classically attributed to its potent antioxidant effects, numerous studies have identified additional mechanisms of neuroprotection.

- In adult rodents, administration of resveratrol resulted in reduced levels of oxidative stress and lipid peroxidation and stabilized endogenous antioxidants following TBI.

- Other studies have demonstrated that resveratrol treatment reduces brain edema and lesion volume, as well as improves neurobehavioral functional performance following TBI. The molecular mechanisms underlying the aforementioned neuroprotection remain largely unknown.

Nutritional Support in Repairing Concussion Damage

Suggested Concussion Supplement Considerations:

1. Omega-3 fats (high yield EPA/DHA fish oil) –the charity "Brain Health Education and Research Institute" (http://www.brainhealtheducation.org/resources/brain-injury-protocol), recommends 5000 mg of concentrated fish oil, providing approximately 3000 mg of omega-3 fat, consumed 3 times a day for a minimum of 1 week before decreasing to twice a day and eventually once a day

2. CDP-choline – 500 -1000 mg/d (until memory deficit and headaches have subsided)

3. Memory Support Complex – (4 capsules per day) each capsule contains CDP- choline (50 mg); Phosphatidylserine (100 mg, 50% grade); Huperzine A (25 mcg); Bacopa Monnieri (50 mg, std to 20% bacosides)

4. Lecithin Capsules -3 capsules (1200 mg) = 540 mg of Choline (180 mg choline per capsule)

5. High Potency Multiple Vitamin and Mineral (including Vitamin C – 1000 mg, Vitamin E – 400 IU, B-50 complex, Vitamin D 1000 IU)

6. Creatine Monohydrate (micronized) – 5,000 mg, twice daily – Increase ATP production

Additional Supplement Considerations

1. Curcumin – 480 mg, three times daily (to reduce inflammation)

2. Alpha-lipoic acid – 600 mg (1-3 times daily) (to improve mitochondrial function)

3. Coenzyme Q10 – 100 mg per day (to improve mitochondrial function)

4. Additional Nicotinamide – 500-1000 mg daily (requires physician monitoring of serum levels of liver enzymes to guard against liver damage) – to repair microtubules

Heavy Metal Toxicity and Detoxification

Important Reference: Sears S.E. Chelation: Harnessing and Enhancing Heavy Metal Detoxification – A Review. Scientific World Journal. 2013. https://www.hindawi.com/journals/tswj/2013/219840 : Children's Hospital of Eastern Ontario Research Institute,

- In modern society we are constantly exposed to heavy metals such as cadmium, lead and mercury, which have no essential biochemical roles in our body, and conversely can cause us a great deal of harm if they build up to toxic levels.

- These heavy metals bind to our tissues, create damaging free radicals (oxidative stress), disrupt our endocrine (hormonal system) and interfere with the absorption and function of important minerals such as magnesium and zinc.

- Cadmium is classified as a possible carcinogen.

- **Lead can damage the nervous system and be particularly harmful to the developing brains of young children.**

- **Mercury is also known to damage the brain and nervous system and there is an increasing number of people being affected by its bioaccumulation in the food chain, especially in regard to fish and seafood consumption. (1)**

- As a result, the FDA and EPA have developed guidelines about eating fish and seafood to help reduce the risk of serious mercury accumulation and nervous system damage in our bodies. (2, 3)

- Nevertheless, all of us ingest a certain amount of mercury and other heavy metals such as cadmium and lead on a regular basis, to some extent. (1)

In addition to mercury bioaccumulation in fish, we are exposed to toxic metals from many sources, some of which include:

- Activities and legacies of mining and toxic waste
- Lead in paint and gasoline
- Ongoing emissions form industrial and electricity-generating (particularly coal-burning) activities
- Chemicals in everyday products
- Novel technologies such as nanomaterials containing toxic elements like cadmium.
- Lead ingested from old drinking water supply pipes. (1)

- The good news is that, in addition to working to reduce our exposure and intake of these toxic metals, there are some natural things we can do to help remove or detoxify and eliminate some of the heavy metals already in our body and block the absorption of some heavy metals in our intestinal tract.

- Certain foods that are **high in sulfur** have been shown to be useful, as heavy metals have an affinity to bind sulfur. **Sulfur also makes this heavy metal complex more soluble** enabling the body to more easily eliminate heavy metals in the urine or via the fecal route.

- Good sources of sulfur-containing foods are **garlic and onions** (and the allium vegetables as they are known) and also the **brassicae family** of vegetables, including broccoli, Brussels sprouts, cabbage, cauliflower, bok choy and turnips.

- These are also known as cruciferous vegetable. These vegetables contain sulfur-containing sulfurophanes as well as indole-3 carbinol, both of which also possess impressive anti-cancer properties, in addition to being good detoxifiers of toxic metals.

- Garlic has prevented cadmium-induced kidney damage and decreased free radical damage due to lead in rat experiments.

- **Fiber ingested from whole grains and fruits has been able to reduce levels of mercury in the brain and in blood.** The use of **psyllium** husk fiber (the active ingredient in Metamucil) has been shown to **block the re-absorption of heavy metals** back into the body once secreted into the gut via the liver and gallbladder following a meal (enterohepatic circulation).

- The ingestion of healthy minerals such as calcium, selenium and iron, at optimal nutritional levels has been shown to block the absorption of heavy metals into the body.

- **Selenium supplementation** was also shown to **increase mercury excretion** from the body and reduce mercury-induced free radical damage in a study of 103 mercury-exposed villagers.

- **Calcium** is known to help block the absorption of **cadmium** and has **reduced lead mobilization** from the bones of women during their pregnancy and period of lactation. **In children,** nutritional **iron has blunted lead accumulation**.

- In addition certain dietary supplements can also be helpful as heavy metal detoxifiers. It is well documented that the mini-protein known as glutathione helps to remove heavy metals from body tissues and excrete them from the body. (1)

- Our bodies naturally make glutathione from the ingestion of three amino acids found in food (glutamic acid, cysteine and glycine).

- The problem is that much of our glutathione gets used up by acting as an antioxidant in our cells and as a conjugating agent for various substances (including acetaminophen) in the detoxification of a variety of agents.

- This often leaves an insufficient amount of glutathione available to maximize its heavy metal detoxifying function.

- However, studies suggest that we can optimize our glutathione status by taking a supplement that boosts glutathione synthesis. These ingredients include alpha-lipoic acid, N-acetyl cysteine, L-glutamine and milk thistle, which contains a glutathione-raising flavonoid known as silymarin.

- Taking glutathione in its preformed state has not been shown to be useful as it is poorly absorbed from the gut.

- But supplementing with these glutathione-boosting agents appears to be a good way to help optimize glutathione status, and thus heavy metal detoxification.

- In fact, **alpha-lipoic** acid has its own heavy metal detoxifying properties, over and above its role in raising glutathione. **N-acetylcysteine** also has its own unique heavy metal detoxifying properties. So, it may be wise to take these glutathione precursors in a combination daily supplement formulation as a means to boost heavy metal detoxification. (1, 4)

- There are other sulfur-containing amino acids that can also be helpful, which include **taurine and methionine.**

- Your body normally has ample methionine if you eat standard protein foods and ingest sufficient amounts of the B-vitamins folic acid and vitamin B12.

- Taurine is the most abundant amino acid in the heart muscle and it may play a key role in helping to prevent congestive heart failure, as it serves a multi-purpose function in the heart muscle.

- Researchers are still looking into its role in heart health, but it certainly has some detoxification ability regarding heavy metals. (1, 5)

- For individuals with serious heavy metal toxicities doctors can administer intravenous pharmaceutical chelating agents, such as DMSA (dimercaptosuccinic acid), DMPS (dimercaptopropane sulfonate), EDTA (ethylenediaminetetraacetic acid: Edetic acid), Penicillamine, which are used to remove specific heavy metals from body tissues, and in some cases are used for the removal of excessive copper (Wilson's disease) and other nutritional metals.

- But this is not something that is typically done as a standard preventive measure on the everyday patient seen in clinical practice. (1)

Detoxification Strategy for Consideration

- So, what does a heavy metal prevention and detoxification strategy look like for most patients? Well, first and foremost individuals should do their best to reduce exposure to heavy metals in the environment and the food you eat. With regard to fish and mercury consumption the FDA and EPA have made the following recommendations for pregnant and nursing women and young children, but we should all pay heed to this advice in my view:

Dietary Fish and Seafood Strategy

- Avoid eating shark, swordfish, king mackerel, and tilefish (also known as golden bass or golden snapper)
- Limit consumption of all other types of fish to 12 ounces per week.
- Limit the consumption of canned albacore ("white") tuna or fresh tuna to no more than 6 ounces per week.
- Limit the fish eaten by young children to even smaller portions per week.
- Check local advisories about the safety of fish caught in local lakes, rivers, and coastal areas. If no advice is available, eat no more than 6 ounces per week of locally caught fish, and do not consume any other fish during that week.
- If more than the recommended amount of fish is eaten in one week, eat less in the following weeks. (2, 3)

Additional information about mercury can be found in references 6 and 7 at end of this section. I have also included a list of the safe and less safe fish to consume, regarding mercury levels, at the end of this section, as a quick reference.

Other Strategies:

- With respect to detoxification of heavy metals, the available research suggests that regular consumption of whole grains and fruits, and at least 3-5 servings per week of a cruciferous vegetable would help to remove some toxic metals from the body on an ongoing basis. Adding garlic and onions to foods being prepared also seems prudent, as well as the possible use of a fiber supplement containing psyllium husk fiber. (1)

- As for supplements, individuals may benefit from the use of a high potency multiple vitamin and mineral supplement preparation that is enriched with the antioxidants vitamin C, vitamin E and selenium, which help to preserve and/or raise gluthatione levels.

- With respect to calcium, consider using a multiple vitamin or an additional calcium supplement plus the food you eat each day. Individuals should aim for at least 1000 mg of calcium per day, and in many cases more optimally between 1200 and 1500 mg per day.

- Regarding selenium, a good multiple vitamin should contain 100-200 mcg of selenium, which is plenty. A multiple vitamin can also help ensure more ideal intake of folic acid and vitamin B12 to help optimize methionine synthesis.

- There is some preliminary evidence that a probiotic supplement may also be helpful in the heavy metal detoxification process.

- Patients may also be advised to take a supplement each day containing glutathione boosters and detoxifiers, including alpha-lipoic acid, N-acetylcysteine, L-glutamine and Milk thistle – standardized to 80% silymarin content. (1,4)

- Finally, sweating with exercise or by using a sauna may be a benefit as well, as toxic metals are also excreted in sweat. So, regular exercise is also a natural detoxifier, along with providing a multitude of other health benefits - another reason to keep doing aerobic exercise. (1)

Fish: High-risk – Lower-risk Varieties

Fish High In Mercury to Avoid:

- Shark
- Swordfish
- King Mackerel
- Tilefish (a.k.a. golden bass, golden snapper)

Lower in mercury but still to be avoided:

- Tuna steak (also used in sushi and sashimi)
- Canned Albacore white tuna

Fish to be eaten in limited quantities by pregnant women, or who may be pregnant, as well as children

- Canned light tuna
- Sea bass
- Gulf Coast oysters
- Eastern Oyster
- Marlin
- Halibut
- Channel catfish (wild)
- Haddock
- Mahi-mahi
- Largemouth bass
- Blue mussel
- Cod
- Pollack
- Gulf Coast blue crab
- Pike
- Great Lakes salmon
- Lake whitefish
- White croaker
- Walleye

Fish Lowest in Mercury Content

- Catfish (farmed)
- King crab
- Scallops
- Fish sticks
- Flounder (summer)
- Trout (farmed)
- Salmon (wild Pacific)
- Shrimp
- Tilapia
- Sardines

References:

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Autism Spectrum Disorder: Research
10 Novel Approaches

Primary Investigative and Integrative Approaches Used by Recognized Health Practitioner Experts in this Field:

1. Food Sensitivities: Dairy, Gluten – most common

2. Feingold – salicylates in food

3. Dysbiosis – OAT Test or stool test (see OAT on next slide)

Urinary Organic Acids Test

OAT- Great Plains Laboratory Inc.

End-products of metabolism found in urine sample that identify:

- Bacterial (clostridia) or Fungal (Candida) toxins from dysbiosis – released into blood and cross-blood brain barrier and disrupt neurotransmitter function: Example Clostridia bacteria secrete HPHPA (3-hydroxyphenyl-3-hydroxyproprionic acid), which is found in high concentration in urine in ASD and Schizophrenia.
- Clostridia also increases dopamine – which has mental health implications
- Candida toxins can inhibit methionine synthesis by inhibiting 5-methylene tetrahydrofolate reductase enzyme – which then inhibits synthesis of SAMe and thus decreases neurotransmitter synthesis

Also Identifies:

- Biomarkers of mitochondrial dysfunction
- Biomarkers of glutathione deficiency
- Biomarkers of oxidative stress
- Biomarkers of neurotransmitter imbalance
- Biomarkers of chemical toxicities

Claim that OAT is more reliable than stool culture testing for low-grade pathogens in gut microflora.

4. **Leaky Gut and Serum Zonulin Test** – increased gut permeability produces immune inflammatory response and promotes neuroinflammation, a known factor in ASD.

Serum Zonulin Test - from gluten inflammation (biomarker of gut inflammation):

In recent years, scientists have identified zonulin as a key biomarker for intestinal permeability, which has been associated with celiac disease, non-celiac gluten sensitivity (NCGS), and other GI and systemic conditions.

Human zonulin is a protein that increases intestinal permeability in small intestine and participates in intestinal innate immunity. Circulating zonulin in serum is considered as a useful marker of intestinal permeability.

In a healthy GI tract, the tight junctions between cells prevent unregulated influx of luminal contents. However, certain situations, such as the presence of gluten for people with celiac disease or NCGS, can lead to high levels of zonulin in the GI tract. This can induce the breakdown of the tight junctions, leading to intestinal permeability and allowing zonulin to enter the bloodstream.

As a result, circulating zonulin is a clinically useful marker of intestinal permeability. What's more, zonulin is the only regulator of intestinal permeability known to be reversible, which makes it valuable in monitoring therapeutic interventions as well.

Several autoimmune, inflammatory and neoplastic diseases have been associated with elevated levels of zonulin or evidence of increased intestinal permeability, which can be identified by our Serum Zonulin test.

Zonulin Reference:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3356365/

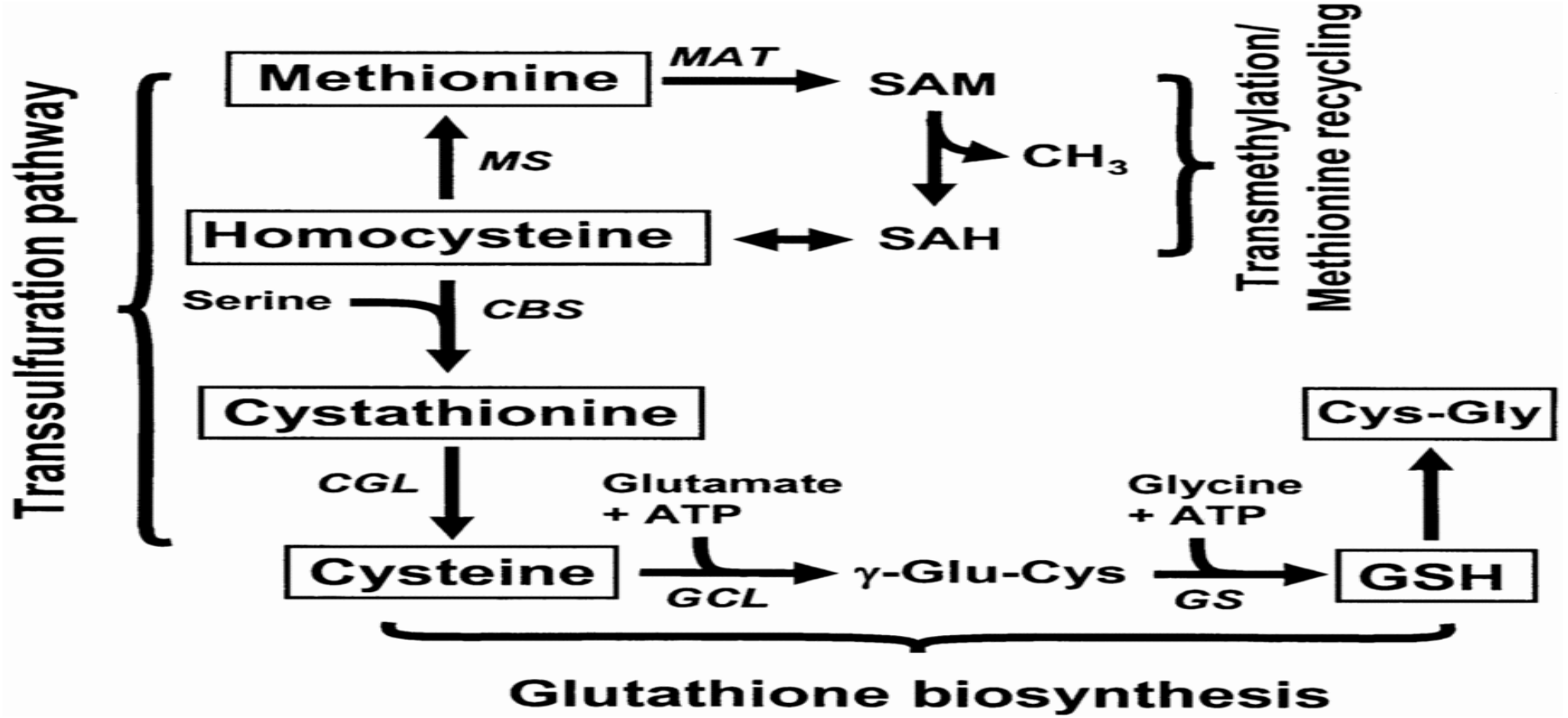
5. Methylation (MTHFR and Methionine defects) – assess homocysteine, RBC folate, serum B12, methylmalonic acid, nutrigenomic testing.

Methylation required for neurotransmitters, phospholipids on nerve cell membrane, detoxification, and sulfur- dependent detoxification and glutathione status (detoxification and antioxidant function)

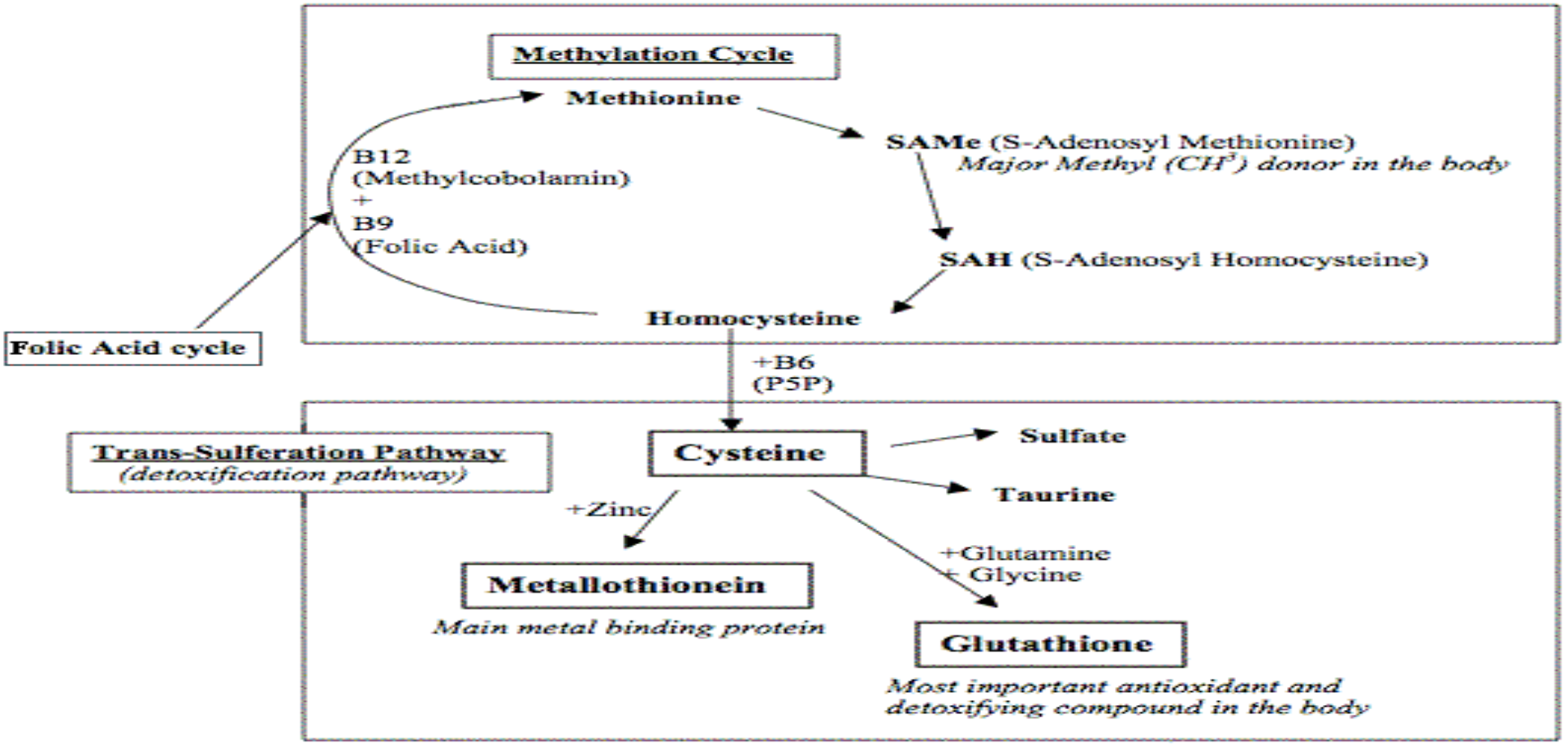
Assess urine for free radical markers or blood MDA

The OAT also helps identify glutathione deficiency

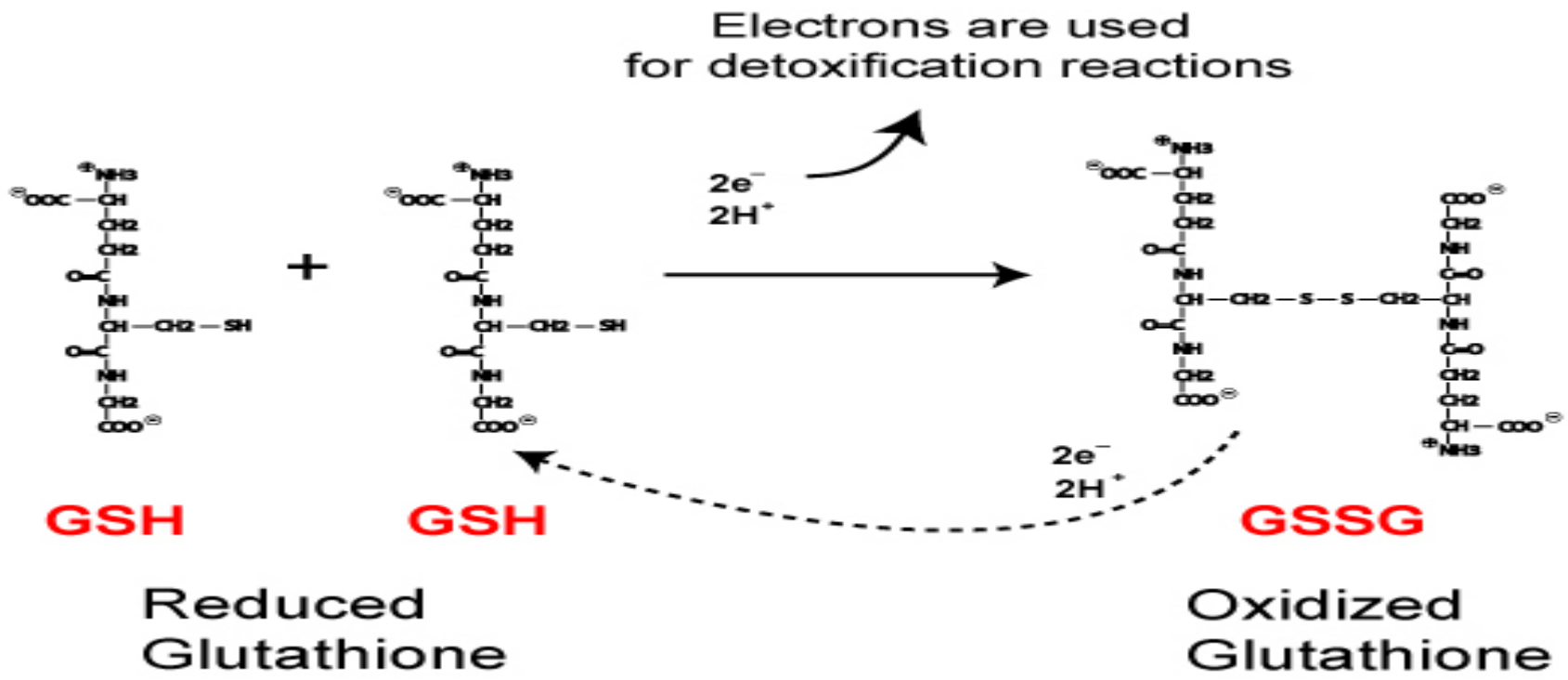
Glutathione Synthesis

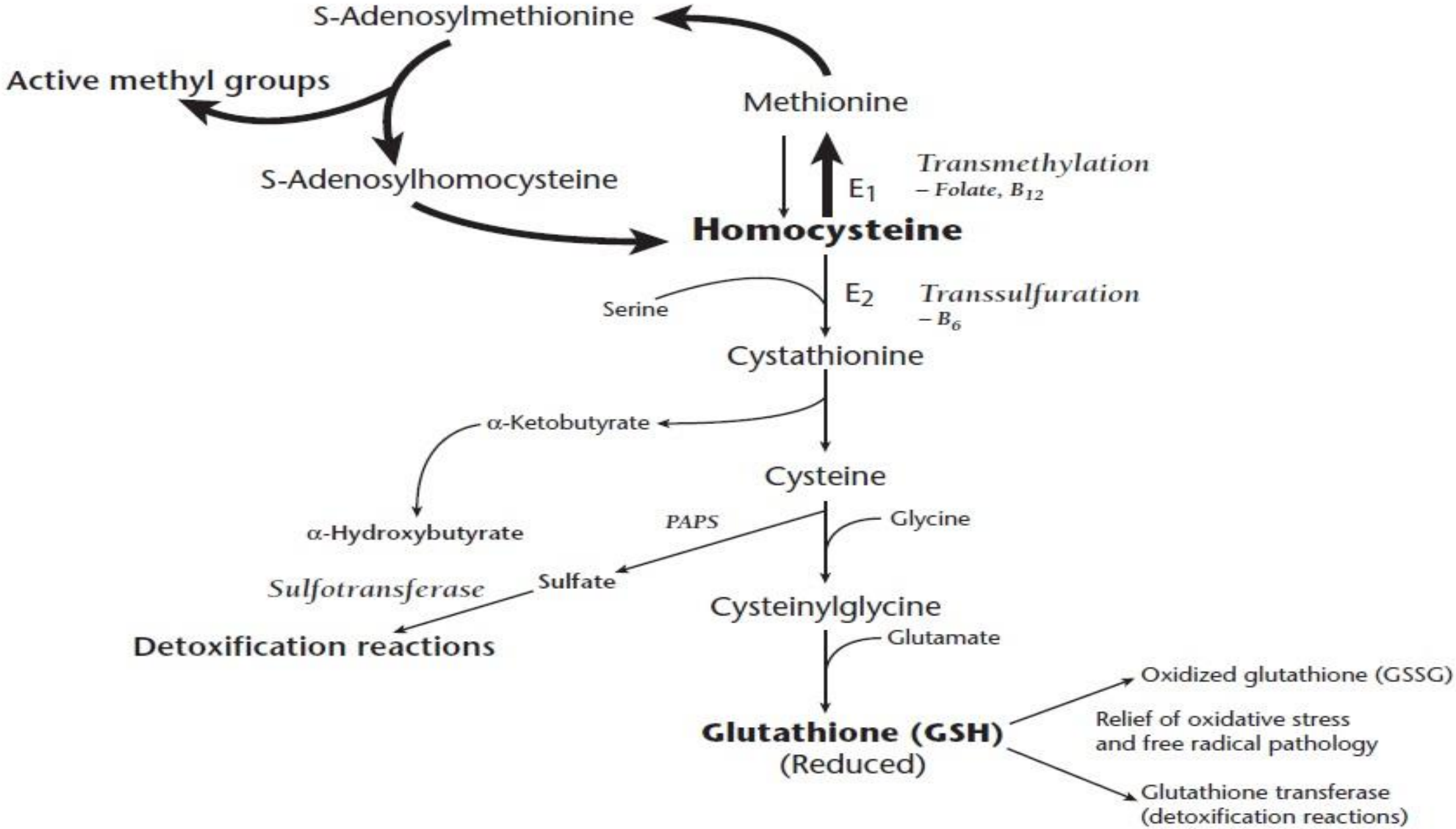


Decreased Glutathione Synthesis – see increased blood and urine MDA levels – oxidative biomarkers



Reduced and Oxidized Glutathione




S-Adenosylmethionine
Active methyl groups
Methionine
S-Adenosylhomocysteine
E1
Transmethylation
– Folate, B12
Homocysteine
Serine
E2
Transsulfuration
– B6
Cystathionine
α-Ketobutyrate
Cysteine
α-Hydroxybutyrate
PAPS
Glycine
Sulfotransferase
Sulfate
Cysteinylglycine
Detoxification reactions
Glutamate
Oxidized glutathione (GSSG)
Relief of oxidative stress
and free radical pathology
Glutathione (GSH)
(Reduced)
Glutathione transferase
(detoxification reactions)

2009 Research Paper: James, S. J., Rose, S., Melnyk, S., Jernigan, S., Blossom, S., Pavliv, O., Gaylor, D. W. Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism.. http://www.fasebj.org/content/23/8/2374.short -

- Plasma biomarkers of oxidative stress have been reported in autistic children; however, intracellular redox status has not yet been evaluated.

- Lymphoblastoid cells (LCLs) derived from autistic children and unaffected controls were used to assess relative concentrations of reduced glutathione (GSH) and oxidized disulfide glutathione (GSSG) in cell extracts and isolated mitochondria as a measure of intracellular redox capacity.

- **The results indicated that the GSH/GSSG redox ratio was decreased and percentage oxidized glutathione increased in both cytosol and mitochondria in the autism** LCLs. Exposure to oxidative stress *via* the sulfhydryl reagent thimerosal resulted in a greater decrease in the GSH/GSSG ratio and increase in free radical generation in autism compared to control cells.

- Acute exposure to physiological levels of nitric oxide decreased mitochondrial membrane potential to a greater extent in the autism LCLs, although GSH/GSSG and ATP concentrations were similarly decreased in both cell lines.

- **These results suggest that the autism LCLs exhibit a reduced glutathione reserve capacity in both cytosol and mitochondria that may compromise antioxidant defense and detoxification capacity under prooxidant conditions.**

6. Stool Testing for parasites and pathogenic bacteria, yeast etc.

7. Endocannabinoid system: cannabinoid compounds from marijuana can interact with endocannabinoid receptors in the CNS and modulate neuroinflammation, and other aspects seen in the brain in autism spectrum disorder (ASD)

This is especially true for CBD (cannabidiol) vs THC. Therefore, no psychoactive effect.

2017 Review Paper: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5535348/ :
Endocannabinoids and Autism Spectrum Disorder (ASD)

- The etiology of ASD is not fully understood but there is consensus that genetics, environmental and autoimmunity factors interact to play a role in its development.

- Neuroinflammtion in ASD has attracted the attention of research in targeting the neuroprotective mechanisms.

- The growing number of medical benefits of Endocannabinoid System (ES), such as their ability to regulate neuroinflammation, neurogenesis and memory, raise the question of their potential role as a preventive treatment of ASD

- Very good review paper (2017)

8. Neurotransmitter Imbalance – OAT (dopamine etc.) – urinary organic acids test (i.e. Great Plains Laboratory) dysbiosis or yeast/fungal or bacterial gut populations produce end-products that disturb normal neurotransmitter function. OAT uncovers end-products in urine and provides dietary, supplement and sometimes prescription anti-microbial drug therapy.

9. Food Allergy Testing – Allergist, plus MRT assessment - MRT = Mediator Release Test (MRT) – http://nowleap.com/mrt-iii-the-future-of-food-sensitivity-testing

- Also: LCAT Food Sensitivity Test https://cellsciencesystems.com

10. Amino Acid Profile – blood assessment of free amino acid pool

Consult Jeffrey Bland Book – Epigenetics and Autism story (The Disease Delusion – P.57-63 (Hard Cover edition)

Four Important Leaders in the Medical World of Integrative Autism Treatment Methods

William Shaw Ph.D. (founder of The Great Plains Laboratory in Kansas Phone Number: 913-341-8949

- https://en.wikipedia.org/wiki/William_Shaw_(autism_researcher)
- Dr. Shaw published a famous study in the journal Nutritional Neuroscience in 2010 (See link below for research abstract):
- https://www.ncbi.nlm.nih.gov/pubmed/20423563

Dr Kurt Woeller D. O. (author and lectures for The Great Plains Laboratory)

- http://drwoeller.com
- http://drwoeller.com/about-dr-woeller

Sandler RH: He did the study on vancomycin and autism:

- See research abstract: https://www.ncbi.nlm.nih.gov/pubmed/10921511

Dr. Anju Usman M.D (Director of True Health Medical Center in Naperville)

- http://theautismintensive.com/interviews/anju-usman-md
- **Autism Video on Diagnosis** - Medical Center in Naperville https://www.youtube.com/watch?v=nzK02jaJwzQ