Nutritional Medicine and the Nervous System: Part 1

Brain Development
ADHD
Alzheimer's, MCI, Dementia
Multiple Sclerosis
ALS
Parkinson's Disease

Nutritional Medicine in Brain Development, the Aging Brain and Neurodegenerative Diseases

Topics Covered:

- Brain and Nervous System Development
- ADHD
- The Aging Brain in Alzheimer's Disease, Mild Cognitive Impairment and Age-Related Dementia
- Multiple Sclerosis
- Amyotrophic Lateral Sclerosis (ALS)
- Parkinson's Disease

Nutrition And Brain Development:

Why Essential Fatty Acids And Specific Vitamins/Minerals Are Critical For Brain Development And Mental Performance

The Effect Of Nutrition On Brain Development And Mental Performance Involves An Understanding Of The Following

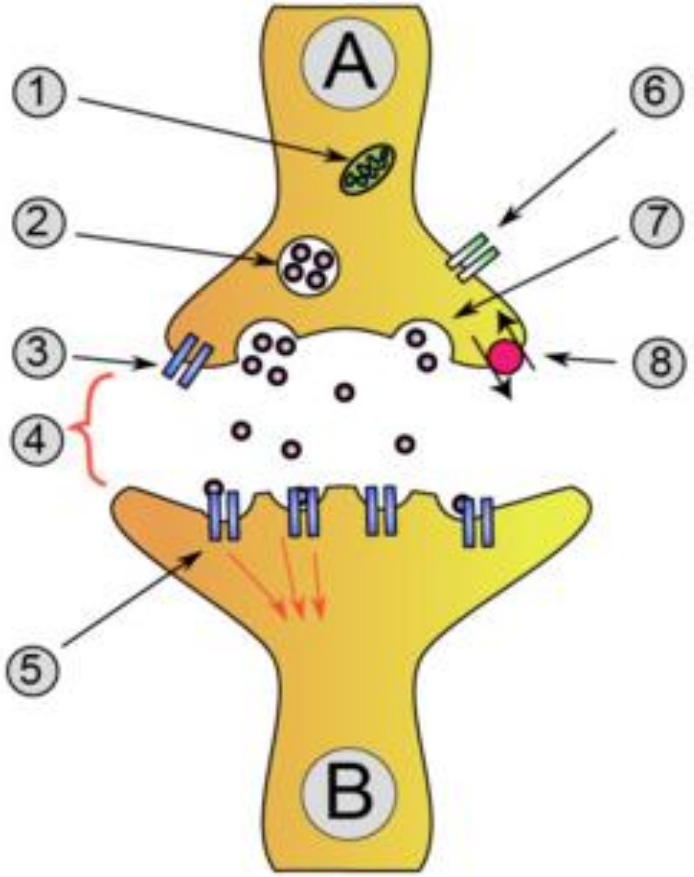
1. Neurotransmitters and the brain
2. Vitamins and minerals and the brain
3. Essential fatty acids and the brain

Part 1 Neurotransmitters and Vitamins And Minerals

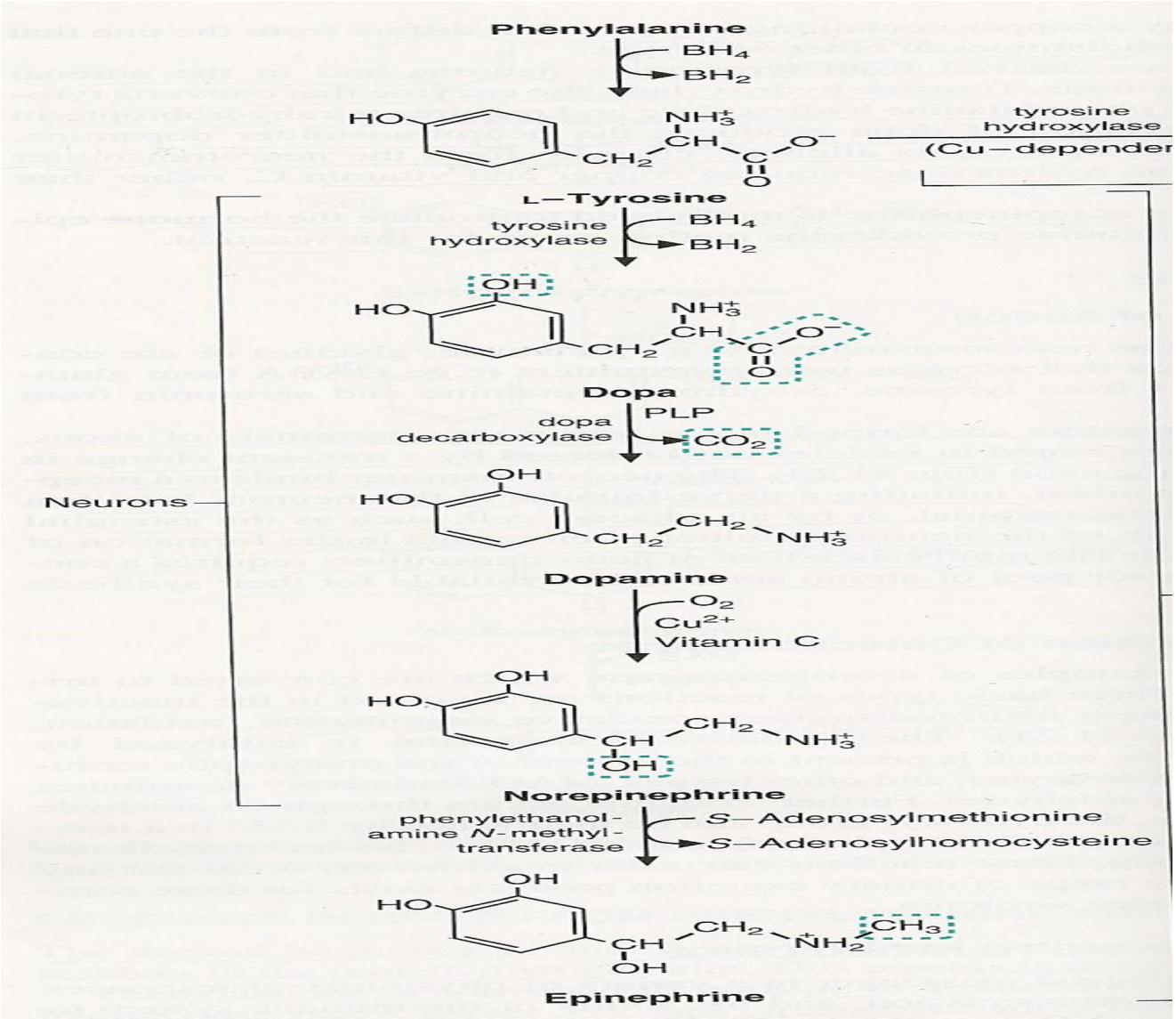
Brain cells make neurotransmitters that act like signaling agents from one nerve cell to the next (synaptic cleft), which are important in:

- Brain development
- Learning and Memory
- Alertness and Focused Attention
- Arousal
- Sleep
- Mood
- Cognition
- Motivation and Reward Behaviour

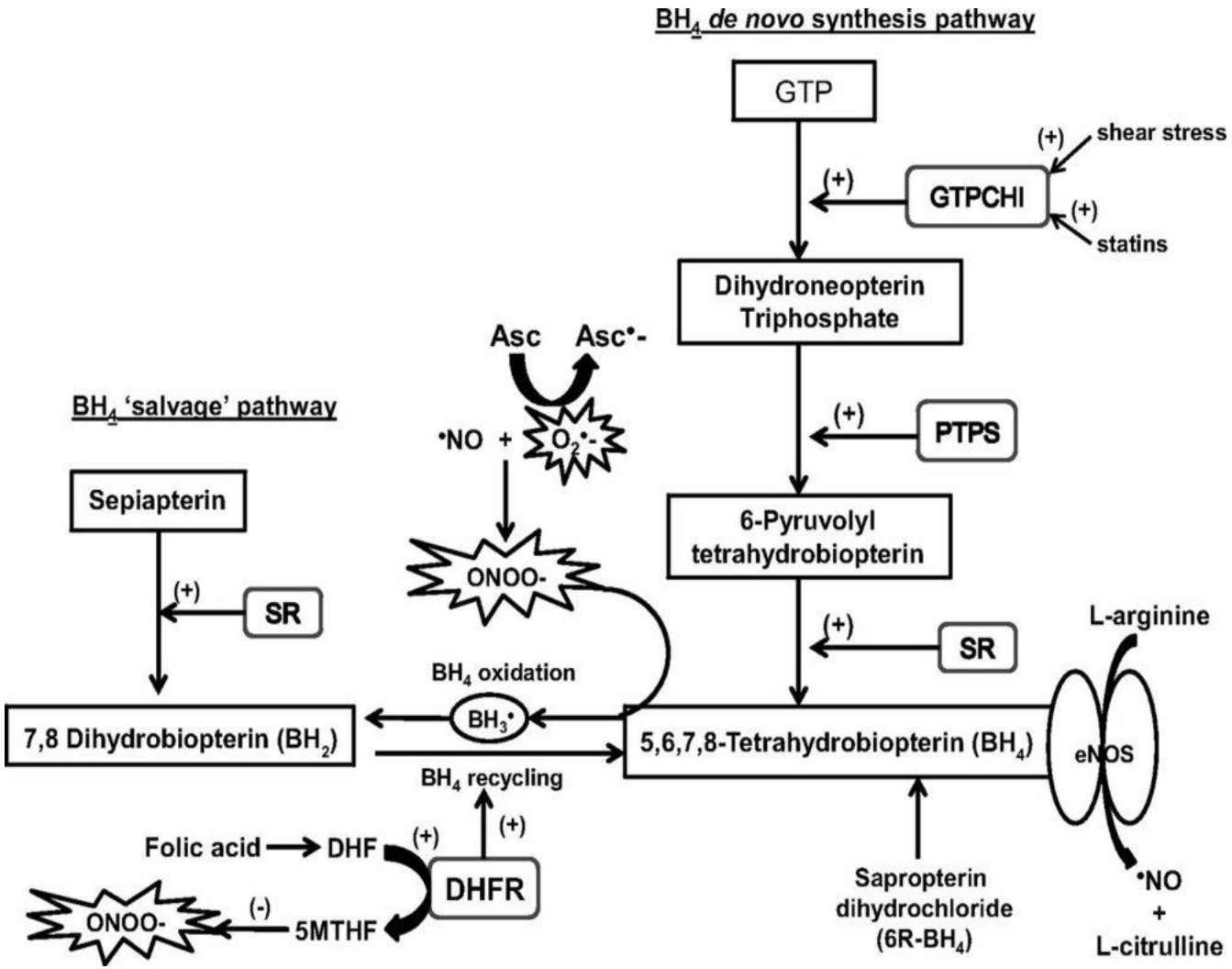
The Synaptic Cleft



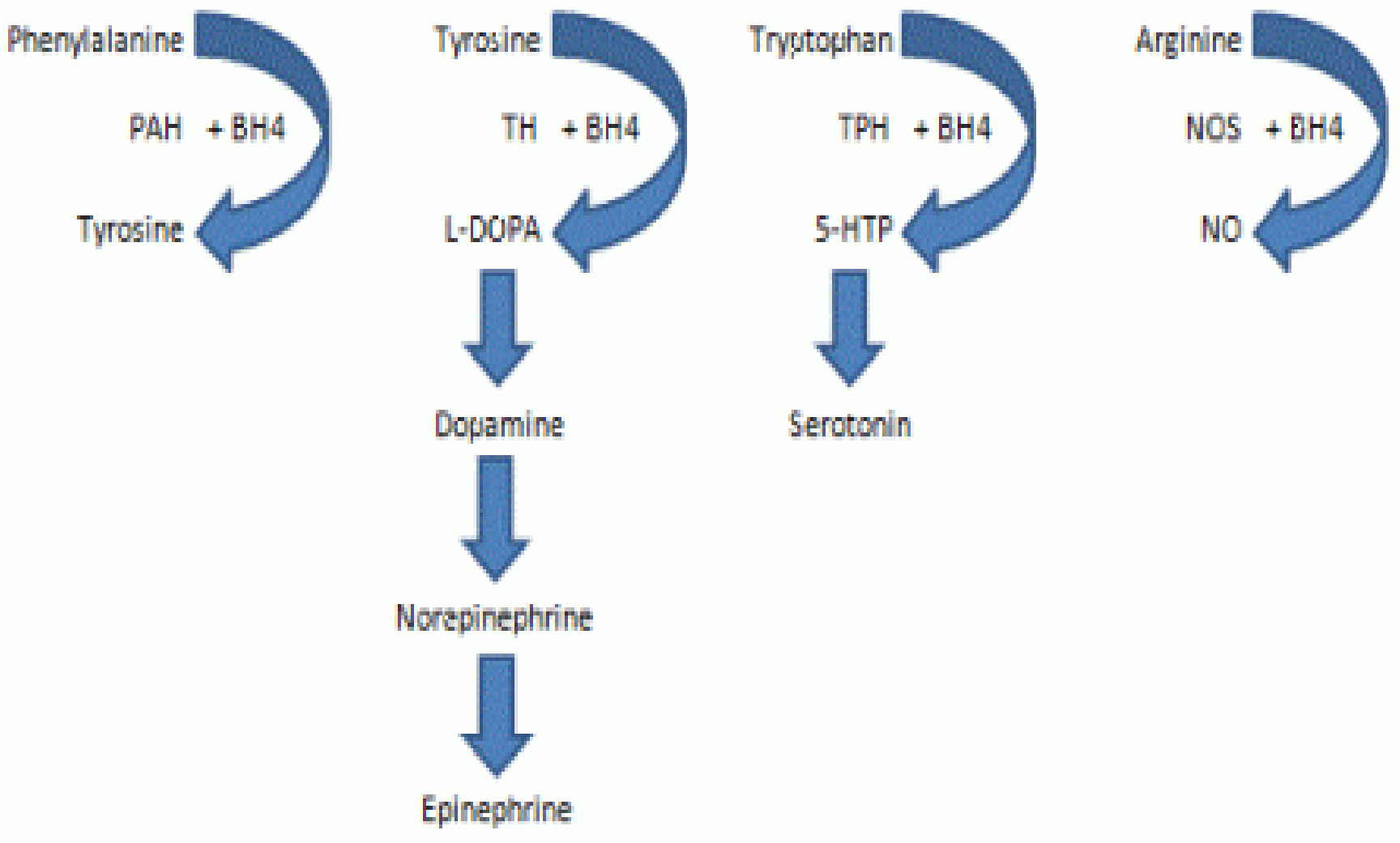
Synthesis of Dopamine, Norepinephrine and Epinephrine: Note dopa-decarboxylase



Note Role of Folic Acid in BH4 Synthesis



Tetrahydrobiopterin (BH4) Pathways



Norepinephrine

Norepinephrine required for **“alertness”** and arousal, and influences on the reward system.

Decreased Synthesis or Release of Norepinephrine is a common factor in:

1. Attention-deficit/hyperactivity disorder (ADHD) – “ADHD drugs (Ritalin etc.) are designed to increase release or effects of **Dopamine**
2. Depression
3. Hypotension

Epinephrine and Dopamine

- **Epinephrine** – required for memory consolidation.
- **Dopamine** - Dopamine has many functions in the brain, including important roles in **behavior** and **cognition**, **motivation** and **reward**, **sleep**, **mood, attention,** and **learning**.
- Deficits in dopamine levels are implicated in attention-deficit hyperactivity disorder (ADHD)
- Thus, a genetic defect in dopa-decarboxylase, or a deficiency in Vitamin B6 or magnesium can dramatically affect mental performance and behavior
- ADHD drugs (Ritalin) – work by inhibiting the dopamine transporter to enable it to remain longer in synaptic cleft

Vitamin B6 And Magnesium In ADHD

- In ADHD, there is often a defect in the enzyme converting dopa to dopamine (dopa decarboxylase enzyme). This enzyme requires Vitamin B6 and magnesium

Ernst M. DOPA Decarboxylase Activity in Attention Deficit Hyperactivity Disorder Adults. A [Fluorine-18]Fluorodopa Positron Emission Tomographic Study. The Journal of Neuroscience, August 1, 1998, 18(15):5901-5907

https://www.ncbi.nlm.nih.gov/pubmed/11443526 (Genetic Polymorphism of dopa-decarboxylase and association with ADHD)

- Some evidence that ADHD can be improved with Vitamin B6 (15–30 mg/kg body weight per day) and/or magnesium supplementation.
- However, high doses of Vitamin B6 can cause neurotoxicity – requires close monitoring
- More recently lower doses have shown good results (0.6 mg/kg vitamin B6) and 6.0 mg/kg magnesium) – see next slide

Coleman M, Steinberg G, Tippett J, et al. A preliminary study of the effect of pyridoxine administration in a subgroup of hyperkinetic children: a double-blind crossover comparison with methylphenidate. Biol Psychiatry 1979;14:741–51.

Brenner A. The effects of megadoses of selected B complex vitamins on children with hyperkinesis: controlled studies with long term followup. J Learning Dis 1982;15:258–64.

Haslam RHA. Is there a role for megavitamin therapy in the treatment of attention deficit hyperactivity disorder? Adv Neurol 1992;58:303–10.

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2006 Intervention Study (B6 and Mg in ADHD Trial)

http://europepmc.org/abstract/med/16846100

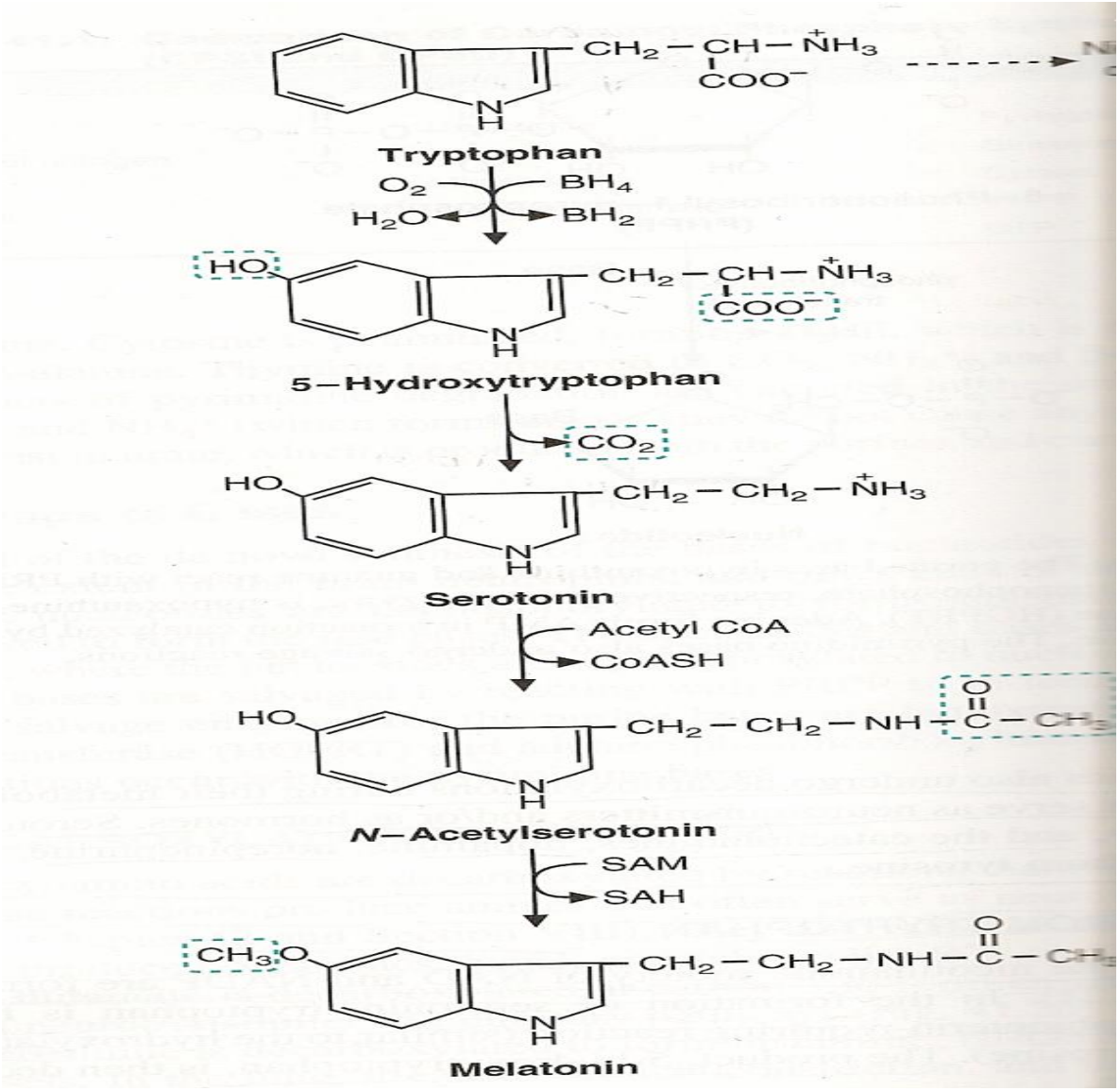
- Some previous studies have reported the involvement of magnesium (Mg) deficiency in children with ADHD syndrome.
- In this study, 40 children with clinical symptoms of ADHD were followed clinically and biologically during a magnesium-vitamin B6 (Mg-B6) regimen (6 mg/kg/d Mg, 0.6 mg/kg/d vit-B6), which was set up for at least 8 weeks.
- Symptoms of ADHD (hyperactivity, hypermotivity/ aggressiveness, lack of attention at school) were scored (0-4) at different times; in parallel, intra-erythrocyte Mg^{2+} (Erc-Mg) and blood ionized Ca^{2+} (i-Ca) were measured.
- Children from the ADHD group showed significantly lower Erc-Mg values than control children (n = 36).
- In almost all cases of ADHD, Mg-B6 regimen for at least two months significantly modified the clinical symptoms of the disease: namely, hyperactivity and hypermotivity/aggressiveness were reduced, school attention was improved.
- In parallel, the Mg-B6 regimen led to a significant increase in Erc-Mg values.
- When the Mg-B6 treatment was stopped, clinical symptoms of the disease reappeared in few weeks together with a decrease in Erc-Mg values.

Vitamin B6 And Brain Development

- Animal Studies show that lack of Vitamin B6 during pregnancy significantly impairs brain development in offspring. Many believe the same is true for humans.

- Thus, during pregnancy and lactation the mother's Vitamin B6 status should be optimal. Thereafter, the infant, child and adult must maintain optimal Vitamin B6 nutritional status during their life for normal brain development, function and mental performance.

Synthesis of Serotonin and Melatonin



Serotonin

In the brain serotonin plays an important role in the modulation of

1. Anger
2. Aggression
3. Mood – depression results from serotonin insufficiency (antidepressant drugs raise serotonin levels as a general rule)

- Sunlight increases serotonin levels as does intake of tryptophan (amino acid) found in foods and supplementation with 5-hydroxy tryptophan. Some foods contain serotonin

Serotonin-Containing Foods

- Serotonin is found in mushrooms and plants, including fruits and vegetables.
- The highest values of 25–400 mg/kg have been found in nuts of the **walnut and hickory genuses.**
- Serotonin concentrations of 3–30 mg/kg have been found in **plantain, pineapple, banana, kiwifruit, plums, and tomatoes**

Other B-Vitamins

Maternal Vitamin B12 deficiency has also lead to a progressive neurological disorder in infant (reversed with Vit B12 treatment)

Stollhoff K. Vitamin B12 and brain development European Journal of Pediatrics Volume 146, Number 2 / March, 1987)

Deficiencies in Folic Acid, Biotin, Pantothenic Acid and/or Vitamin C have all been shown to cause impaired neurological development during early human development (e.g. delayed maturation of the basic electroencepalographic patterns

T. Ramakrishna Vitamins and Brain Development Physiol. Res. 48: 175-187, 1999

Interactions of B-Vitamins and Vitamin C

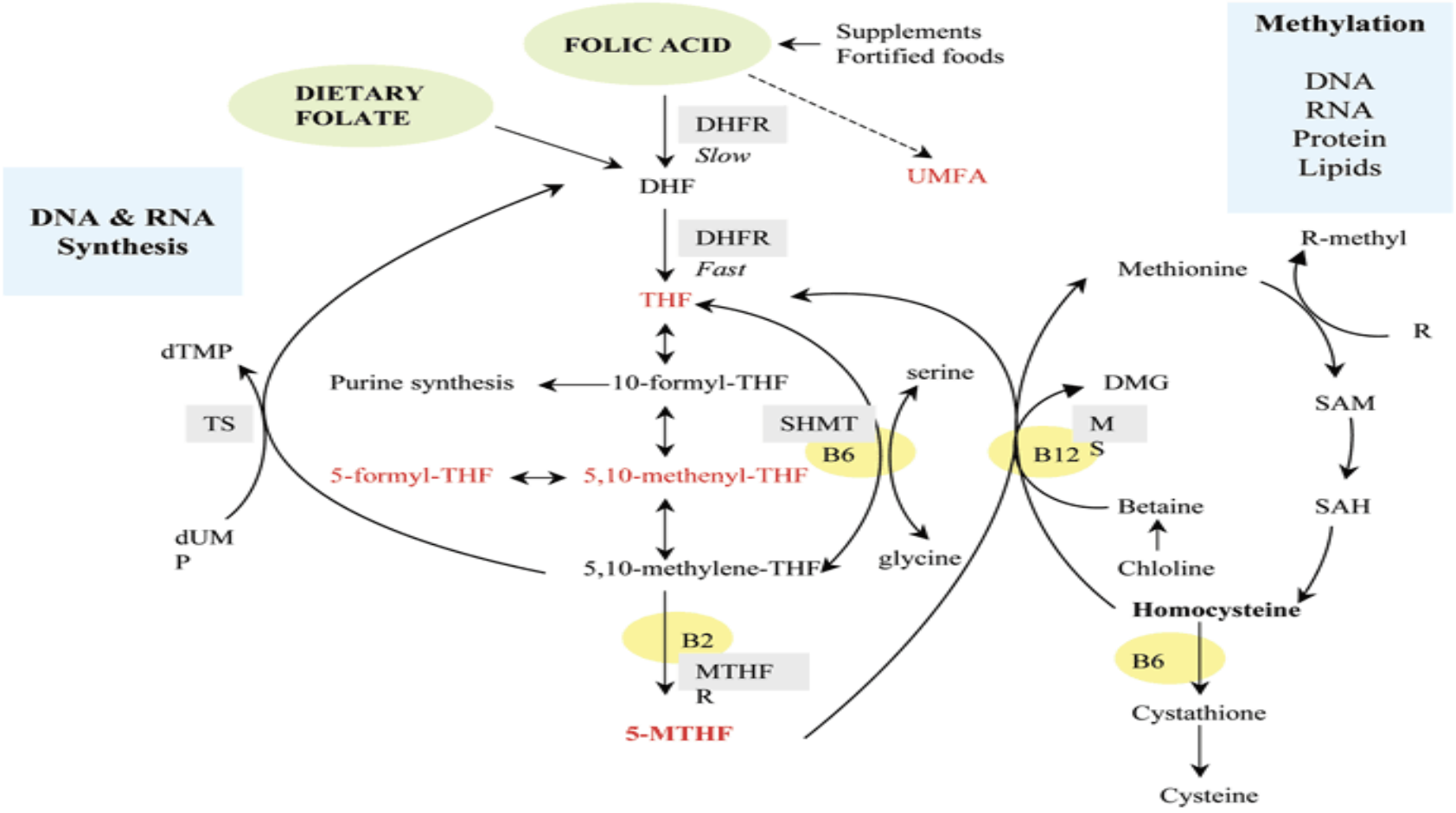
- Vitamin B6 deficiency impairs vitamin B12 absorption
- Biotin deficiency may be aggravated by pantothenic acid deficiency.
- Vitamin C deficiency results in impaired metabolism, which produce symptoms of folic acid deficiency, as Vitamin C is required for folic acid activation

T. Ramakrishna Vitamins and Brain Development Physiol. Res. 48: 175-187, 1999

A Quick Review of Folic Acid and Vitamin B12

1. Folate and Vitamin B12 required to methylate homocysteine, converting it to methionine
2. Certain forms of Folate are required to make thymidine (an important DNA base) and for purine synthesis
3. Methyl Folate is required to methylate cytosine residues on DNA- acting as an important epigenetic switch, and for DNA and RNA methylation.
4. Insufficient Folic acid or inability to form Methylfolate puts developing child at risk for neural tube defects (the same is true for choline – reviewed shortly)

Folic Acid Forms and Activation



Pregnancy and Folate

A genetic defect in the 5-methylene tetrahydrofolate reductase enzyme (5-MTHR) accounts for many neural tube defects and preliminary evidence suggests it may also contribute to Down's Syndrome.

Physicians should monitor homocysteine levels in pregnant women, and ensure adequate folate intake prior to conception and during pregnancy. In cases of 5-MTHR defect, some, but not all of the folate should be taken in methylfolate form.

Nutrigenomic testing can also identify 5-MTHFR defect.

AMA Supports More Choline in Prenatal Vitamins: And Adults Need More Too

- At the 2017 American Medical Association Annual Meeting in Chicago, the AMA announced that it now supports an increase in the nutrient known as “choline” in all prenatal vitamins to 450 mg per day.

- Choline, like folic acid, is proven to help prevent spina bifida defects in the developing fetus and other neural tube deformities that can affect spine and brain development.

- As of 2016, none of the top 25 prenatal multivitamins contains the scientifically-backed choline dose for pregnant women (450 mg per day). This recommended dosage was first established 1998 by the Institute of Medicine, which recognized choline as an essential nutrient.

- But choline isn’t just important to the developing fetus. The growing and adult human body also has a need for adequate choline.

- So, it may be surprising to learn that 90% of adults don’t get the recommended amount of choline each day, according the latest findings from the National Health and Nutrition Examination Survey data or the NHANES in the United States.

- Adults are advised to consume 400-550 mg of choline per day in their diet.

Folic Acid Supplementation During Pregnancy May Reduce Risk of Down's Syndrome, in Addition to Neural Tube Defects

It has been established for some time that folic acid supplementation during pregnancy is associated with a 48% lower risk of having a child with a neural tube defect (e.g., spina bifida, anencephaly).

A study in *The Lancet* [2003; 361(9366):1331-5] showed that folic acid supplementation is also associated with reduced risk of Down's syndrome.

Researchers compared medical data from approximately 490 families at high risk of NTD with data from 516 families at high risk of Down's syndrome, and discovered that Down's syndrome was much more prevalent in pregnancies among at-high-risk families of NTD. The evidence suggested that mothers of children with Down's syndrome experience an abnormal metabolism of folate and methyl, as well as mutations in their folate gene. These traits are also seen in infants affected by neural tube defects.

- Folate (folic acid, a B-vitamin) is unique in nature in that it can obtain a methyl group (CH_3) once converted to active form within the body, which it donates to homocysteine to permit its enzymatic conversion to methionine.

- Once formed within the cells of the body, methionine (a methyl-containing amino acid) extracts the adenosine ring from adenosine triphosphate (ATP) and becomes S-adenosyl methionine. S-adenosyl methionine is then able to donate its methyl group (which was originally derived from folate) to many biochemical reactions, including the synthesis of DNA bases and to methylate DNA residues – important epigenetic switch regulate gene expression

- Thus, DNA synthesis requires a constant and adequate supply of folate each day of our lives. During pregnancy, the rapid cell division rate of the fetus demands an even greater supply of folic acid, and if the demand is not met, DNA-defects occur, which most often manifest as neural tube defects. Evidence from The Lancet study suggests that the same may be true for Down's syndrome. To complicate matters, some individuals have an inborn error of folate or methyl metabolism, in that they show a defect in the enzyme that converts homocysteine to methionine, and thus produce insufficient amounts of S-adenosyl methionine.

- However, studies show that these individuals can significantly improve the conversion of homocysteine to methionine if they are provided with higher supplementation levels of folic acid (which is the coenzyme for this reaction), in many cases.

- Thus, mothers who are identified as high-risk for NTD usually express this type of folate or methyl defect and therefore, are prescribed higher supplemental levels of folic acid.

- *The Lancet* study has provided evidence that these same women are also at higher risk for Down's syndrome, indicating that higher folic acid supplementation may be of great importance in reducing the risk of both NTD and Down's syndrome.

- The researchers conclude that because of the links in the development of the two complications, folate supplementation before conception has the potential to reduce NTD and Down's syndrome during pregnancy.

- Most women would benefit from 400 mcg of folic acid supplementation prior to conception (most multiple vitamins contain this amount) and 800 mcg during pregnancy (the amount contained in prenatal vitamins).

- Women with folate or methyl metabolism problems require additional amounts of supplemental folic acid, some of which should provided in the form of methylfolate. The physician should monitor homocysteine leverls to ensure sufficient folate and/or methylfolate effectively recycling homocysteine to methionine – an important biomarker.

Reference: National Nutritional Foods Association (Supplement) April 28, 2003

Conclusion: Vitamins And Brain

- You need to ensure that children are getting sufficient access to all B-Vitamins, choline and Vitamin C to make optimal amounts of neurotransmitters and for brain development
- A prenatal vitamin is fine in most cases, as are standard children's vitamins up to age 5.
- Additional Choline (450 mg/d) may also be required by pregnant women if insufficient Choline in prenatal vitamin.
- In cases of high maternal homocysteine- some folic acid should be provided in methylfolate form (or when MTHFR defect shown on nutrigenomic testing)
- Once child is 5 years old I often recommend the Adeeva Multiple Vitamin and Mineral at the following dosages:

- 5-9 years – 1 caplet per day
- 10-12 – 2 caplets per day
- 13-15 – 3 caplets per day
- 16 and older – 4 caplets per day (full adult dosage)

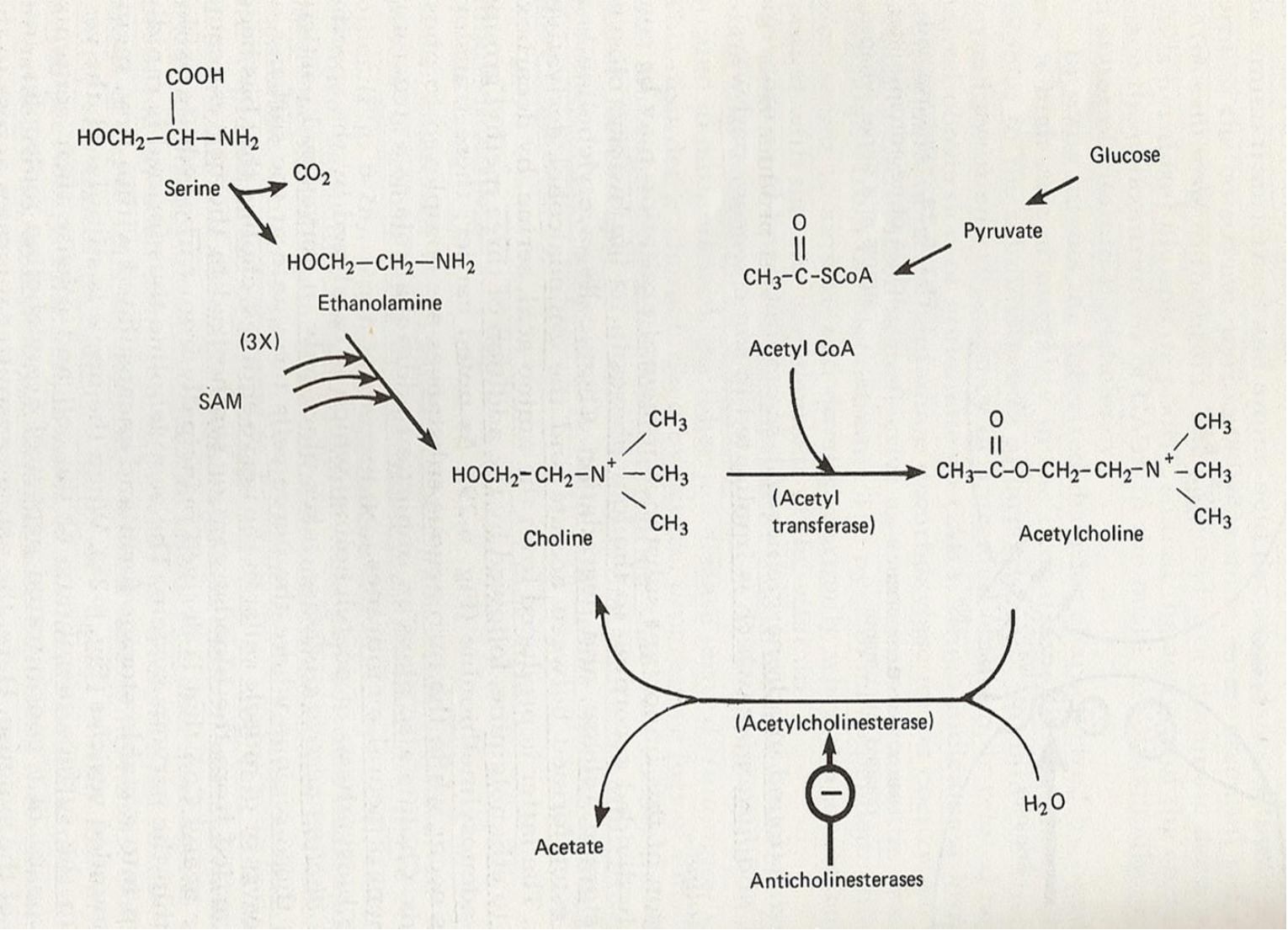
Amount per 4 Capsules

Example: Multiple Vitamin and Mineral		
Vitamin A	Retinyl Palmitate	2,500 I.U.
Beta Carotene		15,000 I.U.
Vitamin C	Ascorbic Acid	1,000 mg
Vitamin D	Cholecalciferol	1000 I.U.
Vitamin E Succinate	D-alpha tocopheryl	400 I.U. (natural)
Thiamin	Thiamine Mononitrate	50 mg
Riboflavin		50 mg
Niacin	Niacinamide	50 mg
Vitamin B-6	Pyridoxine Hydrochloride	50 mg
Folic Acid		400 mcg
Vitamin B-12	Methylocobalmin	50 mcg
Biotin	D-Biotin	300 mcg
Pantothenic Acid	Calcium Pantothenate	50 mg

continued

Example: Multiple Vitamin and Mineral Continued		
Calcium	Calcium Carbonate, Citrate	500 mg
Iron	Ferrous Fumarate	6 mg
Magnesium	Magnesium Oxide	200 mg
Zinc	Zinc Citrate	15 mg
Selenium	Selenium HVP/HAP Chelate	200 mcg
Copper	Copper Gluconate	2 mg
Manganese	Manganese Gluconate	5 mg
Chromium	Chromium Amino Acid Chelate	50 mcg
Molybdenum	Molybdenum Citrate	50 mcg
Bioflavonoids		50 mg
Lutein		6 mg
Lycopene		6 mg

Synthesis of The Memory Neurotransmitter Acetylcholine (requires Choline)



Essential Fatty Acids And The Brain

1. Most of the dry weight of the brain is lipid (fat)

2. The outer skin (membrane) of brain cells require EFA's for nerve conduction (electrical impulse transmission from nerve to nerve)

3. The brain particularly likes access to omega-3 fats. The brain has higher levels of DHA levels than most other body tissues

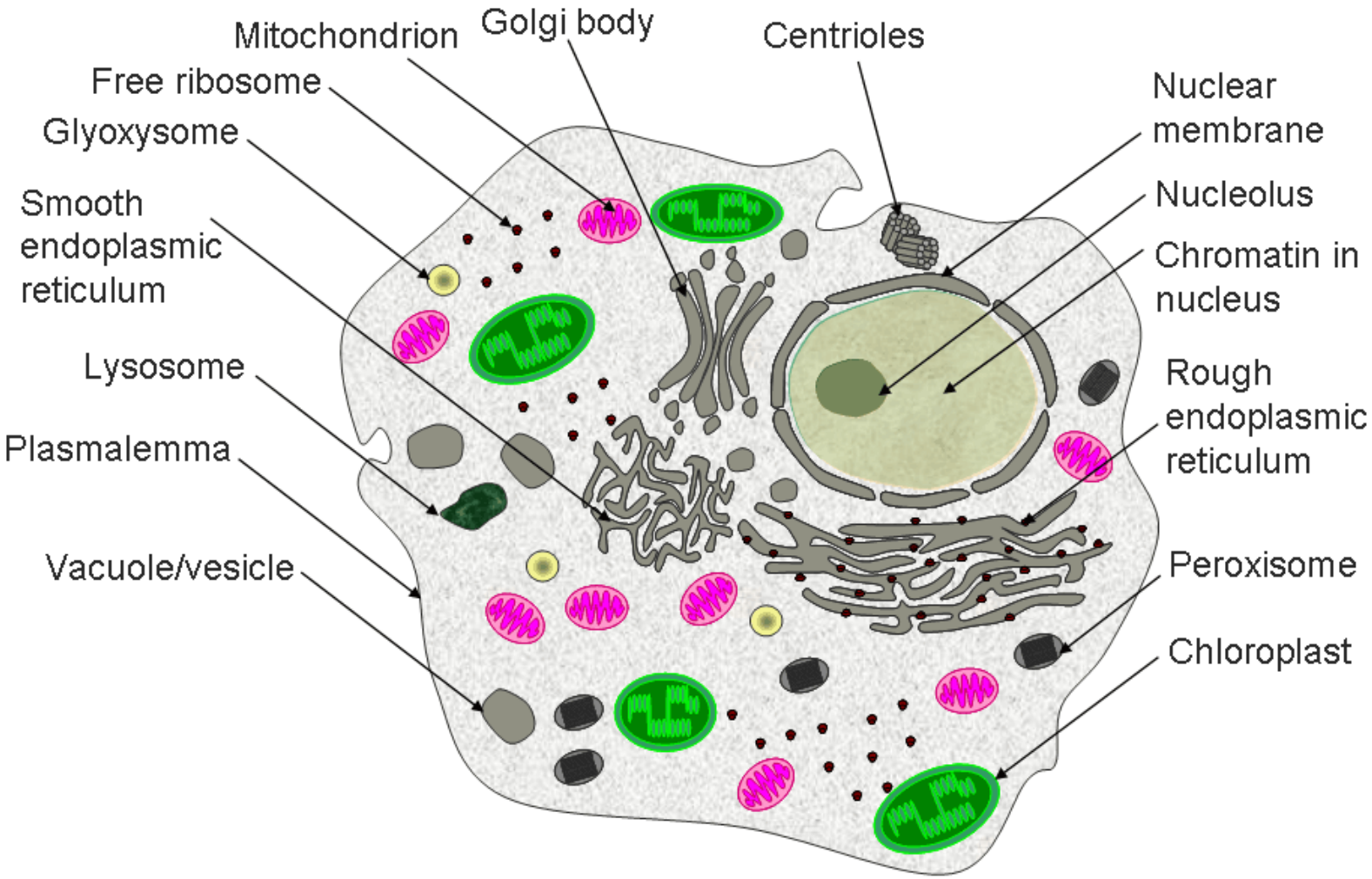
4. Many adults and children are deficient in omega-3 fats, which can impair brain development and function, affecting mental performance

Essential Fatty Acids Affect Brain Maturation And Function

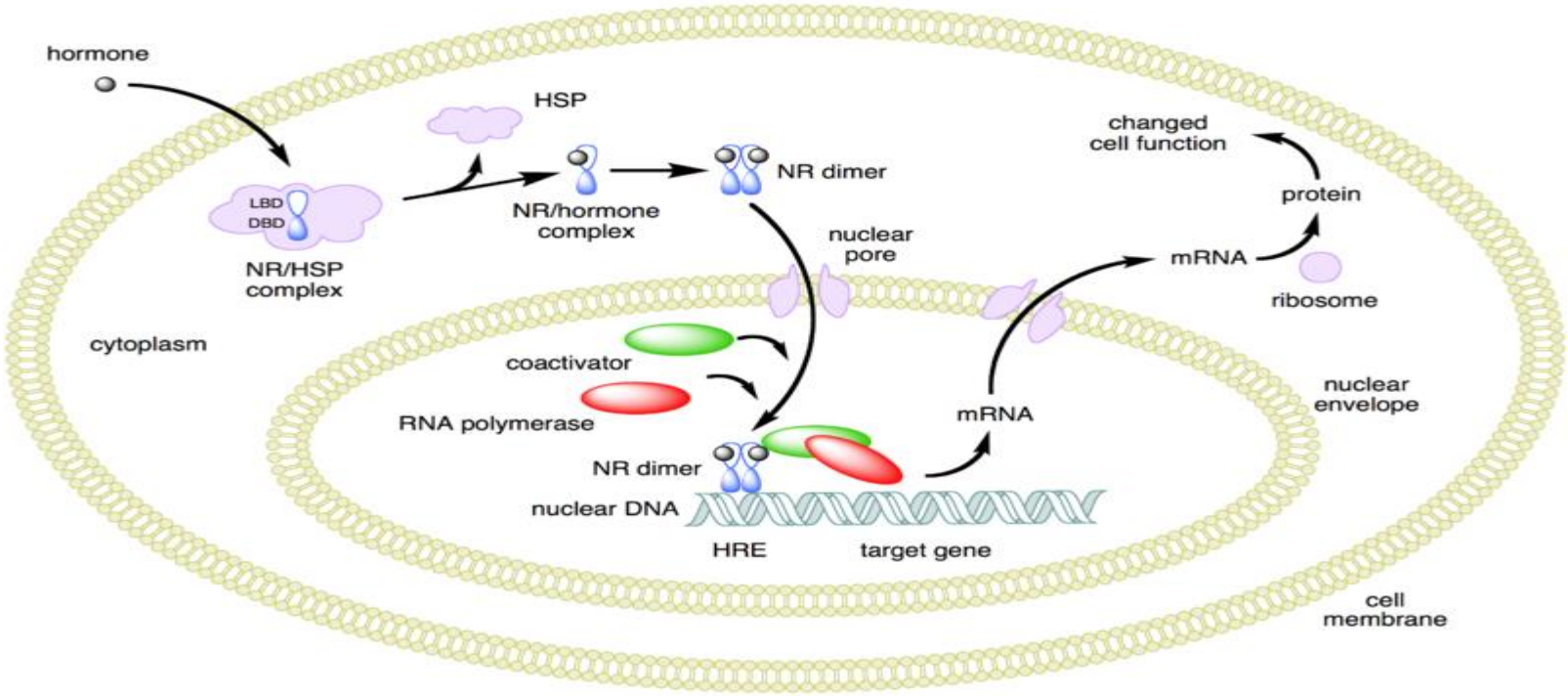
- Essential fatty acids are indispensible structural components of the cell membranes of all tissues.
- The brain, retina and other neural tissues are particularly rich in long-chain polyunsaturated fatty acids (LC-PUFA).
- Intracellular fatty acids or their metabolites (eicosanoids) regulate activation of gene expression during retinal and nervous system development, via activation of nuclear transcription factors.
- “DHA also has significant effects on photoreceptor membranes and neurotransmitters involved in the signal transduction process; rhodopsin activation (night vision) rod and cone development, neuronal dendritic connectivity, and functional maturation of the central nervous system”.

(Ricardo Uauy. Essential fatty acids in visual and brain development. Lipids. Volume 36, Number 9 / September, 2001)

Nuclear Membrane is Site Where EFA's Are Released To Form Eicosanoids (PG-3 from omega-3 fats) That Affect Nerve Cell Development



Hormone or eicosanoid binding triggers dissociation of heat shock proteins (HSP), dimerization, and translocation to the nucleus where it binds to a specific sequence of DNA known as a hormone response element (HRE). The nuclear receptor DNA complex in turn recruits other proteins that are responsible for translation of downstream DNA into RNA and eventually protein which results in a change in cell function



DHA Required For Brain Development

- DHA (docosahexaenoic acid) is required for optimal brain development during fetal and early infant life

- Failure for women to establish adequate DHA nutritional status has been strongly implicated in impaired brain development of their offspring, manifesting as:
- Lower IQ
- Increased propensity for learning disabilities.

DHA Required For Brain Development

- Many women do not ingest sufficient amounts of DHA to provide their offspring with the best chance of establishing optimal brain development and function.

- And there is no way to compensate for this once this critical time (pregnancy and the first three months of lactation) have elapsed.

- Feeding the child DHA after this critical time period cannot substantially affect brain development to the degree that is possible during pregnancy and the first three months of life.

First-born Is Smartest

- Studies show that higher concentrations of DHA provided to the fetus and infant is associated with higher IQ scores throughout life (about 6 points higher on average).

- Studies show that the first-born child generally has a higher IQ than the children that follow.

- Unless the woman adheres to a very aggressive omega-3 fat replenishment program from food and supplements, all of her subsequent children are much less likely to be afforded access to the same concentration of available DHA that was supplied to the first born child.

Why Is DHA So Critical

- The increase in brain size during the final three months of pregnancy is three fold, and this rapid growth in brain development requires appreciable amounts of DHA.

- The Fetal and infant brain (first three months of life) can not make sufficient DHA on its own, and is dependent on mother's body and breast milk to supply what it can't make for itself

EFA and Brain References

References:

1. Maria Makrides, et.al. Are long-chain polyunsaturated fatty acids essential nutrients in infancy? Lancet. 345:1463-1468 (1995)
2. Innis SM. Essential Fatty Acids in Growth and Development. Progress In Lipid Research 30(1):39-103 (1991)
3. J.M. Bourre, et.al. Function of Dietary Polyunsaturated Fatty Acids in the Nervous System. Prostaglandins, Leukotrienes and Essential Fatty Acids 48:5-15 (1993)
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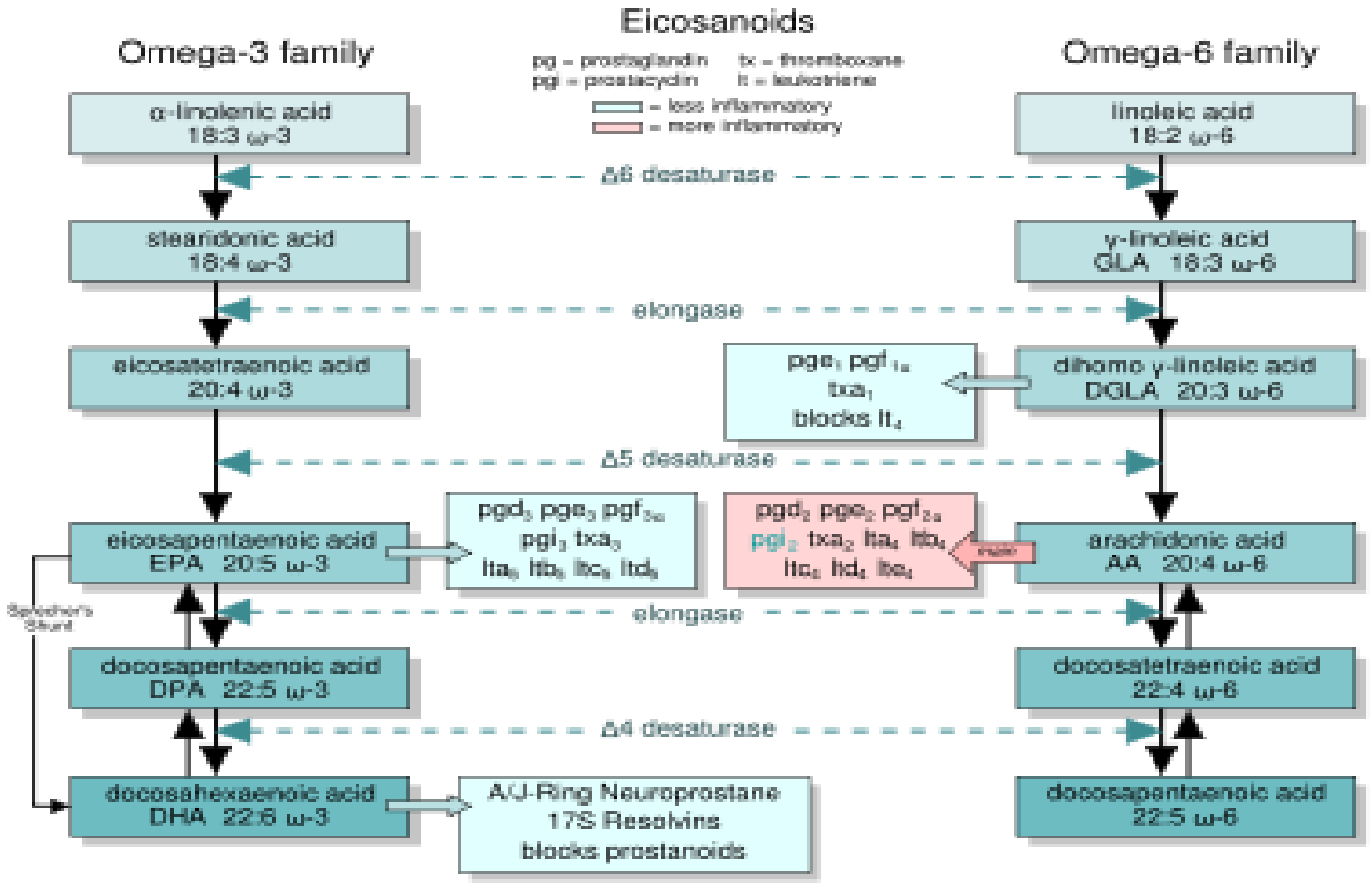
5. Koeman M. EPA/DHA – The intelligence of fish oil. Bioceuticals. Vol 18, 2000
6. Jensen, C. L. Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. American Journal of Clinical Nutrition. 2005 (Vol. 82) (No. 1) 125-132
7. Hiramitsu Suzuki, et.al. Effect of the long-term feeding of dietary lipids on the learning ability, fatty acid composition of brain stem phospholipids and synaptic membrane fluidity in adult mice: a comparison of sardine oil diet with palm oil diet. Mechanisms of Aging and Development. 101:119-128 (1998)

Fish and Fish Oil contain rich amounts of EPA and DHA. ALA from Flaxseed Oil can be converted to EPA and then to DHA. Borage Seed oil supplementation helps produce PG1, which is reduces inflammation, eczema and improves skin smoothness



Supplementation With Essential Fatty Acids Shown To Improve Performance in Children With ADHD and Dyslexia

- In the February 2002 issue of the journal, *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, researchers A. Richardson and B. Puri reported the results of their pilot study, which tested the effects of essential fatty acid supplementation on 41 learning-disabled boys and girls (aged 8-12) with symptoms of dyslexia and attention-deficit/hyperactivity disorder (ADHD).

- The study duration was three months and tested an essential fatty acid supplement containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil, and alpha- linolenic acid (ALA) and gamma-linolenic acid (GLA) - derived from evening primrose oil.

- This study showed that a variety of symptoms characteristic of ADHD improved in the children receiving the fatty acid mixture compared to an olive oil placebo, without any apparent side effects.

- To assess outcomes a questionnaire widely used to assess responses to drugs like Ritalin and Adderall was given to each child's parents to assess changes in behavior and mental performance. This included measures of inattention, restlessness-impulsiveness, anxiousness-shyness, and cognitive problems.

- After three months of daily use, notable improvements were observed in most of the scores among the children receiving the special fatty acid mixture. The study was sponsored by the Dyslexia Research Trust (www.dyslexia.org.uk), an Oxford-based charity dedicated to uncovering the biological basis of dyslexia and related conditions in order to develop better methods of identification and management.

- Abundant evidence suggests that specific fatty acids are important to brain function and development.

- According to the researchers of this study, and other sources, these fatty acids are often under consumed or under produced in children with behavioral and learning challenges. (1,2,3,4) This appears to be especially true for DHA, a member of the omega-3 group of fatty acids, mainly derived from cold water fish, such as salmon, mackerel, herring, sardines and other marine animals.

- DHA is also produced in the body from EPA, which can be produced from the elongation and desaturation of alpha-linolenic acid (the most prevalent fatty acid in flaxseed oil). **DHA** is present in breast milk **and not in cow's milk**

- Due to its importance in brain development and function, as well as the development of the nervous system and the retina, many physicians recommend breast-feeding or the use of infant formula that contains DHA. (5,6)

- One study showed that infants receiving supplemental DHA in their infant formulas scored significantly higher in mental development, as gauged by memory, problem solving, and related skills. (7) It is also stressed that pre-term infants be supplemented with DHA since these infants are incubated and not breast-fed. (8)

- The pilot study by Richardson and Puri, has provided further evidence that essential fatty acid supplementation can be an important aspect of the complementary management of ADHD and dyslexia, and possibly in other learning disabilities cases. (1)

Supplementation With Essential Fatty Acids Shown To Improve Performance in Children With ADHD and Dyslexia

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- Aman MG, Mitchell EA, Turbott SH. The effects of essential fatty acid supplementation by Efamol in hyperactive children. *J Abnorm Child Psychol* 1987;15:75–90
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EFA Strategy

1. Women of child-bearing age should eat fish twice per week (no more than that)
2. Feed your children fish as well
3. Supplement women's diet with an essential fatty acid supplement containing fish, flaxseed and borage seed oil daily (adult dosage – 2 or 3 capsules per day)
4. Supplement child's diet with essential fatty acid supplement containing fish, flaxseed and borage oil (children's dosage 1 capsule per day)
5. Add extra DHA if possible to mother and child's supplementation regiment

Example Essential Oils

One capsule contains:

1. Fish Oil – 400 mg **(30% EPA/20% DHA** = 50% EFA)
2. Flaxseed Oil – 400 mg (58% ALA)
3. Borage Seed Oil – 400 mg (22% GLA)

Dosage: 2- 3 capsules per day for adults

: 1 capsule per day for children (capsule can be opened and poured into juice)

And/or DHA Supplement taken separately

Alzheimer's Disease, Mild Cognitive Impairment and Dementia

Alzheimer's Disease:

- Affects 6-8% of population 65 yrs and older
- Affects 47% of population 85 and older

Hallmark Features Of Disease:

- decreased acetylcholine
- free radical damage to brain cells
- Beta-amyloid protein plaque build up
- neurofibrillary tangles
- loss of insulin (and IGF-1) receptor and signaling on neuron membrane
- shrinkage of prefrontal cortex, hippocampus and enlarged ventricles

Additional Background Info

- Alzheimer's disease is the sixth-leading cause of death in the United States and the only cause of death among the top 10 in the United States where medical treatments are unable to prevent or slow the progression of the disease to any appreciable degree.

- Currently, an estimated 5.4 million Americans are living with Alzheimer's disease. One in eight older Americans has Alzheimer's disease and nearly half of all people over 85 years of age are afflicted.

Genetics and Environmental Influences

- Research reveals that Late-Onset Alzheimer’s disease, which is the most common type of Alzheimer’s disease, affecting those over 60 years of age, is primarily linked to faulty dietary and lifestyle factors.

- As stated by the National Institute on Aging, inherited gene mutations increase risk for Early-Onset Alzheimer’s disease (disease occurring between ages 30 to mid 60s). However, Early-Onset Alzheimer’s disease represents less than 10% of all cases of Alzheimer’s disease.

- “Most people with Alzheimer's have the late-onset form of the disease, in which symptoms become apparent in the mid-60s and later. The causes of late-onset Alzheimer's are not yet completely understood, but they likely include a combination of genetic, environmental, and lifestyle factors that affect a person's risk for developing the disease.

- Researchers “have not” found a specific gene that directly causes the late-onset form of the disease. However, one genetic risk factor—having one form of the apolipoprotein E-4 (APOE ε4) gene on chromosome 19—does increase a person's risk. However, inheriting an APOE ε4 allele does not mean that a person will definitely develop Alzheimer's. Some people with an APOE ε4 allele never get the disease, and others who develop Alzheimer's do not have any APOE ε4 alleles.

- The expression of genes (when particular genes are “switched” on or off) can be affected – positively or negatively – be environmental factors at any time in life. This is known as epigenetic influence of gene expression. These factors include exercise, diet, chemical, or smoking, to which an individual may be exposed, even in the womb.
- There is emerging evidence that epigenetic mechanisms contribute to Alzheimer’s disease. Epigenetic changes, whether protective, benign or harmful, may help explain, for example, why one family member develops the disease and another does not”.

References:

- http://www.alz.org/alzheimers_disease_facts_and_figures.asp
- https://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-genetics-fact-sheet

Alzheimer's Disease And Age-Related Memory Loss

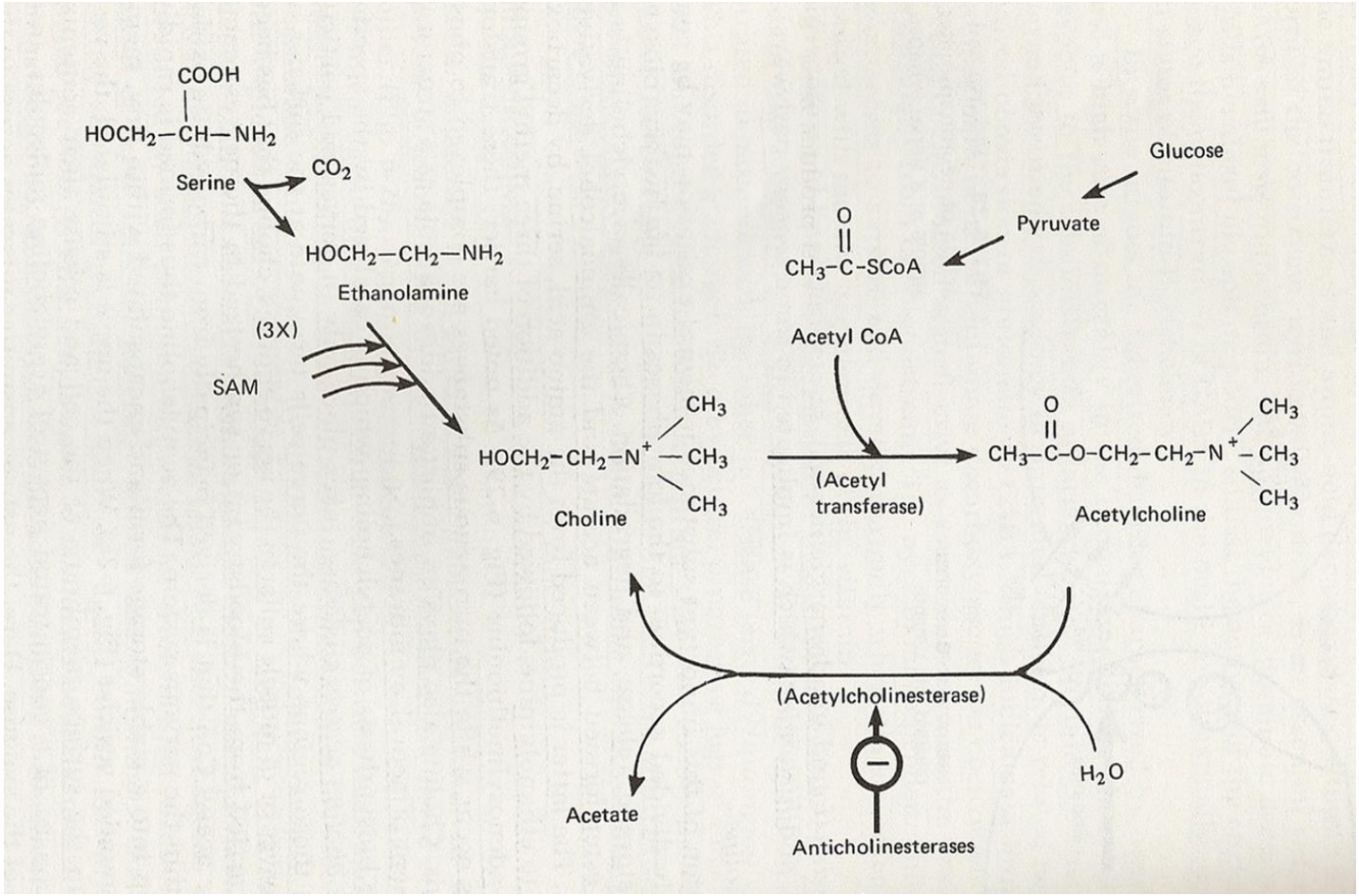
Causes (Three Hypotheses)

1. **Cholinergic Hypothesis** - AD caused by reduced synthesis of the neurotransmitter acetylcholine.

However, medications that boost acetylcholine levels are not effective in the long-run.

Most popular AD drugs act on this pathway

Acetylcholine: most people experience a decrease in acetylcholine after 55 due to decreased brain accessibility to choline. Marked decrease acetylcholine in AD



Amyloid Protein Deposition And AD

- Beta-amyloid protein is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that normally penetrates through the neuron's membrane.

- APP is critical to neuron growth, survival and post-injury repair.

- In AD, APP gets divided into smaller fragments by proteolytic enzymes, producing beta-amyloid fibrils, which form clumps that deposit outside the neurons as senile plaques.

Amyloid Plaque and AD

Amyloid protein deposits are fundamental cause of AD in that the gene for the **amyloid beta precursor protein** (APP) is located on chromosome 21, and people with trisomy 21 (Down Syndrome), who have an extra gene copy, invariably exhibit AD by age 40.

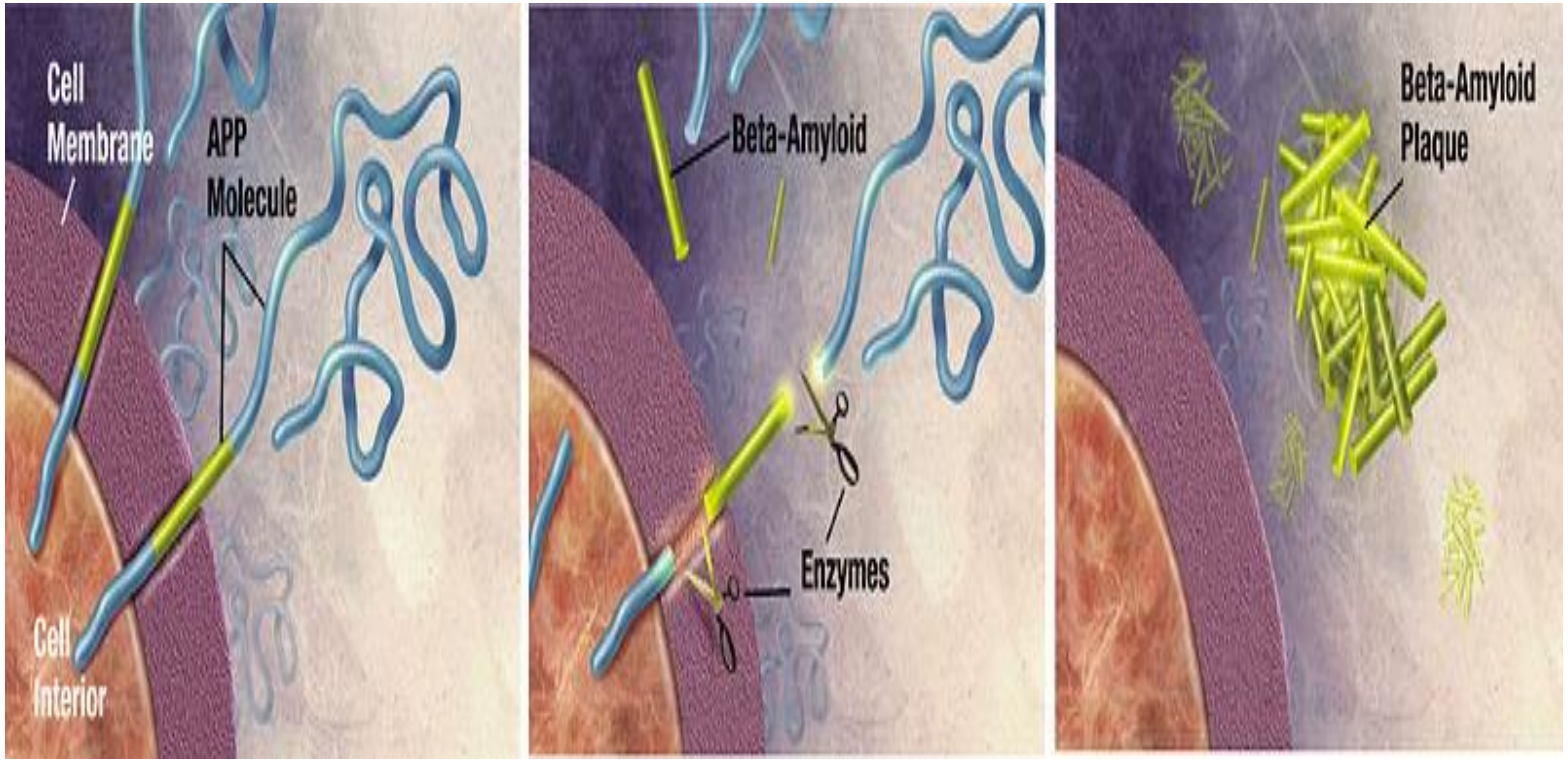
- **Also APOE4,** the major genetic risk factor for AD, leads to excess amyloid buildup in the brain before AD symptoms arise. Thus, beta amyloid protein deposition precedes clinical AD.

- Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits.

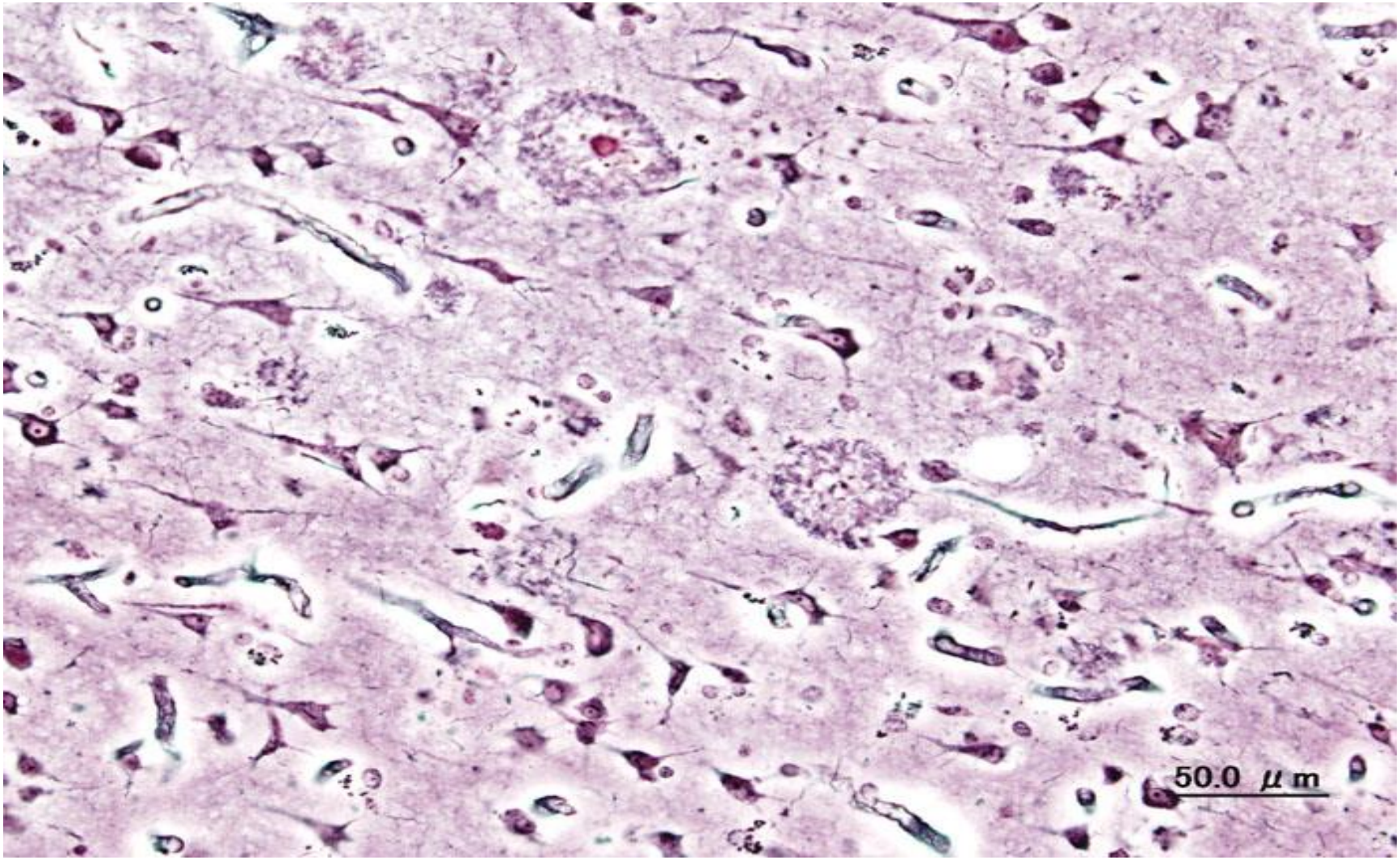
- However, deposition of amyloid plaques does not correlate well with neuron loss.

- Amyloid plaque causes free radical damage and inflammation to nerve cells, which damages brain cells and accelerates AD progression.
(http://health.upenn.edu/news/News_Releases/june01/Domenico_Pratico.html)

Enzymes act on the APP (amyloid precursor protein) and cut it into fragments forming Beta-amyloid plaque



Senile plaques in cerebral cortex of person with Alzheimer's disease. (Silver impregnation)



3. **Tau Hypothesis** - tau protein abnormalities initiate AD, whereby hyperphosphorylated tau pairs with other threads of tau protein forming neurofibrillary tangles inside nerve cell bodies.

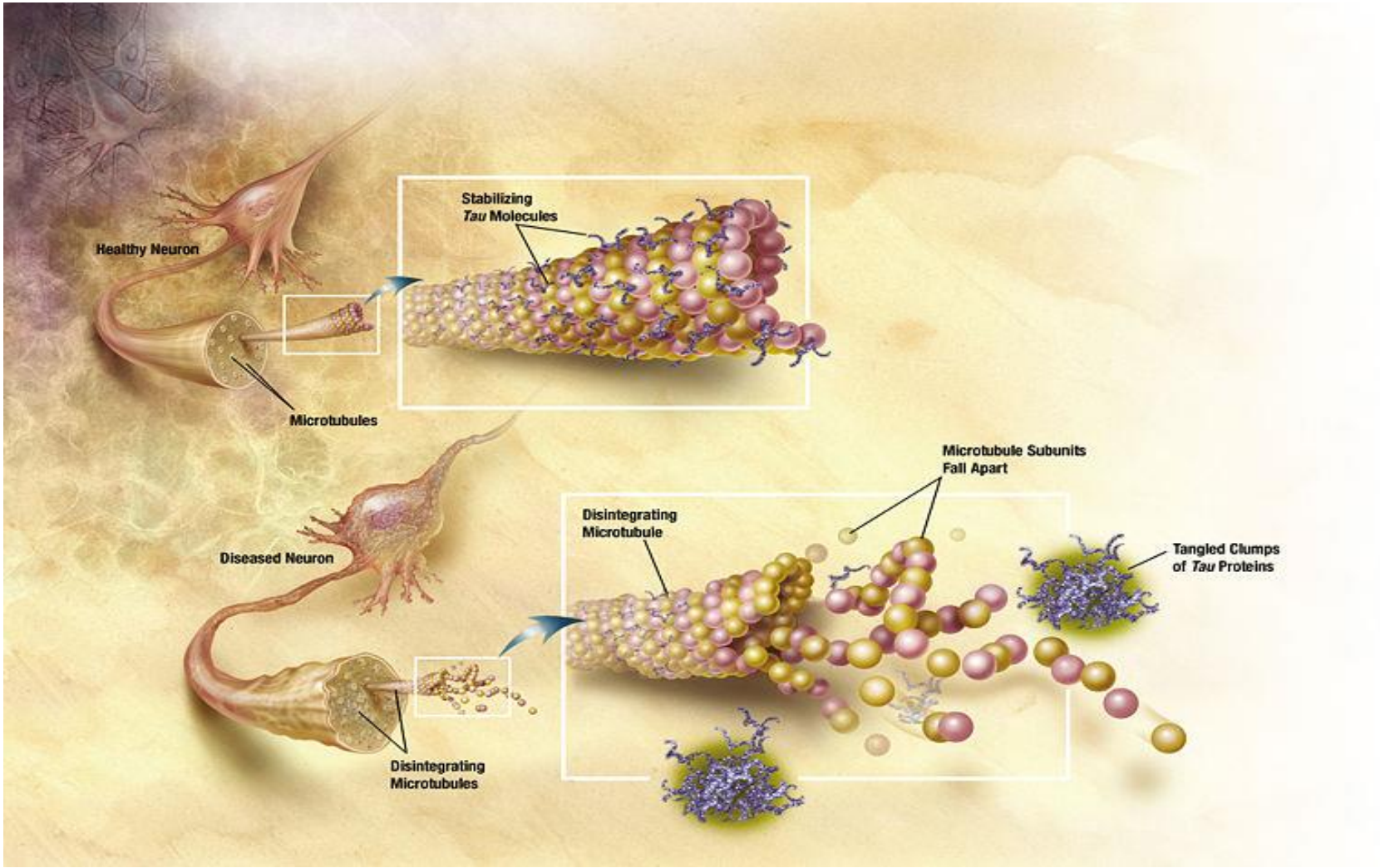
- When this occurs, the microtubules disintegrate, collapsing the neuron's transport system, resulting in malfunctions in communication between neurons, and later in cell death.

- **More Details** - Every neuron has an interior cytoskeleton, partly comprised of microtubules that act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back.

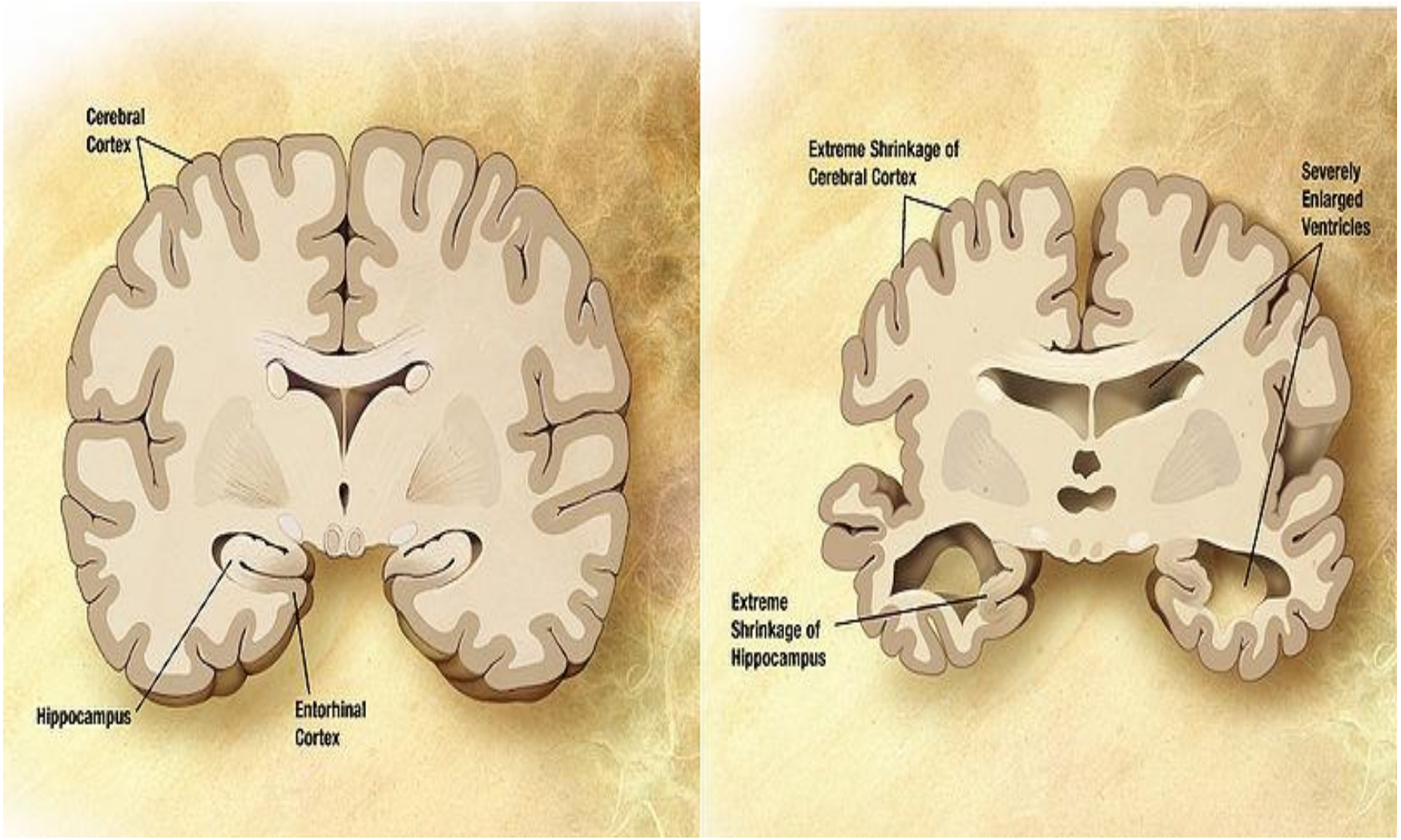
- The tau protein stabilizes the microtubules. In AD, tau undergoes chemical changes, pairing abnormality with other tau protein threads, creating neurofibrillary tangles, which disintegrate the neuron's transport system.

- This eventually leads to cell death.

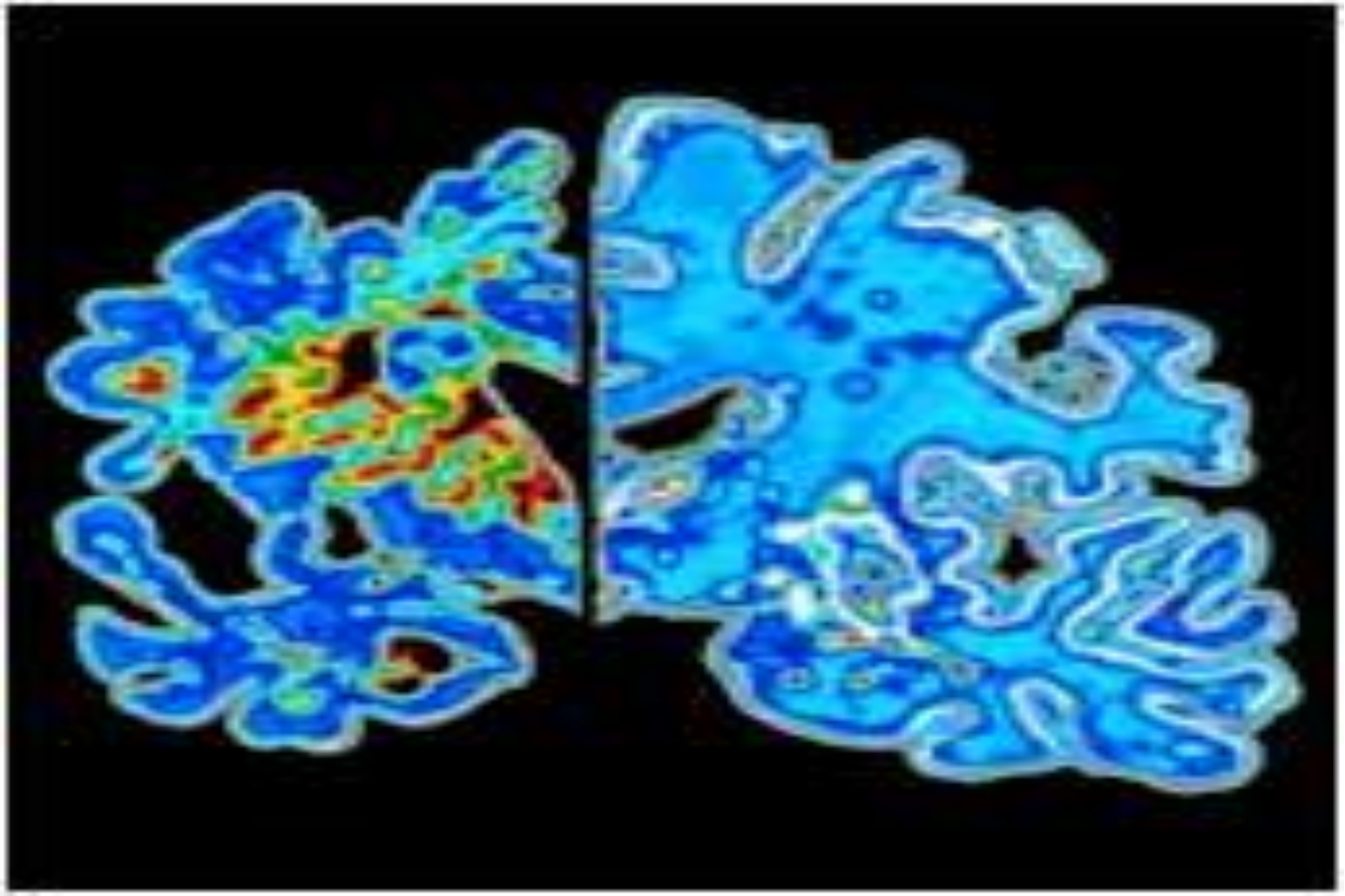
Changes in tau protein lead to neurofibrillary tangles in neurons and cell death



Normal Brain Left: Alzheimer's Brain Right



Normal Brain Right: Alzheimer's Brain Left



Drugs For Alzheimer's Disease

Primarily acetylcholinesterase inhibitors, which reduce rate of acetylcholine breakdown:

1. Donepezil (*Aricept)*
2. Galantamine (*Razadyne*)
3. Rivastigmine (*Exelon* and *Exelon Patch)*

- Some what effective in mild to moderate AD, but are less likely to work as disease progresses

Common Side Effects

* Nausea and vomiting (10-20% of users) - linked to cholinergic excess (cholinergic syndrome) - increased acetylcholine throughout the body-parasympathetic discharge

Less Common Side Effects

- Muscle cramps
- Bradycardia
- Decreased appetite and weight
- Increased gastric acid production
- Tearing
- Increased Salivation

Supplements That Support Acetylcholine Synthesis and Brain Concentrations

Natural Memory Support Supplements

Supplements Proven To Support Memory:

1. Choline, CDP-**choline** and Alpha-glycerophospho**choline**
2. Phosphatidylserine
3. Acetyl-L-Carnitine
4. Bacopa Monnieri
5. Huperzine A
6. Ginkgo Biloba
7. Vinpocetine
8. DMAE (dimethyl amino ethanol)

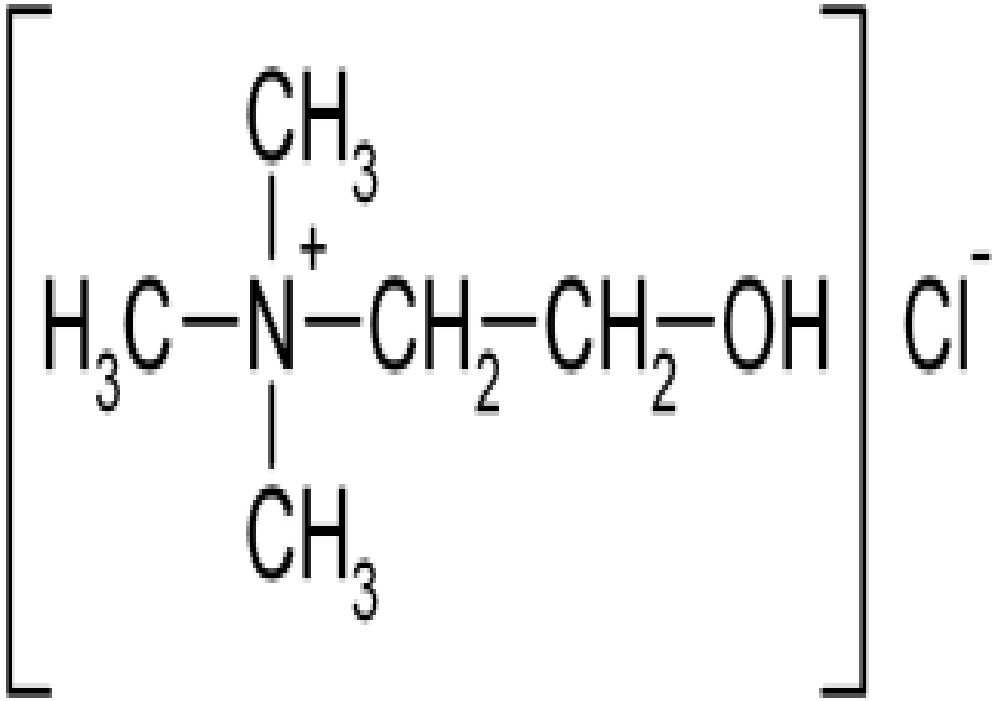
Choline

- Deemed essential dietary nutrient, as body endogenous synthesis cannot meet choline demand for optimal health and development.

- Choline can be oxidized by body to betaine (trimethylglycine), but betaine cannot be converted to choline.

- Diet also contains choline metabolite “betaine”, which cannot be converted to choline, but can be used as methyl donor in the liver, thereby sparing folate-vitamin B12 requirement as methyl donors.

Choline (chloride)

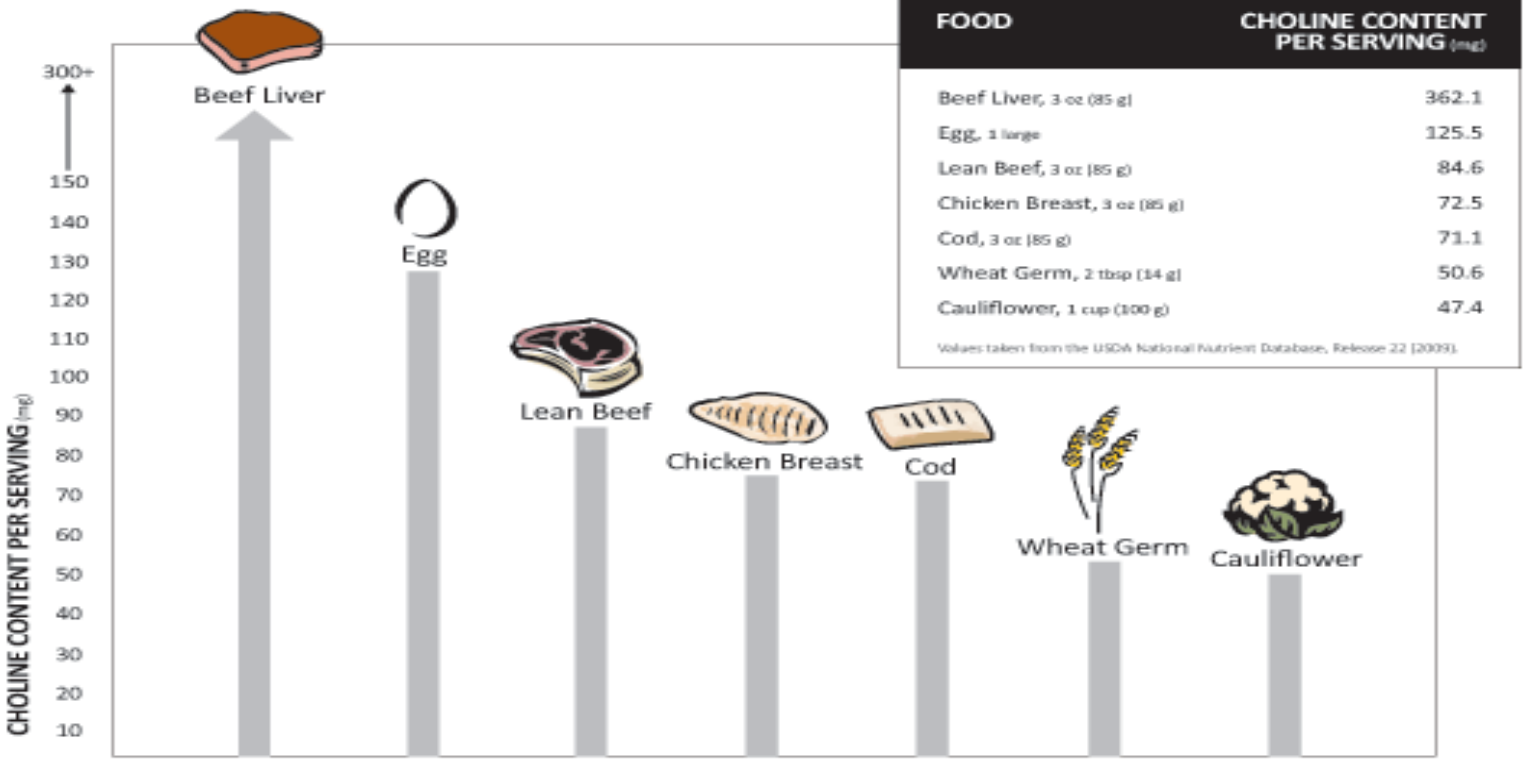


Some Food Sources of Choline:

15 gm soy lecithin = 450 mg Choline -Each tablespoon (7.5 grams) of lecithin granules contains about 1700 mg of phosphatidylcholine, 1000 mg of phosphatidylinositol, and about 2,200 mg of essential fatty acids as linoleic acid. It also contains the omega-3 alpha-linolenic acid.

1 cup many Nuts = 75 mg Choline

2 cups firm tofu = 142 mg Choline



FOOD	CHOLINE CONTENT PER SERVING (mg)
Beef Liver, 3 oz (85 g)	362.1
Egg, 1 large	125.5
Lean Beef, 3 oz (85 g)	84.6
Chicken Breast, 3 oz (85 g)	72.5
Cod, 3 oz (85 g)	71.1
Wheat Germ, 2 tbsp (14 g)	50.6
Cauliflower, 1 cup (100 g)	47.4

Values taken from the USDA National Nutrient Database, Release 22 (2009).

Many Healthy Foods Contain Choline:

Some examples of amount of choline found in 3.5 ounces or 100 gm of the following foods: (goal is 450-550 mg per day) (after age 55 aim for 1,000 mg per day)

- soy beans contain 116 mg
- salmon contains – 91 mg
- chicken contains about 80 mg
- soy protein contains 86 mg
- peanut butter contains 66 mg
- almonds contain 52 mg
- broccoli contains 40 mg
- Brussels sprouts contains 41 mg
- cauliflower contains 39 mg
- wheat germ contains 152 mg
- wheat bran contains 75 mg
- oat bran contains 59 mg
- whole wheat bread contains 27 mg
- 1 cup or 8 ounces of skim milk contains 38 mg
- 1 tablespoon of lecithin granules contains 250 mg of choline
- 1 capsule of 1200 mg of Lecithin – 10-15% is choline (max 180 mg choline)

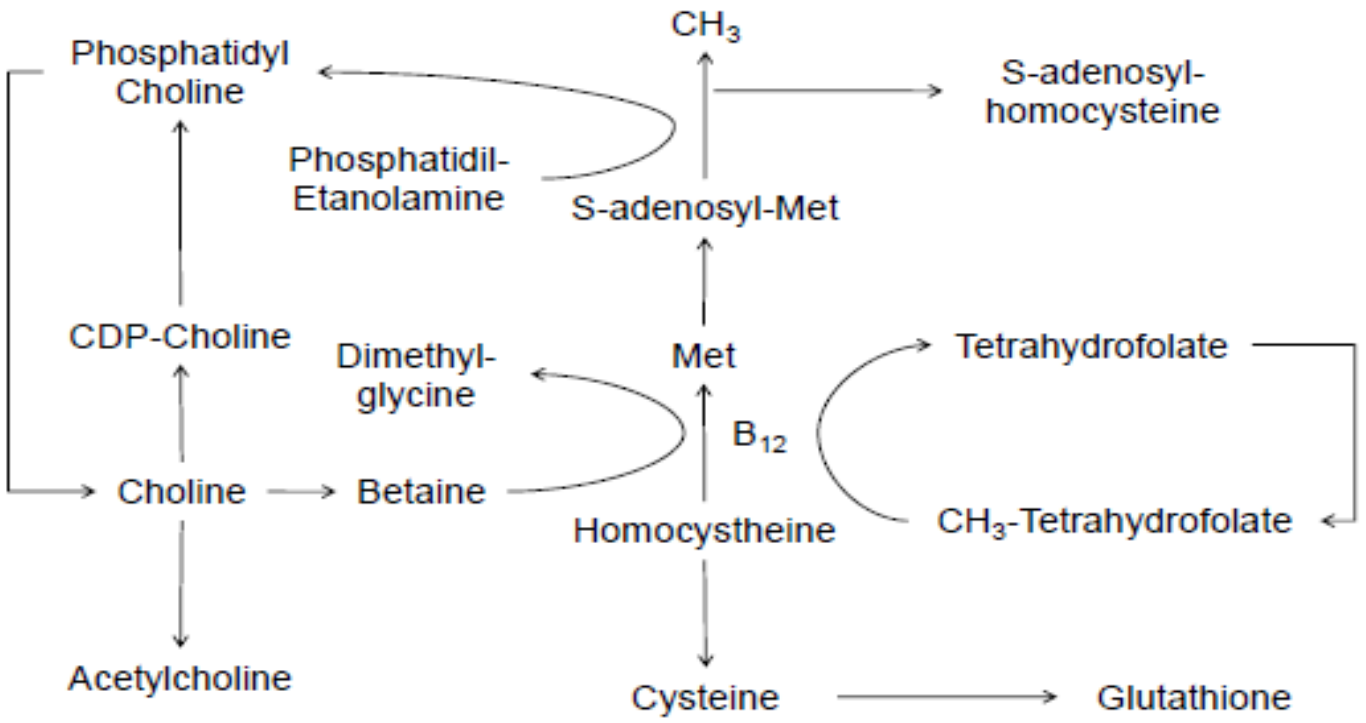
Major Functions

1. Essential for normal functioning of all cells

2. Ensures structural integrity and signaling function of cell membranes

3. Carnitine transport into tissues. Choline deficiency associated with decreased serum and urinary carnitine

4. **Methly donor** in recycling homocysteine to methionine in **liver** – choline oxidized to betaine



5. **Phospholipid Synthesis:**

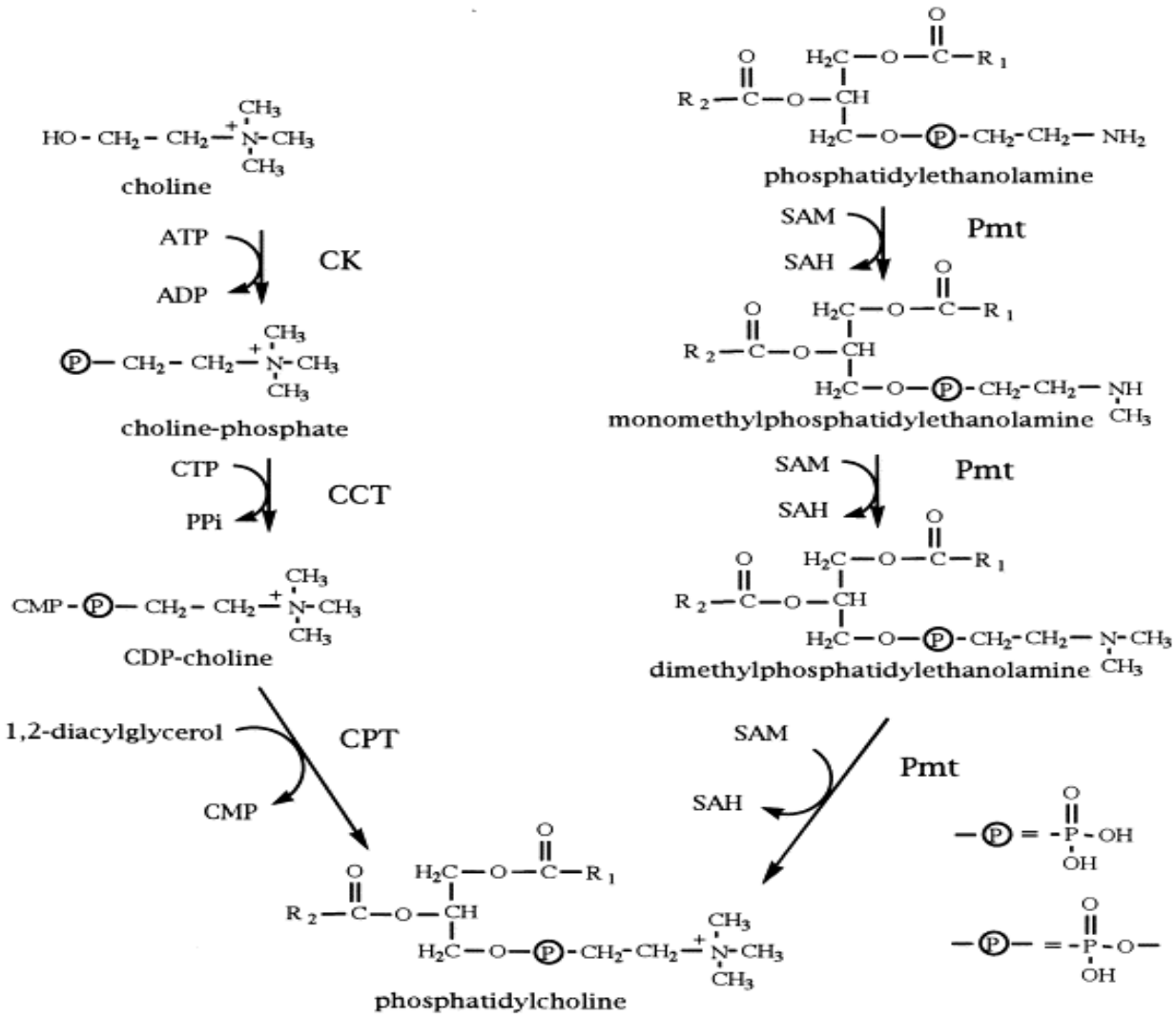
Two Pathways For Phosphatidylcholine Synthesis:

- First Pathway – choline is phosphorylated and converted to CDP-choline (cytidine diphosphocholine), a high energy intermediate, which in combination with diacylglycerol forms phosphatidylcholine and cytidine monophosphate.

- Second Pathway: phosphatidylethanolamine is sequentially methylated to form phosphatidylcholine, using SAMe as methyl donor.

See Next Slide

Phosphatidylcholine Synthesis



6. **Acetylcholine Synthesis in Cholinergic Neurons:**

Special carrier mechanism transports free choline across blood-brain barrier at a rate that is proportional to serum choline concentration. Thus, serum choline levels influence brain acetylcholine synthesis, as choline acetyltransferase enzyme is usually not saturated with choline or acetyl–CoA.

Studies show increased acetylcholine synthesis increases release of acetylcholine into nervous system synapses.

Choline entering the brain is thought to first enter choline pool, especially as phosphatidylcholine in plasma membrane, prior to its incorporation into the memory neurotransmitter, acetylcholine. Thus, choline phospholipids (phosphatidylcholine) in cholinergic neurons comprise a large precursor pool of choline available for use in acetylcholine synthesis.

- Although free choline crosses the blood-brain barrier phosphatidylcholine can also be carried into neurons as part of an apoprotein E (Apo E) lipoprotein.

- With advancing age the carrier mechanism to transport free choline into brain is less efficient, and thus, ApoE containing lipoproteins may be of more significance in acetylcholine synthesis.

- However, ApoE4 is associated with increased risk of Alzheimer's disease and abnormal phospholipid metabolism occurs in Alzheimer's disease and decreased brain levels of phosphatidylcholine and phosphatidylethanolamine, choline and ethanolamine (autopsy findings).

- For these reason choline (CDP-choline) and phosphatidylcholine have been used to treat neurological disorders.

More Details About ApoE

- Apoprotein E (apoE) is synthesized by a number of tissues including the liver, brain, adipose tissue, and artery wall.

- The majority of apoE is found in the plasma associated with specific lipoprotein subclasses and is derived primarily from the liver- VLDL and HDL are main sources, which helps with VLDL and LDL clearance by liver. HDL can carry apoE into brain

- However the fact that apoE expression is sustained in non-hepatic tissues suggests that the local production must have some unique functional attribute- brain makes apoE, which helps with transport of cholesterol within brain **(Astrocytes synthesize apoE)**

- ApoE is involved in many steps in lipid and lipoprotein homeostasis, for the triglyceride-rich lipoproteins and for HDL. ApoE is also important for lipid homeostasis in the brain, artery wall, and adipose tissue through its synthesis by **glial cells**, adipocytes, and macrophages

There are 3 subclasses of apoE (2,3,4)

It appears that apoE4 amplifies free radical damaging effect of beta-amyloid plaque and may amplify damage to microtubules leading to neurofibrillary tangles.

Note that apoE4 phenotype is linked to increased Alzheimer' disease.

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2674757

7. Required for lipid transport and metabolism – transports triglycerides, cholesterol and apo proteins out of liver via lipoproteins, which require phosphatidylcholine as primary phospholipid.

8. In the kidney choline is oxidized to betaine and glycerophosphocholine – both are important **osmoprotectants** within the kidney

Neurological Applications:

- **Alzheimer's Disease** - clinical trials using phosphatidylcholine in Alzheimer's disease are largely disappointing. Better results have been demonstrated with CDP-Choline , phosphatidylserine, acetyl-L-carnitine and Ginkgo biloba.

. **Parkinson's Disease** – CDP-choline (1000 mg per day) shown to improve symptoms in Parkinson's patients, who were receiving treatment with L-Dopa plus a Dopa-decarboxylase inhibitor drug.

. **Concussion** - CDP-Choline shown to accelerate resorption of cerebral edema in various experimental models.

In human 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".

. Memory and Learning in Young Adults

Double-blind study showed 25 gm per day phosphatidylcholine caused significant improvement in college student explicit memory, as measured by serial learning tasks.

A single dose of 10 gm of choline chloride to normal volunteers significantly decreased number of trials required to master a serial-learning word test.

CDP-choline (1000 mg per day for 3-mths) in healthy volunteers resulted in improved immediate and delayed logical memory.

Toxicity

- Choline and Phosphatidylcholine are well tolerated and extremely non-toxic.
- Phosphatidylcholine supplementation can worsen depression in some cases.
- At higher dosages, Phosphatidylcholine may cause reduced appetite, nausea, abdominal bloating, gastrointestinal pain, and diarrhea.
- Choline at high dosages (i.e. 20 gms) produces a fish odor.

CDP-Choline and Alpha-glycerophospocholine

1. Cytidine 5-diphosphocholine or CDP-choline – high energy intermediate (cytidine triphosphate CTP) in brain plasma membrane phospholipid synthesis (phosphatidylcholine)

2. Alpha-glycerophosphocholine (alpha-GPC), which is much more expensive than CDP-choline

– Other forms of choline have not shown any therapeutic effect on brain acetylcholine in Alzheimer's patients

CDP-choline

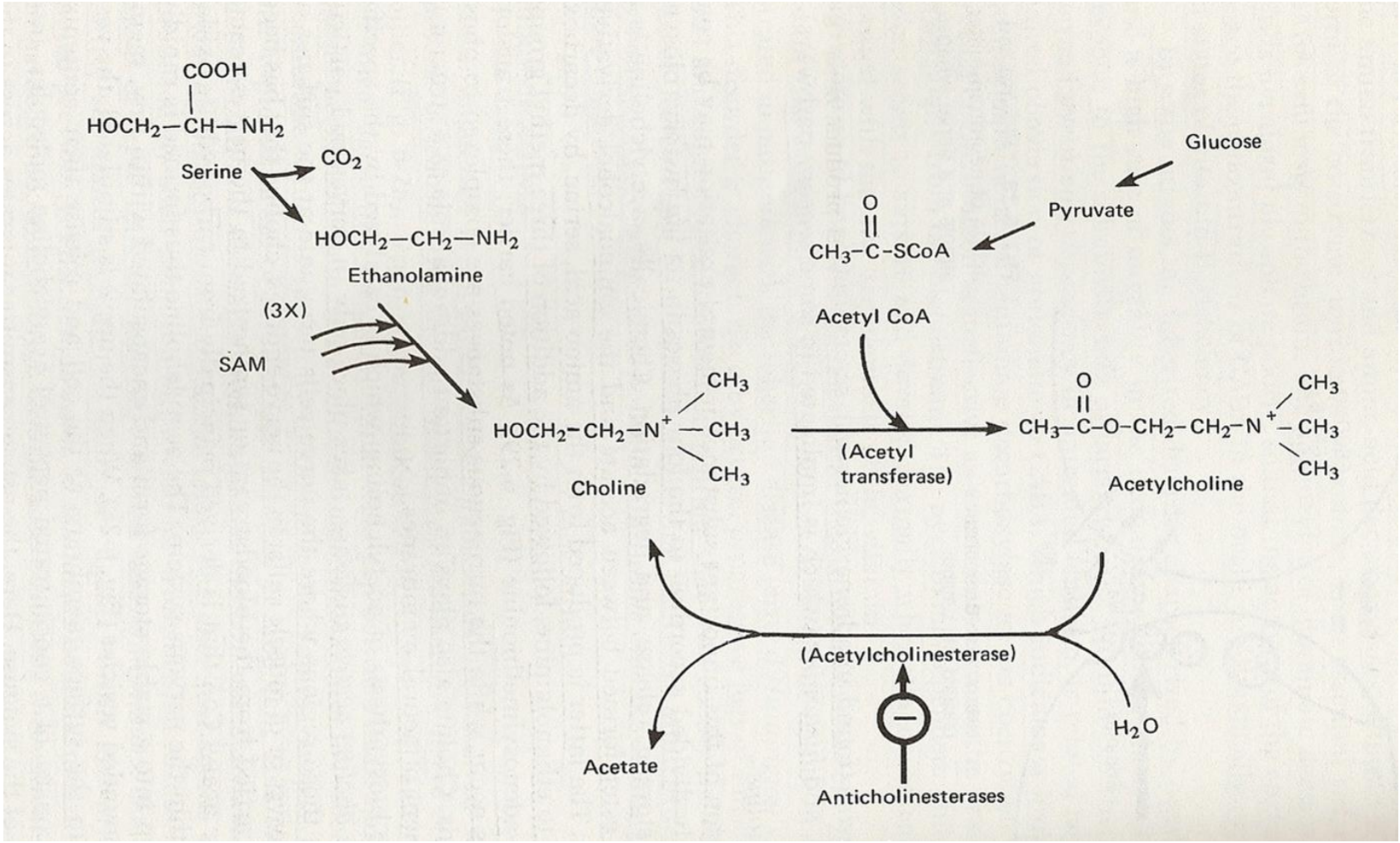
- Component of nerve cell membrane phospholipids (PL) (electrical conduction)
- Increases PL synthesis in brain cells
- Increases NT synthesis (acetylcholine, nor-adrenaline and **dopamine**) – also see decline in dopamine in aging brain

- Clinical Studies (Proven Efficacy):
  - Alzheimer's Disease
  - Parkinson's Disease (slows progression)
  - Age-related dementia
  - Head trauma (post traumatic concussion syndrome) – accel healing, edema resorption, earlier walking ability, decreased hospital stay, decreased memory loss and cognitive impair

- Safety:
  - No serious side effects (even at 1,000 mg/day)
  - Well tolerated
  - Toxicity studies (negative)

- Phosphatidylserine:
  - Major PL in nerve cell membrane
  - Decreased PS synthesis with aging
  - Low levels of brain PS assoc with impaired cognitive function and depression in elderly

Note: Serine can become converted to choline for acetylcholine synthesis



- Mechanism of Action:
  - 1. Increases brain PS levels in membrane (fluidity and nerve conduction)
  - 2. Increases acetylcholine production (serine converted to choline)

- Clinical Studies (Italy, Scandanavia other):
  Proven Efficacy:

  1. Dementia and mental decline

  2. Elderly depression and personality changes

- Dosage and Safety:
  - 100 mg, three times per day
  - Side effects (rare): mild GI distress (non toxic)
  - Bovine vs soy based (different molecule)

- Acetyl-L-Carnitine:
  - Liver synthesizes L-Carnitine
  - High levels found in brain, muscle, liver, kidney, testes
  - Aging – see decreased synthesis and brain concentrations

- Mechanism of Action:

    1. Fat burning (ATP production)

    2. Cardiolipin synthesis (nerve cell PL)

    3. Acetyl portion used for acetylcholine - Proven to increase brain concentrations of acetylcholine

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**

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

Acetyl-L-Carnitine Supplementation Studies

- Clinical Studies (Proven Efficacy)
  - 1. Early to moderate stage Alzheimer's disease – especially in younger subjects
  - 2.Age-related cognitive decline

- Safety and Dosage:
  - 1,000-2,000 mg per day
  - Side effects (rare): skin rash, nausea, vomit, agitation)
  - Non toxic
  - Now available in Canada. For many years it was not permitted to be sold in Canada as a supplement

- Bacopa monnieri (water hyssop)
  - Leaf used in Ayruvedic med since 6th century in AD to improve mental performance
  - Active ingredients – bacosides A, B

- Mechanism of Action:

    1. Enhance nerve transmission

    2. Potent brain antioxidant

- Clinical Studies (Proven Efficacy):
  - 1. Improves memory and mental performance in adults
  - 2. Improves intellectual performance in children
  - (increases learning ability in lab animals)

- Dementia Study (placebo-controlled)
  - 1. Increase speed of visual info processing
  - 2. Increase learning rate
  - 3. Increase memory consolidation
  - 4. Decrease anxiety

- Dosage and Safety:
  - 300 mg per day
  - No side effects
  - Strong safety profile

- Huperzine A
  - Extract from a club moss
  - Used for centuries in China
  - Hupa A is an alkaloid, synthesized since 1990 (increased availability in market)
  - Standardized grade (usually 95% Hupa A content)

- Mechanism of Action:
  - Highly selective acetylcholinesterase enzyme inhibitor (slows brkdwn of acetylcholine)
  - More selective than other Alzheimer's drugs
  - Longer acting and fewer side effects than Alzheimer drugs -lower dosing due to selectivity

- Hupa A also protects nerve cells against some neurotoxins

- Clinical Studies (Proven Efficacy):
  - Alzheimer's disease – used on more than 100,000 Alzheimer's and dementia pts in China

  - Outperformed Fodine and other drugs

- Adolescent Middle School Students: 100 mcg/2x daily for 4 weeks:
  - Increased memory
  - Increased learning performance
  - Long term safety at this high dosage in young people in unknown

- Dosing and Safety:
  - 100-200 mcg, twice daily
  - Side effects (rare, 3%): dizziness, GI upset

What I Take For Prevention After Age 55:

- CDP-choline - 50 mg
- Phosphatidylserine - 50% grade - 100 mg
- Huperzine A - 25 mcg
- Bacopa Monnieri - std to 20% Bacosides content - 50 mg

(2 caplets per day)

Plus – 2 capsules of Lecithin (1200 mg capsule)

Mechanism of Action Review:

1. **CDP–choline** – increases acetylcholine levels and maintains phospholipid structure of nerve cell membrane, enhancing nerve conduction

2. **Phosphatidylserine**- similar role as CDP- choline

3. **Bacopa Monneiri** – brain antioxidant and maintains nerve conduction

4. **Huperzine A** – inhibits breakdown of acetylcholine (more specific than drugs and largely without side effects)

- **Drug-Nutrient Interactions:**
  - Never recommend these nutrients with Dementia or Alzheimer's Drugs (potentiation effect), unless proper monitoring is in place.
  - Examples: Doneprizil and Tacrine
  - Potential Side Effects: Cholinergic Syndrome: vomit, salivation, tearing, sweating, bradycardia

- Other Memory Nutrients Requiring Monitoring:
  - 1. Ginkgo biloba
  - 2. Vinpocetine
  - 3. DMAE (dimethyl amino ethanol)

- Ginkgo Biloba
  - World's oldest tree
  - Leaves contain flavone glycosides
  - Mechanism Of Action:
    - 1. Vasodilation
    - 2. Anti-coagulant
    - 3. Increase Acetylcholine and brain nutrient delivery

- Clinical Studies (Proven Efficacy)
  - 1. Cerebrovascular Insufficiency
  - 2. Alzheimer’s disease

- Dosing and Safety:
  - 40-80 mg, two to three times daily (std to 24% flavone glycosides) – not in evening
  - Side effects: Bleeding in head and brain (reports)
  - Contraindications: anticoagulant use (including garlic extract, vitamin E above 400 IU/d, etc)

- Vinpocetine
  - Active ingredient in lesser periwinkle
  - Mechanism of Action;
    - 1. Vasodilation
    - 2. Anticoagulant
    - 3. Increases nutrients to brain

- Clinical Studies (Proven Efficacy)
  - 1. Alzheimer’s disease
  - 2. Ischemic stroke
  - 3. Dementia
  - 4 Cerebrovascular insufficiency

- Dosage and Safety:
  - Dosage: 30-60 mg per day
  - Side effects: Bleeding Potential (no reports)
  - Contraindications: anticoagulant drugs (include garlic extract, Vit E above 400 IU/d etc)

- Ginkgo Biloba and/or Vinpocetine supplementation require monitoring of prothrombin time (INR)

- DMAE (Deanol)
  - May increase choline conc (controversy)
  - Side effects: drowsy, confuse, lucid dreams, depression, headache, jaw and muscle tension, insomnia

Nutrition, Cognitive Function and Memory: Other Considerations

1. Cumulative free radical damage (oxygen, cigarette smoke etc)

2. B-vitamin deficiency (B12, B6, homocysteine accumulation)

3. Decreased neurotransmitter synthesis (acetylcholine, dopamine, epinephrine, norepinephrine, serotonin)

4. Effects of Hyperglycemia, Metabolic Syndrome and Diabetes (glucose intolerance)

1 Cumulative Free Radical Damage

- 20% of all oxygen used by brain
- Encourage amyloid protein formation and amyloid plaque generates free radicals
- Reduction in melatonin synthesis with age, decreases brain antioxidant protection

Antioxidant Supplementation And AD:

- Vitamin E – Alzheimer Cooperative Study and 2009 Intervention Trial.

- Vitamin C – epidemiological evidence
- Beta-carotene – epidemiological evidence
- CoQ10 (also Parkinson's Disease Association)
- Vitamin D – higher intake levels linked to less AD (animal studies show decrease amyloid plaque in hippocampus area - http://www.meschinohealth.com/blog/alzheimers-disease-and-cognition/2012/06/27/vitamin-linked-prevention-alzheimers-disease)

- Melatonin – experimentally prevents build up of plaque (Russel Reiter). More recently shown to decrease MCI progression to AD in 3 major studies (dosage 3-9 mg per day) - http://www.meschinohealth.com/blog/anti-aging/2012/03/06/melatonin_suppl_alzheimers

Antioxidant Supplementation (Vitamin C – 1,000 mg per day, Vitamin E- 400 IU per day)

- Studies indicate that free-living individuals within the population, who take vitamin C and/or vitamin E supplements at a minimum threshold dosage, had a lower risk of Alzheimer's disease compared with people who did not take these antioxidants.

- **Alzheimer's Cooperative Study-** showed that providing early stage Alzheimer's patients with 2000 IU per day of Vitamin E supplementation significantly slowed progression of disease compared to placebo group.

- The Vitamin E group did not show increased incidence of heart disease, cancer or any other major disease state.

2009 Study – Vitamin E Supplementation Benefits Alzheimer's Patients

Title - "Vitamin E Use Is Associated with Improved Survival in an Alzheimer's Disease Cohort,"

Journal - Dementia and Geriatric Cognitive Disorders 2009, Vol. 28, No. 6

Pavlik VN et al

Study Design

- 847 Patients with Alzheimer's disease supplemented with vitamin E (1000 IU, twice/day)
- ½ Patients in treatment group received Vit E and Alzheimer's Drug
- ½ Patients in treatment group Received only Vit E supp
- Control Group – Received no Vit E or Drug

Results:

- Vitamin E on its own reduced mortality by 23% compared to patients receiving no therapy

- The Alzheimer's **drug** taken on its own ***slightly increased mortality*** compared to patients receiving no treatment

- Vitamin E and Alzheimer's drug together showed the best overall results (about 30% reduction in mortality and improved overall function)

Conclusion:

- Vitamin E helpful to Alzheimer's patient, the sooner you start the better
- Dosage – 1000 IU, twice per day (antioxidant)
- Alzheimer's Cooperative Study Showed Same Protective Result a few yrs ago

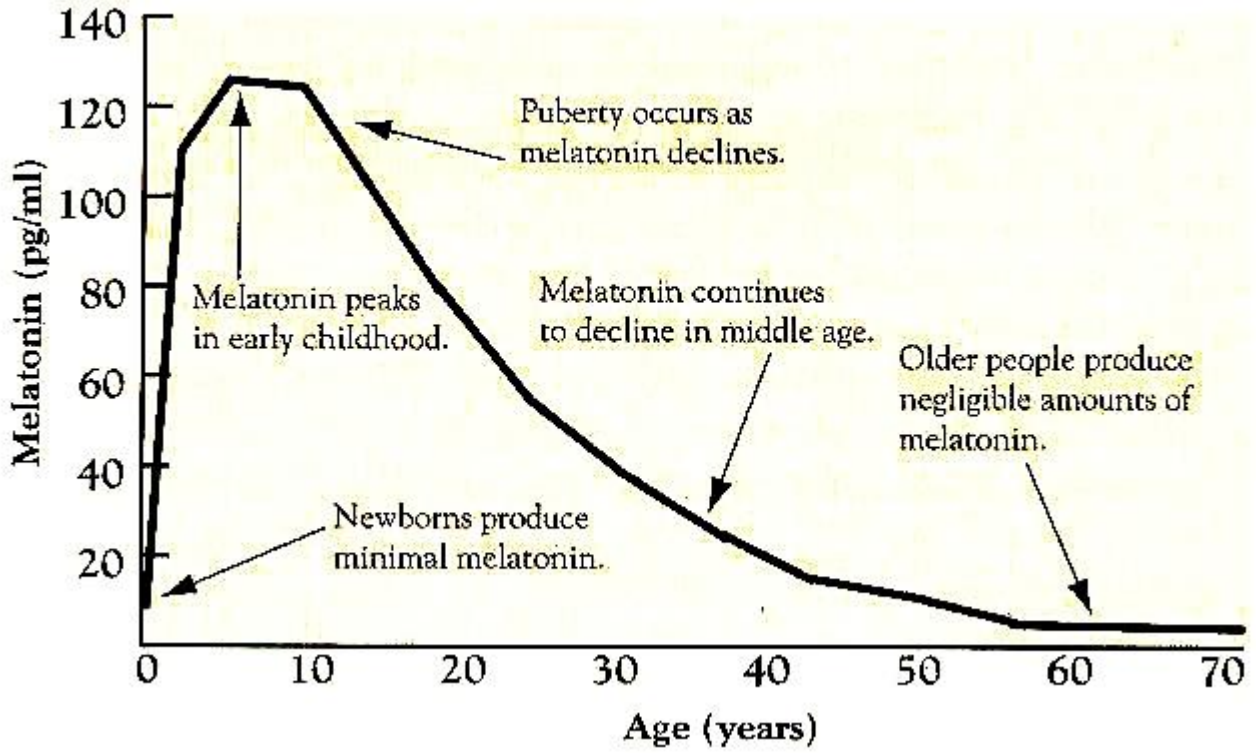
- Vitamin E can be taken with Alzheimer's drugs (first time shown)'

- Few Antioxidants can cross into brain

- 20% oxygen used by brain – ROS

- Loss of Melatonin protection as we age increases brain susceptibility to oxidative damage.

Age-Related Decline In Melatonin



Melatonin (.5 – 3 mg one hour before bedtime after age 40-45) - melatonin secretion by the pineal gland in the brain declines with age and this may, in part, account for the brain's increased susceptibility to dementia and Alzheimer's disease that accompanies aging.

In addition to helping to improve sleep quality, and acting as an important brain chemical and immune system modulator, melatonin has also been shown to reverse the protein complex that is the hallmark of Alzheimer's Disease, according to a study published in the December 11, 2001 issue of the journal, *Biochemistry*, published by the American Chemical Society.

See Study Results On Next Slide

- The findings of the study are based upon experiments with animals and human cell cultures. The researchers conclude, “Our results clearly demonstrate the ability of melatonin to inhibit the process of forming the signature amyloid protein bundles seen in Alzheimer’s disease”. In Alzheimer’s disease, toxic fibrillar aggregates of a protein called amyloid beta protein are the pathologic hallmark of the disease.

- In this study melatonin inhibited the formation of amyloid beta protein, which is toxic to nerve cells and accelerates free radical damage to neurons.

- What is intriguing is the fact that persons with Alzheimer’s disease have been shown to have significantly lower levels of melatonin in their brains.

- Thus, taking a melatonin supplement after age 45 may help to improve the brain’s ability to prevent the build up of damaging amyloid protein. As well, melatonin helps to induce deeper levels of sleep and resets the body’s day-night clock (this is why it is used to combat jet lag). The amount taken should help to provide a good night’s sleep, but not so much as to produce morning drowsiness.

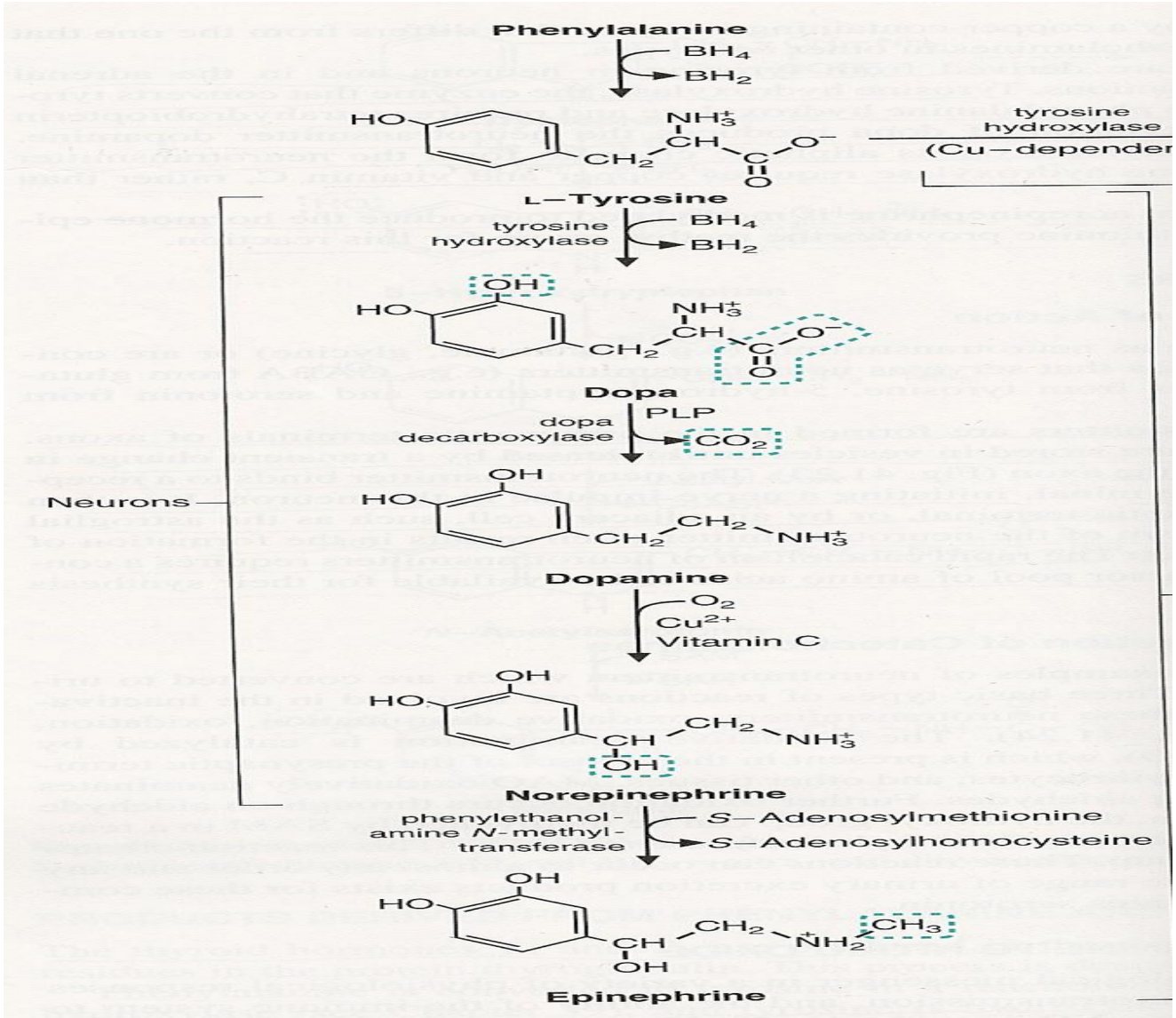
- **More Recently: Melatonin**: 3 – 9 mg – proven to reverse MCI in three human clinical trials (see details in course notes)

B Vitamins and Cognitive Function

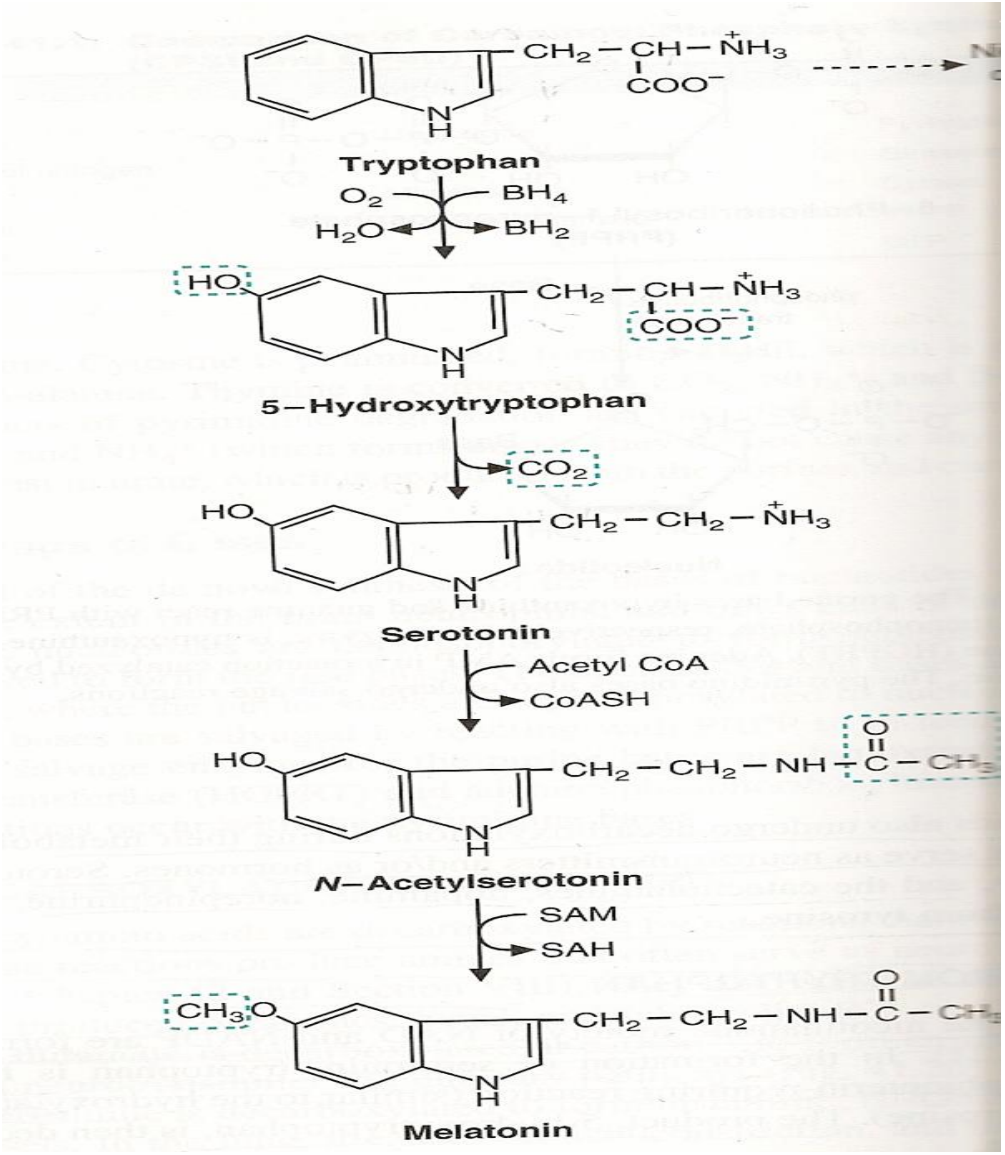
1. Required for neurotransmitter synthesis

2. Required to keep homocysteine in ideal range (Hcyt damages cerebral blood vessels- cerebrovascular disease)

Synthesis of Dopamine, Norepinephrine and Epinephrine



Synthesis of Serotonin and Melatonin



B-vitamins and Dementia: the evidence

1.Vitamin B12 Deficiency Common In Elderly:

- Decreased B12 absorption due to age-related decreased stomach acidity, and intrinsic factor synthesis, and common use of antacids, proton pump inhibitors (omeprazole, nexium) and/or histamine receptor blocker medications (e.g. Tagamet)

2. B-vitamin supplementation proven to improve mental function and reverse depression in clinical trials (B12,B6)

Recent Report

Subject: Old Age and Vitamin B-12

New York Times Personal Health

- **It Could Be Old Age, or It Could Be Low B12**
- By JANE E. BRODY Published: November 28, 2011

(Excerpt)

- Ilsa Katz was 85 when her daughter, Vivian Atkins, first noticed that her mother was becoming increasingly confused.

- A workup at a memory clinic resulted in a diagnosis of early Alzheimer's disease, and Ms. Katz was prescribed Aricept, which Ms. Atkins said seemed to make matters worse. But the clinic also tested Ms. Katz's blood level of vitamin B12. It was well below normal, and her doctor thought that could be contributing to her symptoms.

- Weekly B12 injections were begun. "Soon afterward, she became less agitated, less confused and her memory was much better," said Ms. Atkins. "I felt I had my mother back, and she feels a lot better, too."

- http://www.nytimes.com/2011/11/29/health/vitamin-b12-deficiency-can-cause-symptoms-that-mimic-aging.html?ref=health

Oxford Project to Investigate Memory and Ageing (OPTIMA study) – 2010

Source: Online journal *Public Library of Science ONE*
Chief Researcher: D Smith et al – Oxford University England

Study Group - 168 individuals over 70 y old with mild cognitive impairment.

Treatment: Supplementation with B- vitamins:

- folic acid - 800 mcg
- vitamin B12 - 500 mcg and
- vitamin B6 - 20 mg/d

vs Placebo

Main outcome measured - change in rate of whole brain atrophy (shrinkage) on MRI

Results:

1. On **average,** B vitamins slowed rate of brain atrophy by **30 percent.**

2. In some cases, reductions as high as **53 % were seen**

3. A **greater rate of atrophy** was associated with **lower cognitive test scores.**

Why B- vitamins (researchers comments):

1. FA, B6 & B12 – prevent rise in Homocysteine - damages brain and blood vessels.

2. Higher Hcyt – related to accelerated brain atrophy in many studies

3. B- vitamins – Increase **Neurotransmitters**

The Aging Brain

In elderly, the brain shows progressive atrophy.

Atrophy occurs even in cognitively healthy subjects, but is much accelerated in patients suffering from Alzheimer's disease

An **intermediate rate** of atrophy is found in people with mild cognitive impairment **(MCI)**

- People over 60 yrs **without** MCI normally have brain shrinkage **0.5 %** a year.

- Normally **twice** as fast in people with **MCI (1%)**

- **Alzheimer's** can lose **2.5 %** brain volume each year

Thus far, the only intervention shown to slow **brain shrinkage** in aging persons is supplementation with targeted B-vitamins.

Presently no drugs or lifestyle measures, other than B- vitamin supplementation have been shown to do this

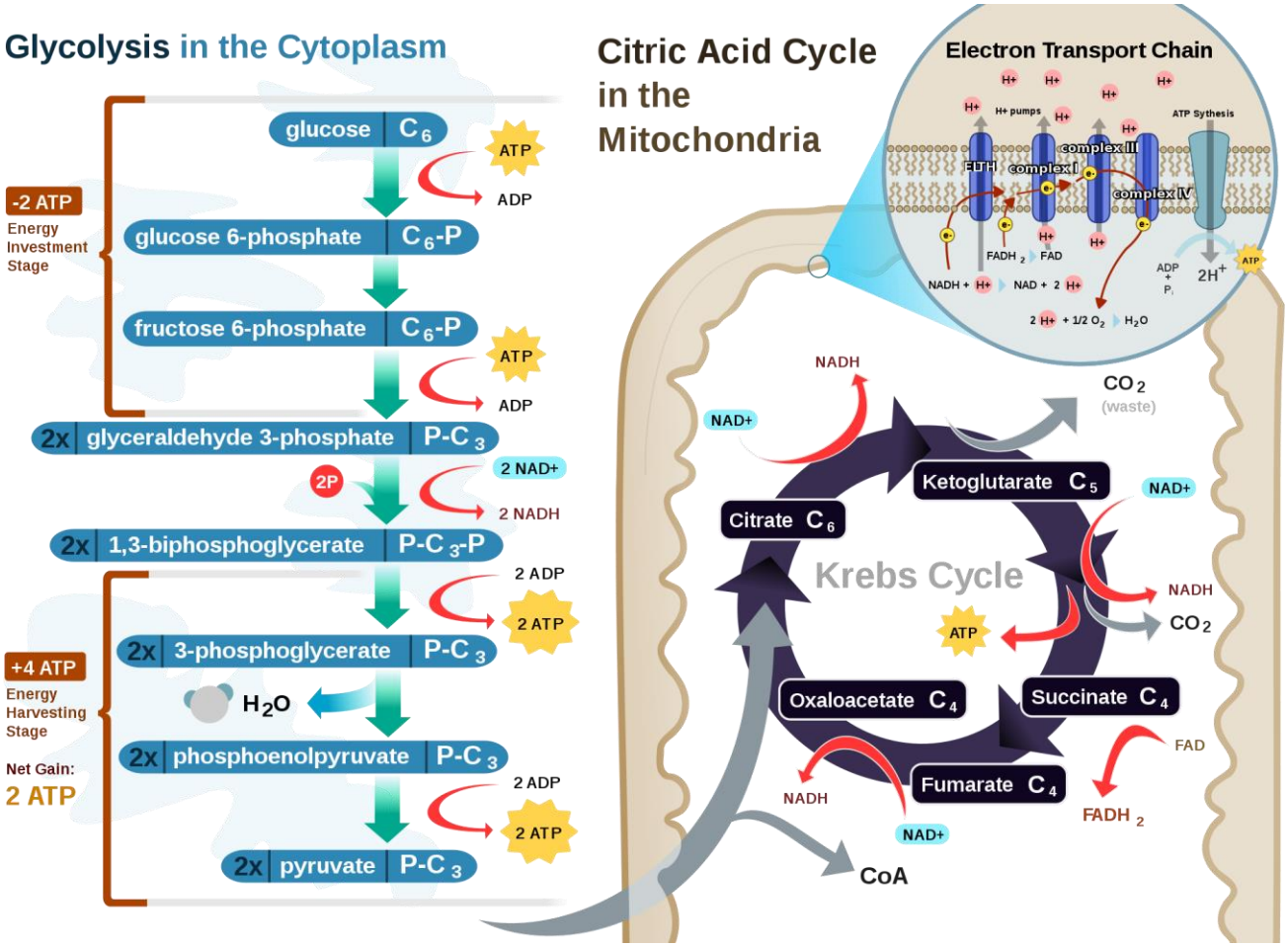
Vitamin B1 Thiamine

- Marginal Thiamine deficiency may contribute to decline in acetylcholine synthesis, seen in age-related dementia and Alzheimer's disease.

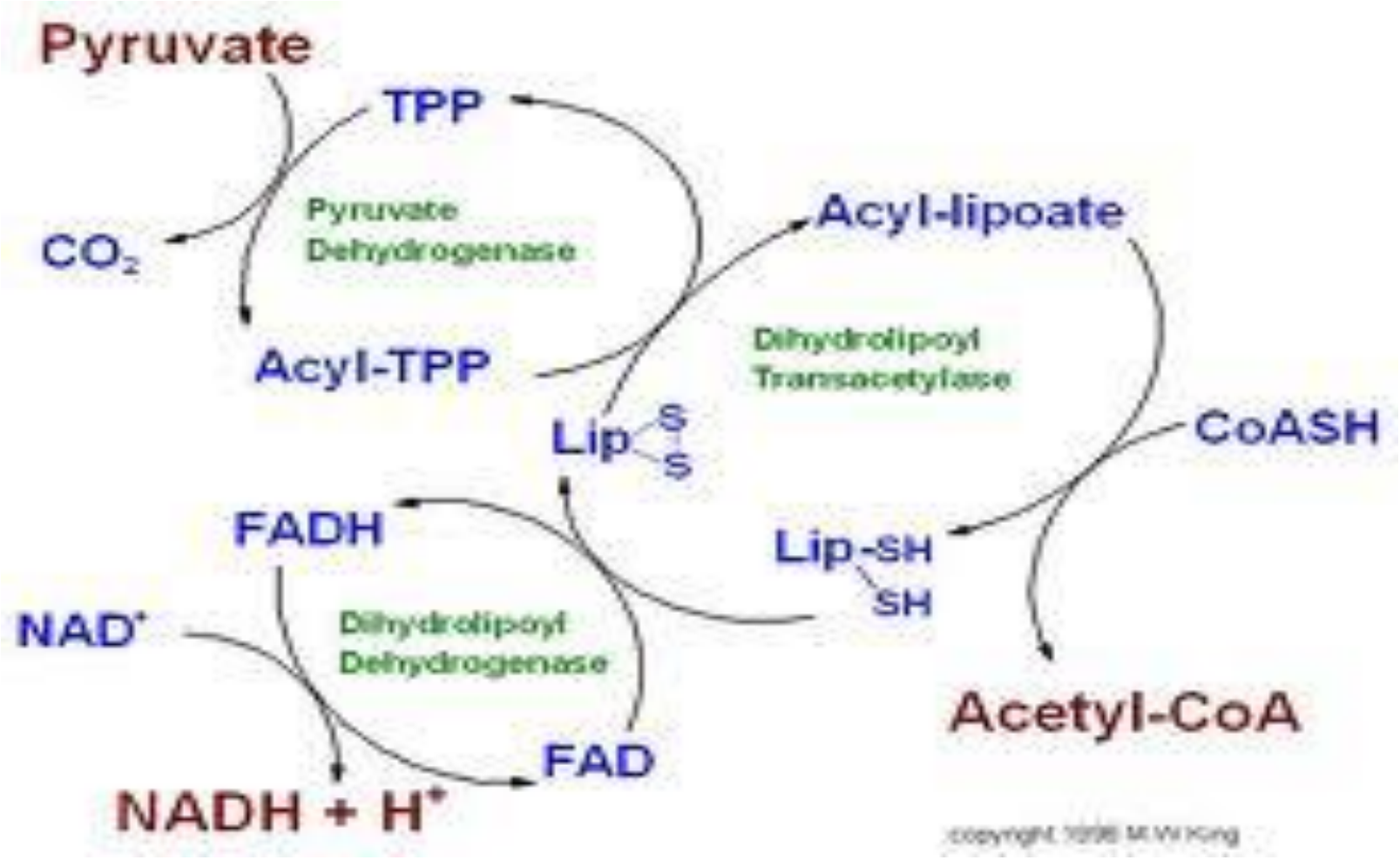
- Thiamine supplementation at pharmacologic dosages (3 to 8 grams/day thiamine administered orally) showed mild beneficial effect in dementia of Alzheimer's type. (Meador, K; Loring, D; Nichols, M; Zamrini, E; Rivner, M; Posas, H; Thompson, E; Moore, E (1993). "Preliminary findings of high-dose thiamine in dementia of Alzheimer's type". *J. Geriatr Psychiatry Neurol.* **6** (4): 222–9). https://www.ncbi.nlm.nih.gov/pubmed/8251051

- Brain tissue obtained at autopsy from patients with Alzheimer's disease contains reduced activities of TDP-dependent enzymes, particularly alpha-ketoglutarate dehydrogenase. Decreased Alpha-KGDH activity also seen in Parkinson's disease and progressive subnuclear palsy.(Modern Nutrition in Health and Disease 10th edition p.431).

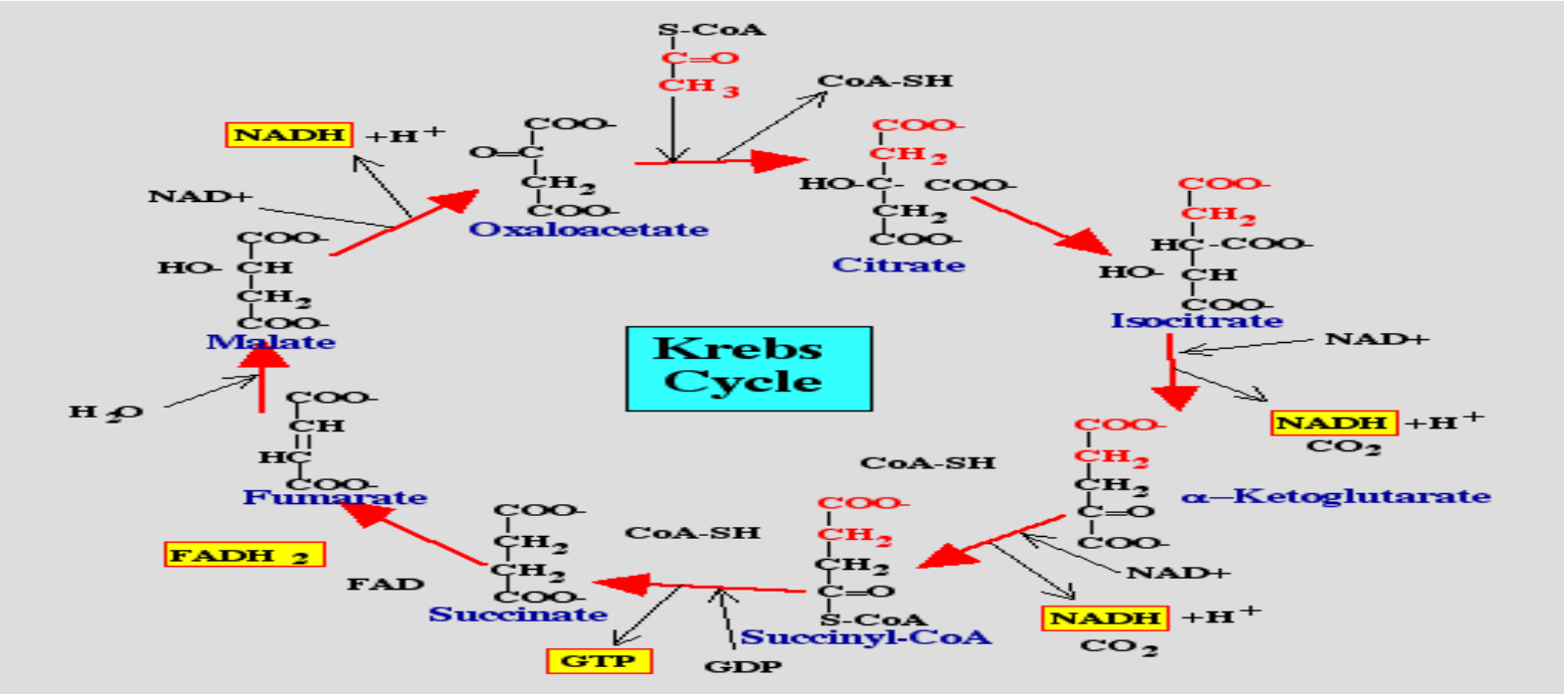
Pyruvate Enters Krebs cycle and Converted to Acetyl-CoA by PD (needs coenzymes)



Pyruvate Dehydrogenase and Coenzymes (including TPP or TDP – B1)



Within Krebs cycle conversion of alpha-ketoglutarate to succinly-coA (via alpha ketoglutarate dehydrogenase AKGD) requires B1 (TDP). Decreased conversion reduces brain ATP energy required for synthesis of acetylcholine and GABA. Decreased AKGD also increases brain glutamate, which is toxic to brain cells – partly responsible for Werniche Encephalopathy seen in alcoholics with B1 deficiency



Niacin: Emerging Info

- Niacin (NAD) required for ATP energy in nerve and brain cells – oxidative phosphorylation
- Niacin also required to preserve integrity of tau protein in microtubular structures within nerve and brain cells
- Degradation of microtubular structures leads to neurofibrillary tangles of tau protein in final stages of Alzheimer's disease

Epidemiological studies suggest that adequate niacin intake protects against Alzheimer's disease:

- Rush Institute for Health Aging in Chicago, and colleagues studied 3,718 65-and-older residents of three south Chicago neighborhoods for more than five-and-a-half years. They also performed clinical tests on 815 of these people over four years.

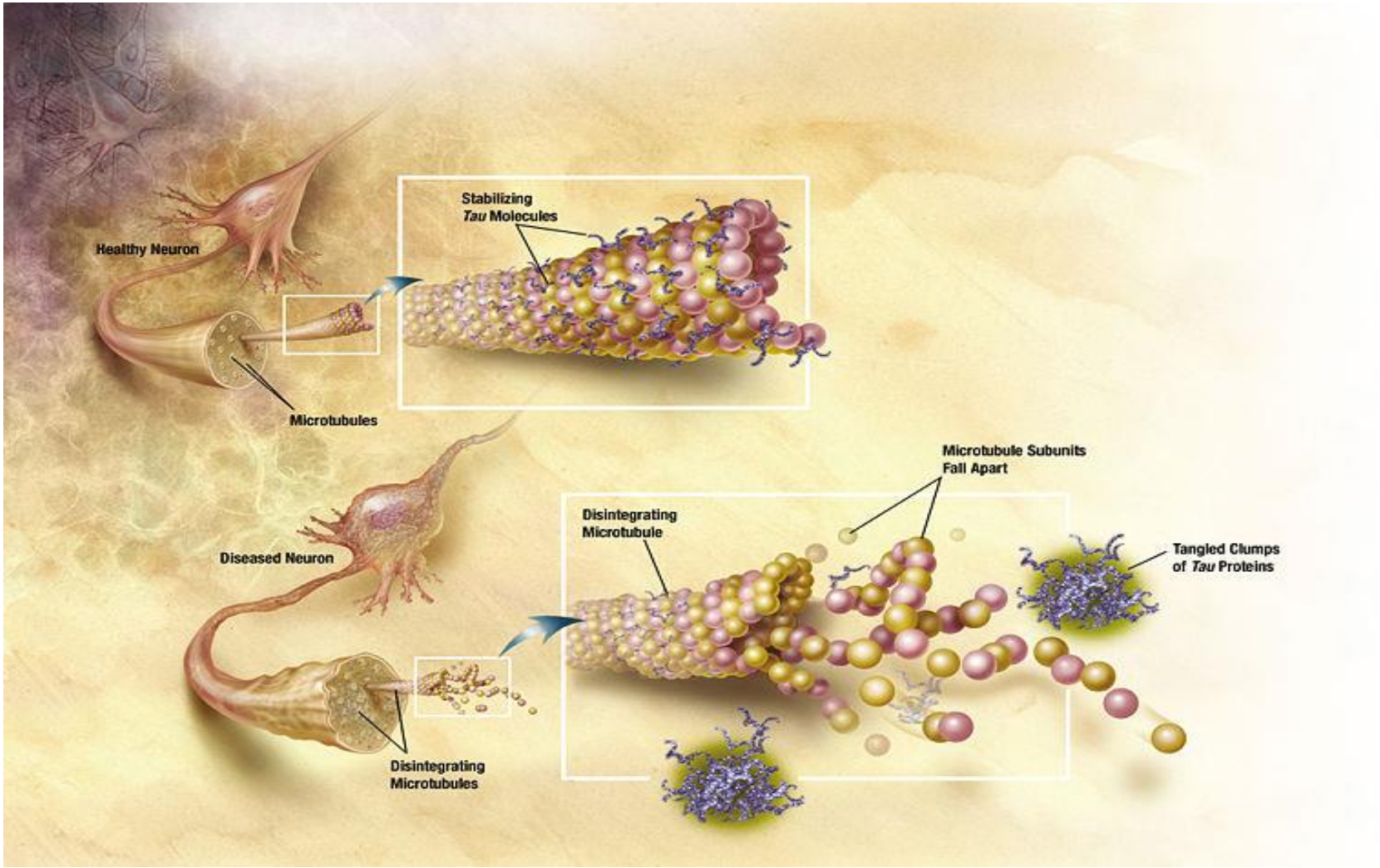
- They found that those who got the least niacin were 70% more likely to develop Alzheimer's disease than those who got higher amounts (45 mg)

- People who get dangerously little niacin in their diets develop a disease called pellagra (Dementia, Diarrhea, Dermatitis). Pellagra usually isn't seen in people who get at least 11 mg of niacin a day. In the Morris team's study, the group at the lowest niacin level was getting a median 14 mg a day in diet and in vitamin supplements. The current recommended daily allowance for niacin is 16 mg per day for men and 14 mg per day for women.

- Benefits of higher niacin intake began in men and women at a median intake of 17 mg per day. Those at the study's highest niacin level were getting 45 mg per day in diet and supplements.

http://www.webmd.com/food-recipes/news/20040714/niacin-in-diet-may-prevent-alzheimers

Changes in tau protein lead to neurofibrillary tangles in neurons and cell death



Niacin Continued

Animal Studies And Niacin

- Animal studies show that niacin supplementation reduces neurofibrillary tangle development in simulated Alzheimer's disease experiments

- Nicotinamide 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)

- Also – Nicotinamide has fewer side effects than nicotinic acid (flushing etc)

http://bvftd.blogspot.ca/2011/05/niacin-vitamin-b3-and-dementia.html (2011 update)

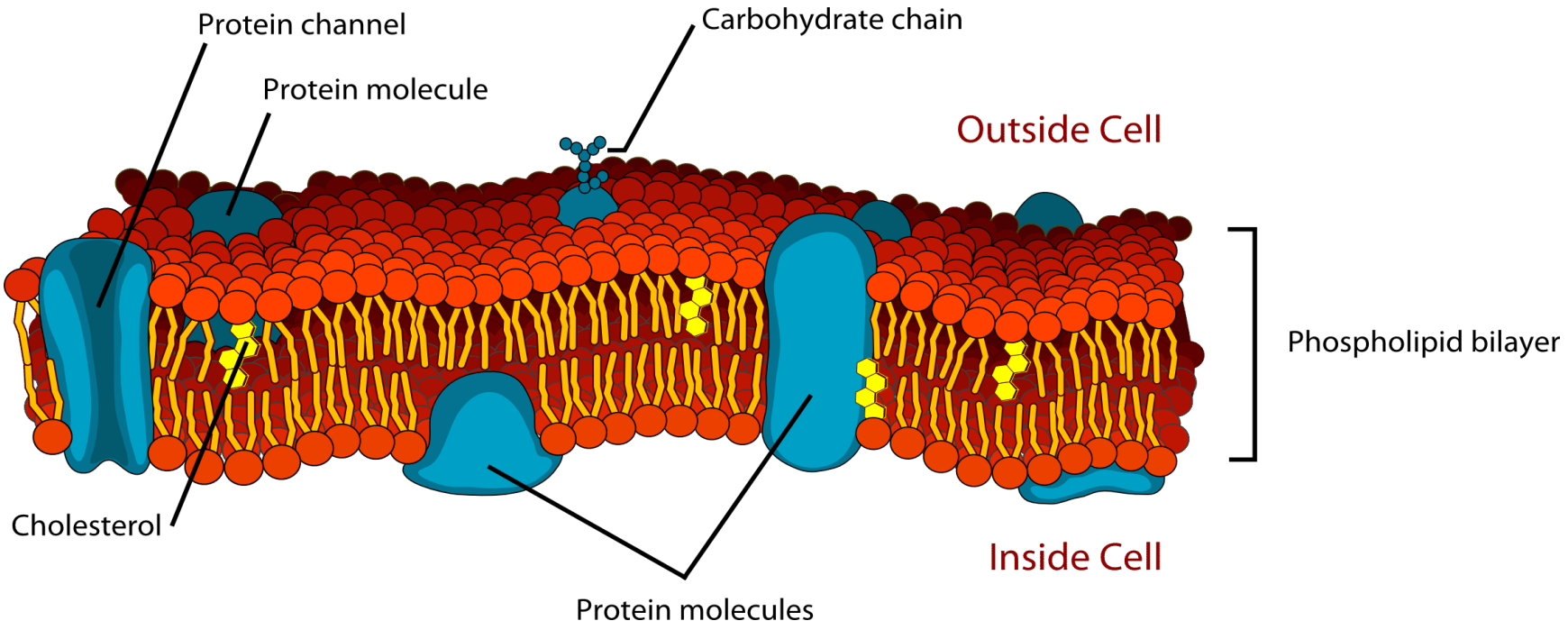
Omega – 3 Fatty Acids And Alzheimer's Disease

Omega-3 Fats (EPA & DHA) Associated With Decreased Alzheimer's Disease In Various Prospective Studies

Proposed Mechanisms Of Action:

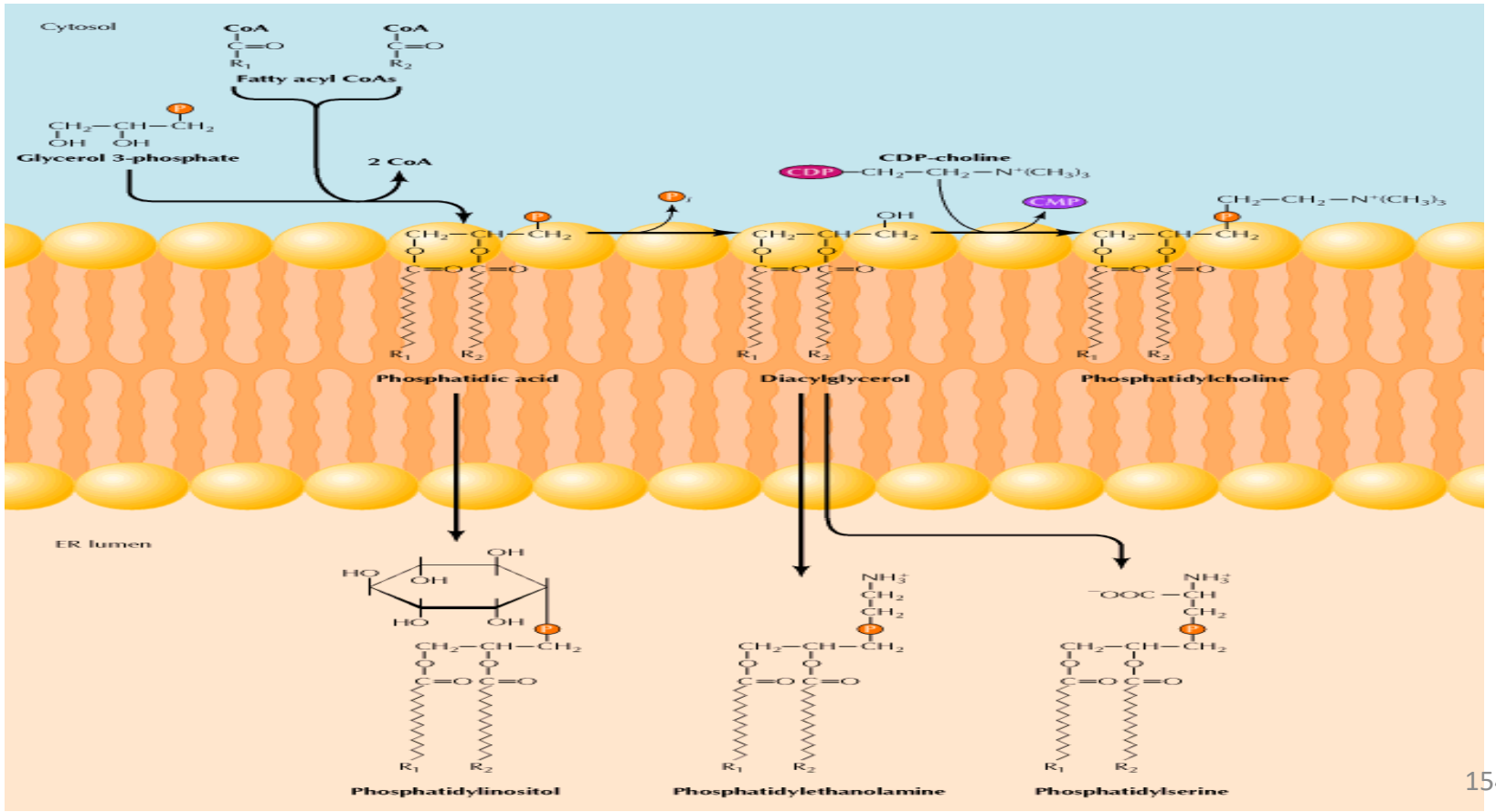
- decrease inflammation (via PG-3)
- increase brain circulation (via PG-3)
- increase membrane fluidity and conduction
- stimulate and increase number of LR11 receptor – decreasing beta- amyloid synthesis (DHA acts as ligand)

Cell Membrane – biphospholipid layer

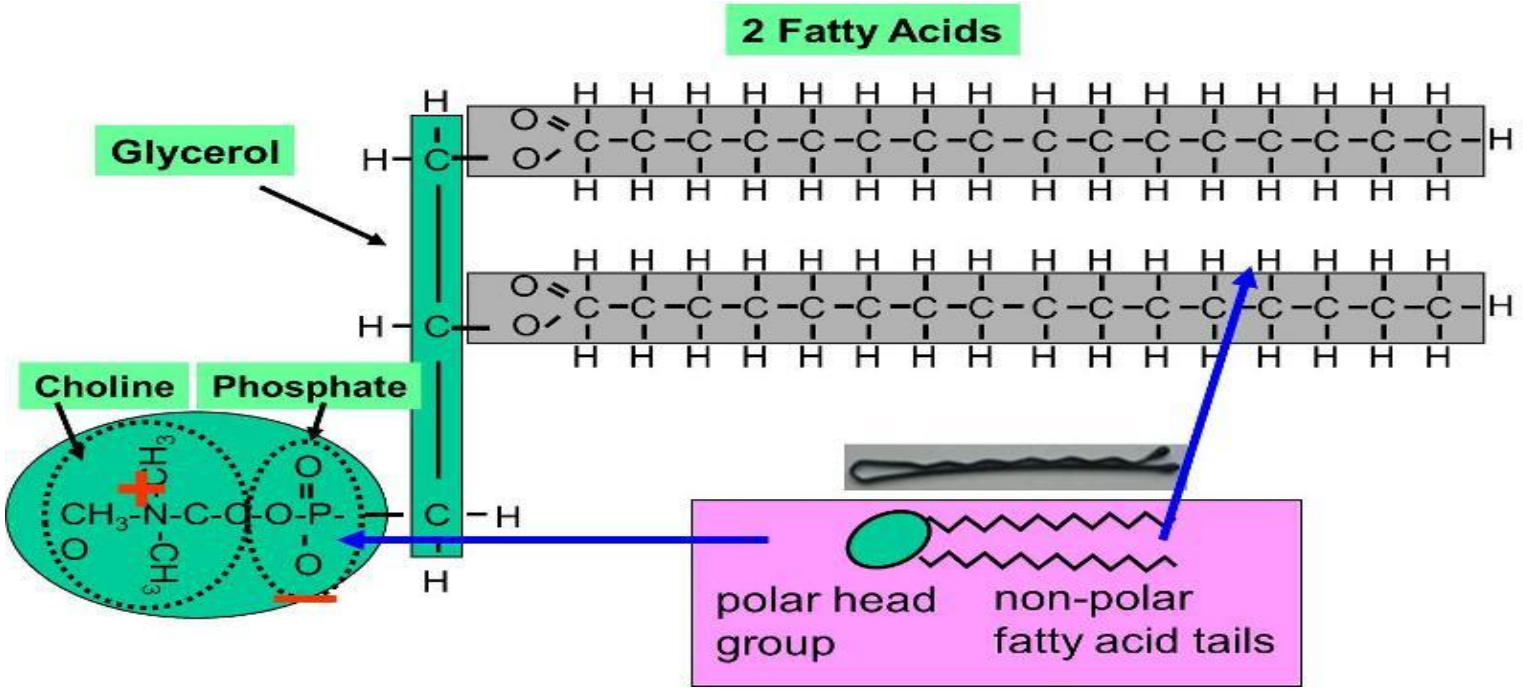


Synthesis of phospholipids. Two fatty acids linked to coenzyme A (CoA) carriers are first joined to **glycerol-3-phosphate**, yielding phosphatidic acid, which is simultaneously inserted into the membrane. A phosphatase then converts phosphatidic acid to diacylglycerol. The attachment of different polar head groups to diacylglycerol then results in formation of phosphatidylcholine, phosphatidylethanolamine, or phosphatidylserine. Phosphatidylinositol is formed from

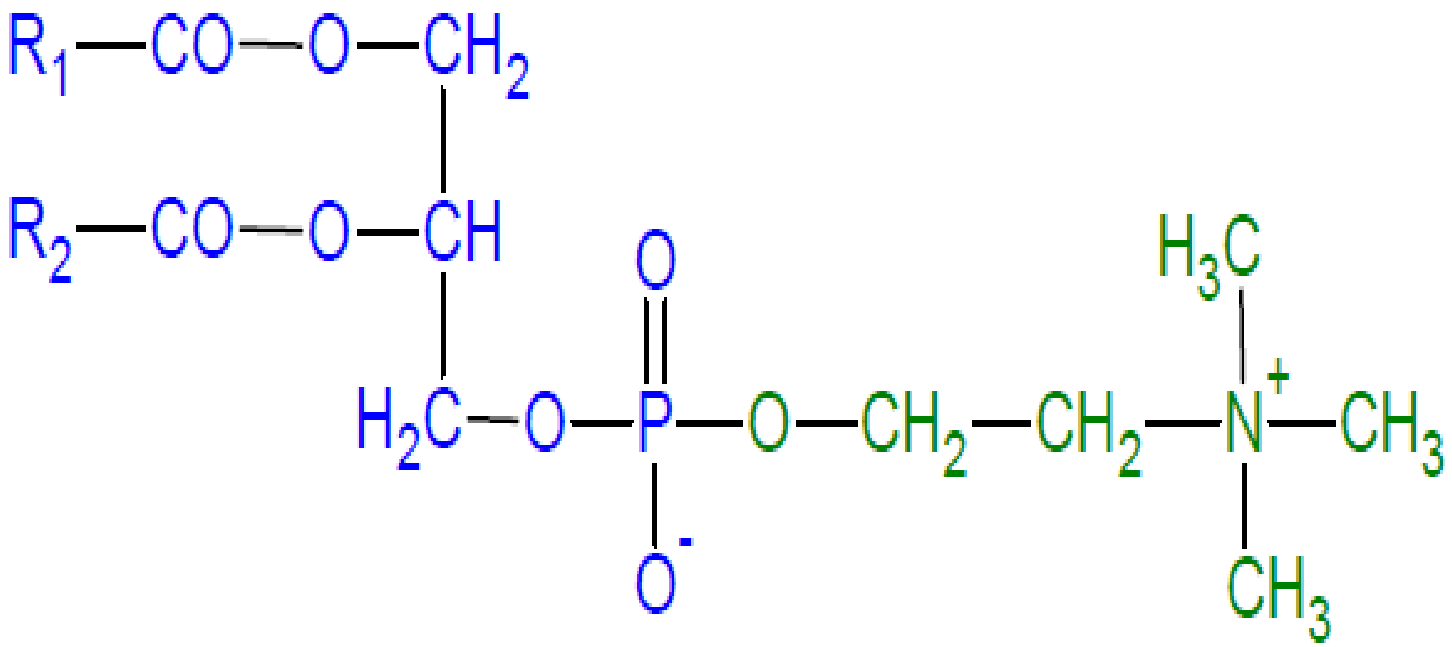
phosphatidic acid, rather than from diacylglycerol (Cell Membrane)



Phospholipid Structure. When R2 is DHA – get increased Phosphatidylcholine synthesis – omega-3 fat increase cell membrane fluidity

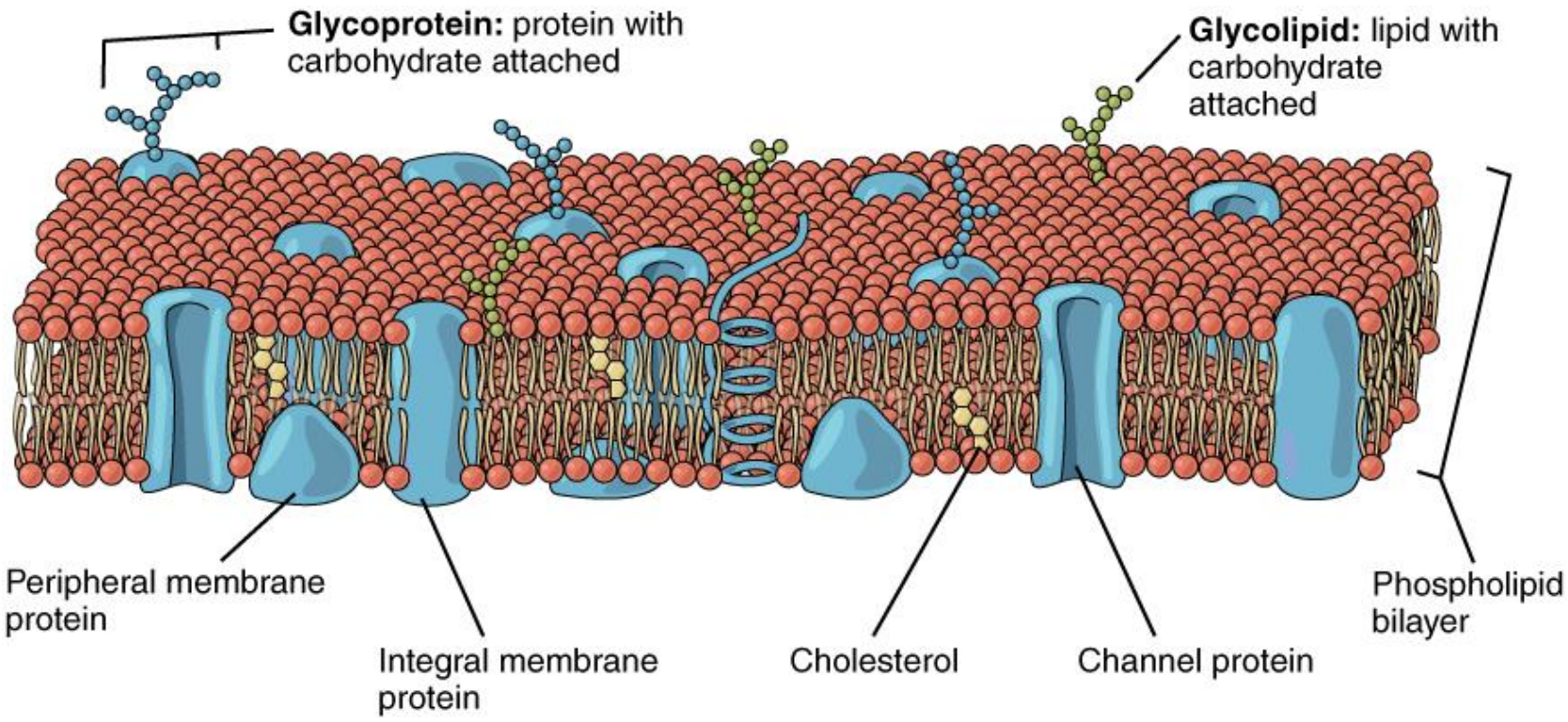


Omega-3 fats esterify phospholipids of brain cell = increased fluidity and improved receptor function on cell surface. Saturated fats and trans-fats make phospholipids more rigid, impairing fluidity and receptor function

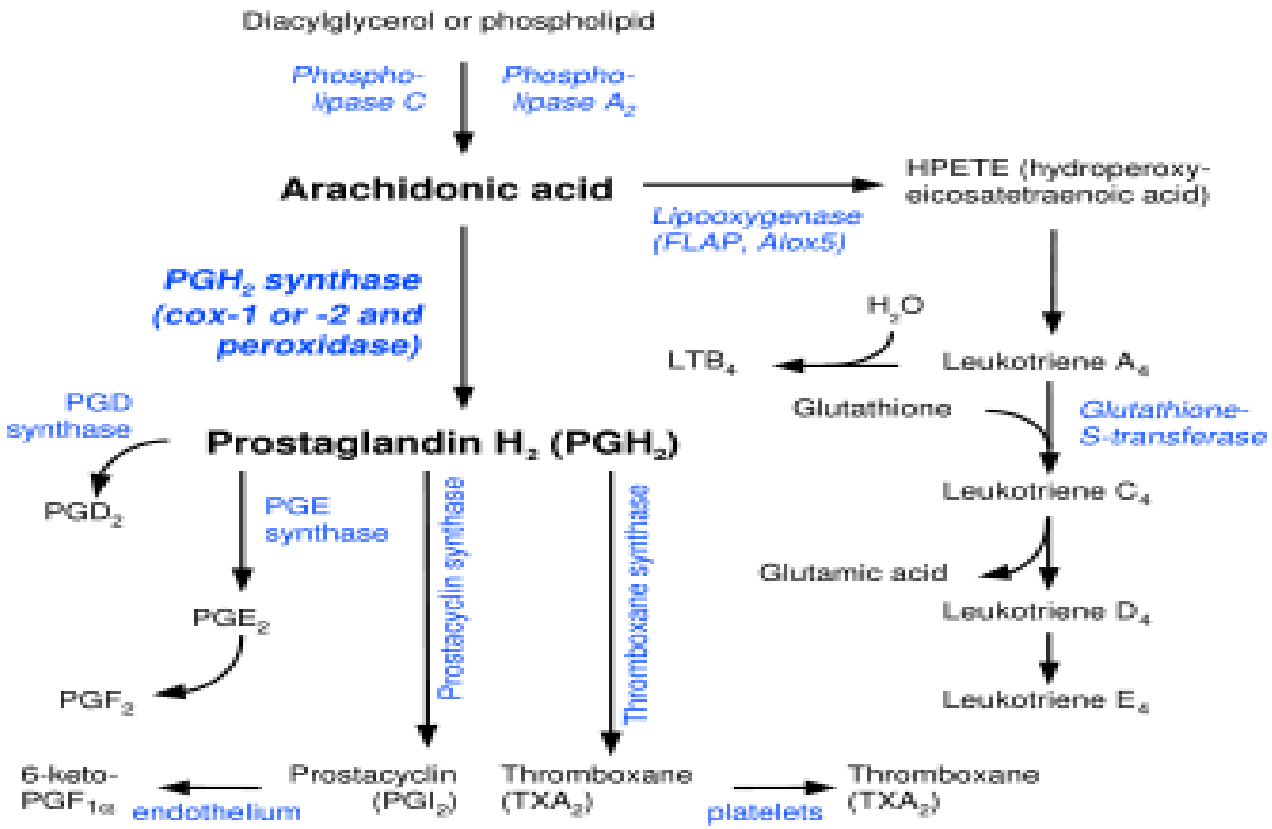


Phosphatidylcholine

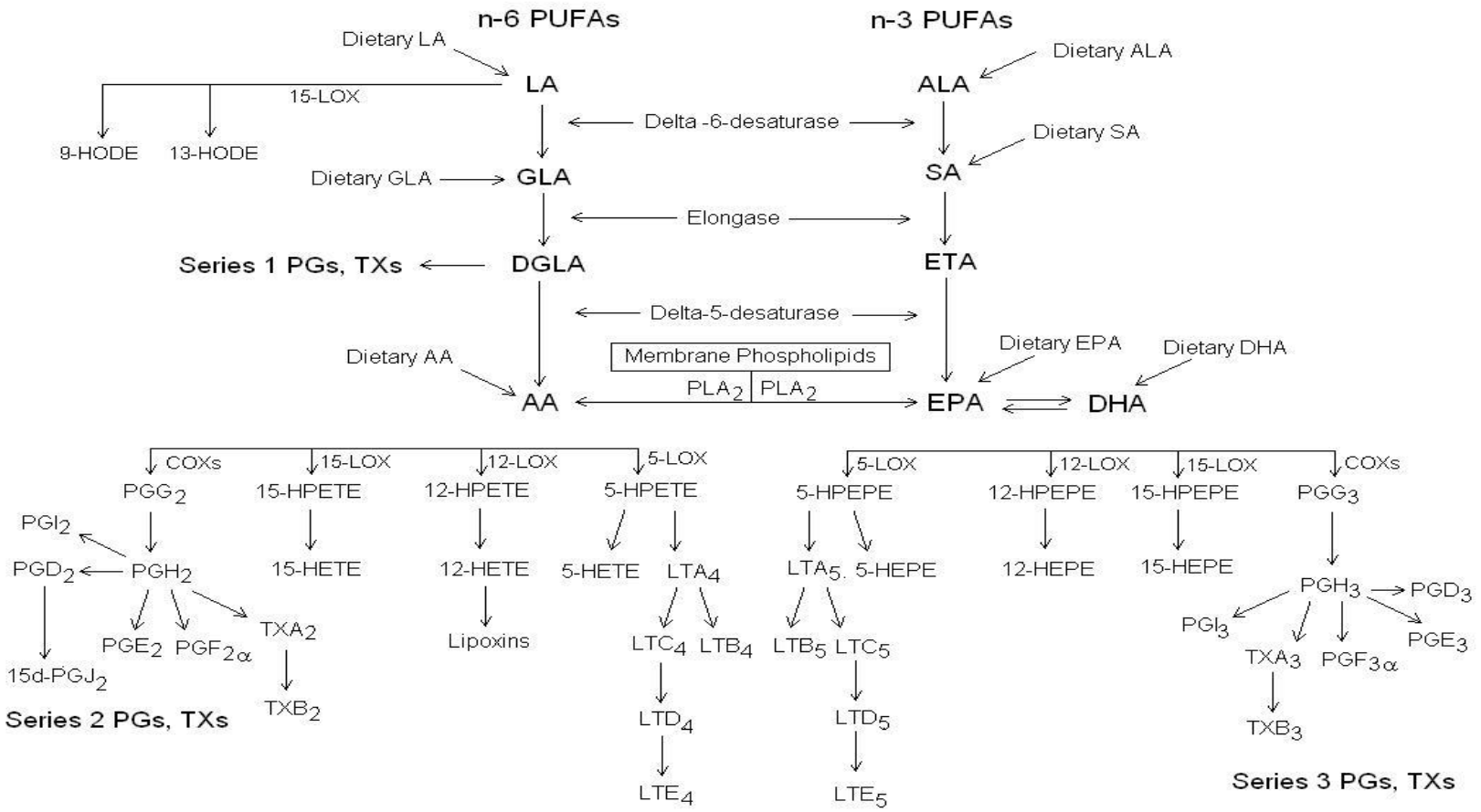
Receptors on Cell Membrane- increased fluidity of phospholipids improves receptor function



Arachidonic Acid – increases inflammatory brain eicosanoids and may decrease blood circulation via increased Thromboxane A2 production in platelets.

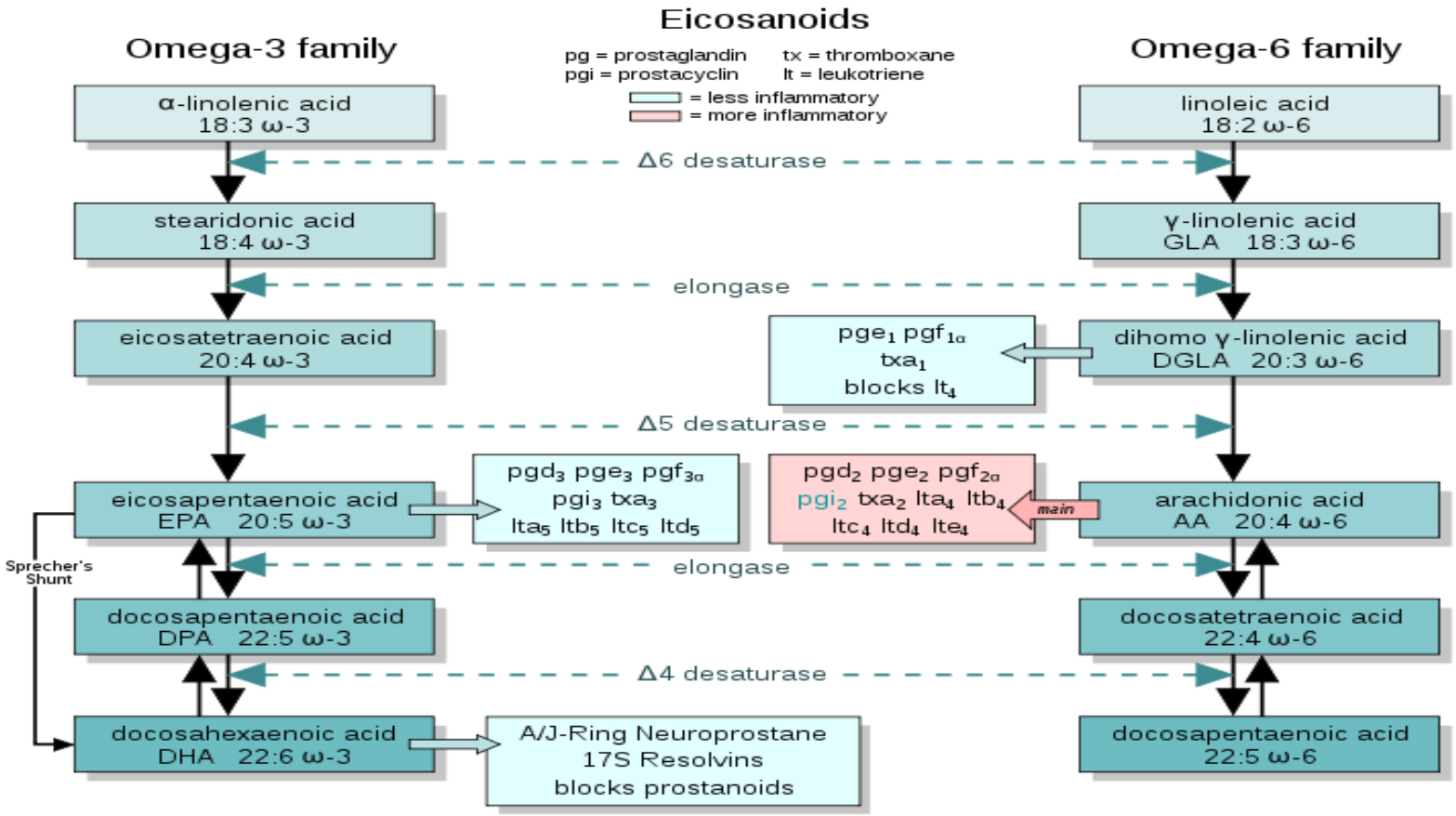


Omega-3 Fats – produce series 3 eicosanoids that cause vasodilation and reduce platelet stickiness = improved blood flow



Omega-3 Fats (EPA) is precursor to PG-3, which reduces inflammation, improves circulation (vasodilation) and reduces platelet stickiness (decreased thromboxane A2)

DHA increases expression of LR11 receptor – down-regulating beta-amyloid plaque synthesis and increases synthesis of phosphatidylcholine in presence of choline and cytidine



Omega-3- Fats (EPA & DHA) – 400 mg of omega-3 fat per day associated with significant decrease in Alzheimer's disease risk (Zutphen Elderly Study).

Several recent studies have suggested that higher intake and blood levels of omega-3 fatty acids may help to reduce risk of age-related cognitive decline, dementia and Alzheimer's disease. (see references next slide and accompanying course notes)

LR- 11 Receptor down-regulates synthesis of beta-amyloid protein upon stimulation from DHA

References Omega 3 Fats and Alzheimer's Disease

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Hyperglycemia, Diabetes, Metabolic Syndrome And Alzheimer's Disease:

Diabetics have higher risk of Alzheimer's disease

- The research linking diabetes and AD has its roots in the groundbreaking Rotterdam study.

- Of 6,370 elderly subjects studied for 2.1 years, 126 developed dementia; 89 of these were specifically diagnosed with AD.

- **Type 2 diabetes doubled** the risk of a patient having dementia and **patients on** i**nsulin had four times** the risk

- The term type 3 diabetes was coined in 2005 by Suzanne de la Monte, MD, MPH, Associate Professor of Pathology and Medicine and neuropathologist at Brown Medical School.

- Her team, examining post-mortem brain tissue of AD patients, found that AD may be a neuroendocrine disease associated with insulin signalling.

- The team termed it **type 3 diabetes** because it harbours elements of both types 1 and 2 diabetes, since there is both a decrease in the production of insulin and a resistance to insulin receptors

Pathophysiological Connections between Insulin and AD

- AD is characterized by both low insulin levels and insulin resistance within the central nervous system (CNS), as opposed to type 2 diabetes, which is characterized by high insulin levels and insulin resistance outside of the CNS**.**

- **"Both Insulin resistance and hyperinsulinemia cause a reduction in brain insulin**"

- Insulin receptors are found in areas of the brain responsible for cognition. **Insulin activates signalling pathways associated with learning and long-term memory.**

- According to de la Monte, insulin helps to regulate processes such as neuronal survival, energy metabolism, and plasticity. These processes are required for learning and memory. Peripheral insulin resistance, therefore, negatively affects cognition.

- In addition to regulating blood sugar levels, insulin functions as a growth factor for all cells, including neurons in the brain. Insulin also required to support tau protein and microtubule integrity. Thus, lack of brain insulin, contributes to beta-amyloid plaque and neurofibrillary tangle synthesis in AD

- When insulin levels reach an exceedingly high level in the blood, the beta-amyloid peptide, the hallmark of AD that accumulates in senile plaques, is modulated.

- Exaggerated elevation of plasma insulin levels causes amyloid peptide levels in the cerebrospinal fluid to increase, resulting in memory insult.

References:
http://acam.typepad.com/blog/2010/04/the-relationship-between-alzheimers-disease-and-diabetes-type-3-diabetes-.html
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769828/

Hyperglycemia Effects:

- Advanced glycation end products (AGEs) are found in higher concentration in both hyperglycemia and AD, contributing to oxidative stress and nerve cell damage.

Exercise Breaks Down Plaque in Alzheimer's disease

Exercise Breaks Down Plaque Responsible For Alzheimer's disease: Study shows

- There is good evidence from human studies that a high fat diet increases risk for Alzheimer's disease, and there is absolute proof that a high fat diet increases the development of Alzheimer's brain damage in rodent studies.

- One of the ways that a high fat diet increases risk of Alzheimer's disease is by stimulating production of the beta-amyloid plaque, which is a hallmark feature of the disease.

- Beta-amyloid plaque is a protein that forms between brain cells from fragments of a protein found on brain cell surface receptors. The accumulation of beta-amyloid plaque damages brain cells in various ways, including increasing free radical damage.

- Researchers have been looking for ways to inhibit the accumulation of beta-amyloid plaque in the human brain, which would be a giant step forward in the ability to prevent the disease. So far, no drugs are able to do this.

Omega-3 fats, Melatonin, Exercise in AD Prevention

- There is evidences to show that certain supplements can prevent synthesis of beta-amyloid plaque, such as the **omega-3 fat DHA** as well as **melatonin.**

- Recently Vitamin D has been shown to help break down beta-amyloid plaque, and thus, all of these supplements may be key factors in helping to prevent Alzheimer's disease as we age.

Exercise Shows Remarkable Promise

- A 2012 study in the Journal of Biological Chemistry (M. Maesako/2012) has shown that regular exercise was able to break down and eliminate the beta-amyloid plaque formed in the brains of mice, after feeding them a high fat diet.

- In other words, the amyloid plaque formed in the brains of mice as a result of feeding them a high fat diet, was reversed by providing them with an exercise regiment after the plaque had already formed. This is a remarkable finding suggesting that some of the damage in Alzheimer's disease may be reversible (1).

- There is already evidence in humans to show that providing exercise to patients with memory loss problems improves their cognitive function (2). The study by M. Maesako (2012) may help to explain this result. If, indeed, exercise can help breakdown the beta-amyloid plaque in the human brain, as it does in mice, then we are really on to something.

- In the meantime, two important strategies to help prevent Alzheimer's disease entail following a diet low in saturated fat, cholesterol, transfats, and deep fried food, and exercising.

- Not only might these factors reduce the build up of beta-amyloid plaque in your brain, but they will help to keep your body fat, blood sugar and insulin levels lower, which are also linked to lower risk of Alzheimer's disease.

References:

1. Masato Maesako, Kengo Uemura, Masakazu Kubota, Akira Kuzuya, Kazuki Sasaki, Ayae Kinoshita, et al. "Exercise is more effective than diet control in preventing high fat diet-induced [beta]-amyloid deposition and memory deficit in amyloid precursor protein transgenic mice." The Journal of Biological Chemistry, 287, 23024-23033, June 29, 2012

2. Lautenschlager N et al. Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease. JAMA. 2008;300(9):1027-1037.

American Academy of Neurology 66th Annual Meeting 2014:

Aerobic Exercise Preserves Cognition in Nondemented Elderly

- Study included 39 older individuals who were in geriatric institutions.

- Of these, 22 patients (8 women and 14 men; mean age, 77.94 years) had been randomly assigned to the exercise group and 17 patients (7 women and 10 men; mean age, 83.59 years) to a control group.

- Patients in the experimental group completed at least 15 minutes of aerobic activity in the form of continuous stationary cycling every day for 15 months.

- The mean weekly exercise duration in this group was 134.21 minutes, or roughly 18 minutes a day.

- Those in the control group carried out nonphysical activities, such as reading and playing cards.

Results

- Compared with control group, the exercise group had improved cognitive status according to the MEC score.

- "There was a statistically significant worsening in the control group in terms of global cognition; however, the experimental group improved," said Dr. Seijo-Martinez.

- The exercise group, which initially did worse than the control group on the SDMT, improved significantly in the assessment of psychomotor speed. The Symbol Digit Modality Test (SDMT) measures psychomotor speed and attention

- The positive outcomes may have been due to improved blood circulation to brain, improved heart function or other influences (breakdown of amyloid plaque etc).

Melatonin Decreases Transition from MCI to Alzheimer's disease

- Based on experimental data showing that melatonin blocks the build up of beta-amyloid plaque, as well as the finding that Alzheimer's patients tend to have lower melatonin levels than non-Alzheimer's patients, clinical studies have been performed in recent years to test the value of administering melatonin to patients with mild cognitive impairment.

- Mild cognitive impairment is the stage of memory loss and functional brain capacity decline that is the forerunner to the development of full-blown Alzheimer's disease.

- The studies by Furio et al, and Peterson et al, have shown that patients with mild cognitive impairment (MCI), who were administered melatonin **supplementation** showed better outcomes over time than MCI patients not taking melatonin supplements.

- In these studies the dosage range was 3-9 mg, taken one hour before bedtime .

- However, two preliminary studies showed improved cognitive performance in MCI patients who were using melatonin dosages as low as 1 mg and as high as 6 mg.

References:

1. Furio AM, Brusco LI, Cardinali DP. Possible Therapeutic Value of Melatonin in Mild Cognitive Impairment: a Retrospective Study. *J. Pineal Res. 2007;**43:404–409.***
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild Cognitive Impairment: Clinical Characterization and Outcome. *Arch. Neurol. 1999;**56:303–308***

- In addition, recent findings show (BMJ Open – Feb 2012) that prescription sleeping medications are linked to an increased risk of cancer, heart disease, premature death and other health conditions.

- I have argued that taking melatonin in a supplement that also includes 5HTP, GABA and Bacopa monnieri, is a much safer and effective strategy to remedy age-related (after age 40) insomnia, and sleep disturbances.

- With recent studies now showing that melatonin supplementation may be an important measure to help prevent **Alzheimer's disease** and stabilize cases of MCI (which is very common after age 60), the argument in favor of using a melatonin supplement as a sleep aid, instead of prescription sleeping pills, becomes even more compelling.

- Remember that too much melatonin can give you vivid dreams that might actually awaken you, or leave you feeling drowsy in the morning.

- As such, I suggest you begin with a supplement that provides no more than 500 mcg (0.5mg) per capsule, as a starting dosage.

- To improve sleep quality begin with no more than 500 mcg of melatonin, one hour before bedtime. If that is not sufficient then increase the dosage to 1 mg (1000 mcg) or two capsules. Slowly increase the dosage until you find the dosage that gives you a good night's sleep and allows you be refreshed the next morning.

- For patients with established MCI higher dosages may be more appropriate (3-9 mg) to prevent the transition to Alzheimer's disease, according to recent human intervention trials.

- Any dosage above 3 mg requires physician monitoring to ensure that liver function, in particular, is not adversely affected.

Catechins in Green Tea Linked to Better Memory

- A 2012 study in the journal, *Molecular Nutrition & Food Research, shows that a frequently touted constituent of green tea may help improve memory and preserve memory as we age. The constituent in green showing this effect is the organic chemical* EGCG, (epigallocatechin-3 gallate)

- EGCG is a well established antioxidant, and some studies show its benefits in reducing risk of cardiovascular disease and cancer. Clinical studies on humans has shown its ability to aid weight loss by stimulating the burning of fat in brown adipose (fat) tissue, enabling the body to give it off as heat to the environment (thermogenesis).

- The most recent test tube and animal studies suggest that EGCG may also improve cognitive function by impacting the generation of nerve cells in the brain cells.

- This process is known as neurogenesis. This study assessed the impact of EGCG on the hippocampus, the part of the brain which processes information from short-term to long-term memory. In **Alzheimer's disease** the hippocampus shrinks (atrophies) to a significant degree, which is a common finding in this disease.

- Researchers found that EGCG boosts the production of the rudimentary nerve cells (neural progenitor cells) that morph into specialized brain cells in hippocampus area of the brain.

- Neural progenitor cells are similar to stem cells, which can mature into adult cells in various tissues or divide and produce more stem cells as well.

- The researchers went on to show that laboratory mice not only increased nerve cell production in the hippocampus of the brain, but they also demonstrated an advantage in memory or spatial learning (in maze tests), compared to mice not giving the EGCG

Reference:

- Yanyan Wang, Maoquan Li, Xueqing Xu, Min Song, Huansheng Tao, Yun Bai. **Green tea epigallocatechin-3-gallate (EGCG) promotes neural progenitor cell proliferation and sonic hedgehog pathway activation during adult hippocampal neurogenesis**. *Molecular Nutrition & Food Research*, 2012; 56 (8): 1292 (weblink: http://onlinelibrary.wiley.com/doi/10.1002/mnfr.201200035/abstract)

THC and Alzheimer’s

Experimental evidence suggests that THC (from cannabis) can inhibit the breakdown of acetylcholine and the synthesis of beta-amyoloid plaque in the brain, in models of Alzheimer’s disease

Tetrahydrocannabinol (THC), competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE-induced amyloid β-peptide (Aβ) aggregation, the key pathological marker of Alzheimer's disease.

“THC provides an interesting Alzheimer's disease drug lead, it is a psychoactive compound with strong affinity for endogenous cannabinoid receptors. It is noteworthy that THC is a considerably more effective inhibitor of AChE-induced Aβ deposition than the approved drugs for Alzheimer's disease treatment, donepezil and tacrine”.

“Therefore, AChE inhibitors such as THC and its analogues may provide an improved therapeutic approach for Alzheimer's disease, augmenting acetylcholine levels by preventing neurotransmitter degradation and reducing Aβ aggregation, thereby simultaneously treating both the symptoms and progression of Alzheimer's disease”.

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562334

14 Nutrition/Lifestyle Steps to Prevent Alzheimer's disease

1. Keep your blood cholesterol below 3.9 mmol/L (150 mg/dL) by consuming a low animal fat diet, avoiding as much trans-fats, hydrogenated fats, and organ meats as possible, as well as other foods high in cholesterol (e.g. egg yolks). These foods elevate blood cholesterol levels, which clog brain arteries leading to cerebrovascular disease – a major contributing factor to dementia and Alzheimer's disease. Vascular dementia, which is the second most common form of dementia after Alzheimer's disease, is caused by insufficient blood flow to brain cells. It is a direct extension of atherosclerosis due to high cholesterol levels, and often compounded by hypertension, diabetes and smoking (3).

2. Keep your fasting blood sugar (glucose) level below 5.0 mmol/L (90 mg/dL), as higher glucose levels (and insulin levels, which result from high glucose) lead to type 3 Diabetes – a form of Alzheimer's disease caused by high blood glucose and insulin. It is well established that individuals with type 2 diabetes have twice the risk of developing Alzheimer's than non diabetic patients. Insulin-dependent diabetics have four times the risk. **One reason for this is explained by the fact that there is an enzyme in the brain that breaks down both insulin and amyloid plaque – a hallmark feature of Alzheimer's disease. Thus, in cases where insulin levels are high, which occurs when blood sugar is too high, the brain enzyme is so busy breaking down insulin that it allows amyloid plaque to build up**. High levels of amyloid plaque (a protein known also as beta-amyloid protein), in essence, strangles brain cells from the outside and generates copious amounts of free radicals – which further damages brain cell structure and function.

High blood sugar also increases brain inflammation, which contributes to Alzheimer's disease development (4). As well, Alzheimer's brains demonstrate insulin resistance, which is triggered by sustained high blood sugar levels (5).

3. Remain at your ideal body weight. Over weight individuals have a higher risk of Alzheimer's disease, primarily due to higher circulating insulin (insulin resistance produced by larger fat cells) and glucose levels – leading to type 3 Diabetes (1,2).

4. Consider a high potency multiple vitamin and mineral each day that contains a B-50 complex, 1000 IU of Vitamin D (6) and the following antioxidant levels (Vitamin E- 400 IU, Vitamin C – 1000 mg). Studies show that after age 60 the brain begins to shrink (atrophy) by 0.5 – 2.0% per year. People who develop cognitive dysfunction (a prelude to Alzheimer's disease) and Alzheimer's disease show a faster rate of brain atrophy. The only intervention shown to slow brain atrophy, thus far, is supplementation with B-vitamins (7). Other studies show that Vitamin E and Vitamin C supplements act as antioxidants in the brain, slowing brain oxidation (free radical damage to brain cells). Brain oxidation is a consistent feature in Alzheimer's disease, and some studies show that individuals taking Vitamin E and Vitamin C supplements (at a minimum threshold dosage) are less prone to future onset of Alzheimer's disease (8). Vitamin E supplementation has been shown to slow the progression of Alzheimer's disease in several clinical trials (9).

5. Consider an essential fatty acid supplement each day that contains fish, flaxseed and borage seed oil. The capsule should contain 400 mg each of these three oils. The daily dosage of 3 capsules per day provides the amount EPA and DHA shown to reduce risk of Alzheimer's disease in large population studies (epidemiological studies). Eating fish twice per week is also helpful in this regard. Eating fish more than three times per week is linked to increased risk of mercury toxicity, which may damage the brain, according to the Environmental Protection Agency. Thus, essential fatty acid supplementation is a critical component of Alzheimer's disease prevention (10-21).

6. After age 40, consider a melatonin supplement one hour before bedtime. By age 40 melatonin secretion rates from the pineal gland in the brain have declined significantly. Melatonin is a vital brain antioxidant, sleep inducer and immune modulator. Low melatonin levels are linked to cognitive impairment and Alzheimer's disease. Studies show that providing cognitively impaired patients with melatonin supplements blocks the transition to Alzheimer's disease in a high percentage of cases. No medical treatment is available that shows a similar effect (22-29).

I recommend that individuals over 40 take a supplement containing the following:

- Melatonin – 500 mcg
- 5 HTP – 10 mg
- GABA – 25 mg
- Bacopa monnieri – 15 mg (22-29).

Take one to four capsules, one hour before bedtime, based on the dosage that enables one to fall asleep, remain asleep through the night, and wake up refreshed in the morning. Start with one capsule, and increase the dosage until arriving at the ideal dosage. As one gets older the dosage usually increases due to the steady decline in melatonin secretion with advancing age.

7. Increase Acetylcholine Synthesis After Age 55 - One often overlooked aspect of Alzheimer's disease risk and age-related dementia involves age-related changes to the choline transporter (which acts like a pump), which becomes more sluggish as we approach our 60's. As such, less choline is pumped across the blood-brain barrier from the bloodstream. Normally choline is stored in brain cells as phosphatidylcholine (part of the outer skin or membrane of brain cells). On an ongoing basis nerve cells access this choline to produce the memory chemical acetylcholine.

However, with aging less choline enters the brain, a decline in phosphatidylcholine ensues and brain cells are less able to make the memory chemical acetylcholine. The result is a decline in memory capacity. Reduced levels of phosphatidylcholine, as well as choline and other choline-dependent brain phospholipids and molecules including phosphatidylethanolamine and ethanolamine, are classic features seen in the Alzheimer's brain upon autopsy (Textbook: Modern Nutrition in Health and Disease -10th edition. Editors: Shils M, Shike M, Ross A.C, Coballero B, Cousins R. Lippincott Williams & Wilkins: pages 528 and 532).

- Drugs used to treat Alzheimer's disease primarily work by slowing the breakdown of acetylcholine, but no drugs increase the amount of choline entering the brain or stimulate acetylcholine synthesis. However, there are supplements that can do both. These supplements have been shown to cross the blood-brain barrier, without the help of the choline transporter, and help to synthesize and maintain more optimal acetylcholine levels after age 55 yrs. Each of these supplements have been shown to stabilize or reverse early stage memory loss in dementia, but their most important application lies in the prevention of memory loss in those 55 and older – in the stage of life when the choline transporter functioning is declining. Supplement ingredients that are important from this standpoint include:
- CDP-choline
- Phosphatidylserine
- Huperzine A
- Bacopa monnieri

No foods or drugs can increase acetylcholine synthesis after age 55. Only specific supplements have been shown to produce this important outcome in the aging brain. This is one more example of how targeted nutritional supplements can complement best medical and lifestyle practices, helping to combat the genetic time bombs of aging, and thereby help preserve more youthful function of key body organs and systems (30-60).

8. Avoid known brain-damaging substances. Don't drink or limit alcohol. Alcohol kills brain cells. If you drink then have no more than 3 alcoholic drinks per week. Don't smoke. Free radicals in cigarette smoke cause brain oxidation and increase risk of cerebrovascular disease. Don't use recreational drugs, as many are known to cause brain damage (61).

9. Keep your brain active by learning a new activity or new language. Some examples include learning a musical instrument, taking dance lessons, playing ping pong (mind-body activity), or learning a new skill or subject that is outside of your usual skill set, career endeavour, or leisure time hobbies. This helps to carve new brain circuits, which keep the brain young. It may interest you to know that individuals with lower education have higher rates of Alzheimer's disease. Use your brain power throughout all of adult life, and continue to learn things outside of your usual frame of reference. This is vital to preserving brain health (61).

10. Avoid head injuries by wearing a helmet when cycling, skiing, rollerblading etc., and avoiding high-risk head injury activities (61).

11. Keep Your Blood Pressure in the Normal Range. High blood pressure has been shown to increase risk of Alzheimer's disease and biomarkers for Alzheimer's disease. Reducing high blood pressure has also shown benefit in reducing risk of Alzheimer's disease (62, 63, 64).

12. Participate in Endurance Exercise. Endurance exercise has been shown to help breakdown beta-amyloid plaque in experimental studies and has improved cognition in older human subjects, compared to age-matched controls who did not participate in formal endurance exercise. Middle-aged adults who regularly participate in endurance exercise have been shown to be at significantly lower risk for Alzheimer's disease and other degenerative diseases as they age (65,66,67)

13. Drink Green Tea Daily. Epidemiological studies suggest that the consumption of green tea may be protective against Alzheimer's disease. Animal studies have shown that polyphenolic compounds (EGCG) in green tea stimulate the production of new nerve cells in the hippocampus brain area of aging mice and improved their memory performance, compared to controls (68).

14. Ensure Optimal Blood Vitamin D Level. Animal studies show that vitamin D helps the body breakdown and clear the beta-amyloid plaque that normally builds up in the Alzheimer's brain. Amyloid plaque build up is a hallmark feature of Alzheimer's disease. Human observational studies suggest that low intake of vitamin D and low blood levels of vitamin D are associated with an increased risk of Alzheimer's disease (69,70). Vitamin D shows a variety of neuroprotective effects against Alzheimer's disease and one large major study has shown that older subjects with blood vitamin D levels below 25 nmol/L have a four-fold increase in risk of cognitive impairment compared to those with a blood vitamin D level at or above 75nmol/L (71).

Bonus Step – keep an eye on marijuana research with respect to THC, as a molecule that may help to preserve acetylcholine levels and inhibit the synthesis of beta-amyloid plaque.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562334

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My Brain Preserving Recommendation :

1. Lifelong High Potency Multiple Vitamin with B-50-Complex and Antioxidants

2. Lifelong Essential Fatty Acid Supplement (400 mg per day of EPA-DHA)

   and eat Fish- twice per week

3. Maintain Vitamin D blood levels above 75nmol/L (30ng/ml)

4. After 55 – Memory Support Supplement– to maintain acetylcholine

5. Don’t eat foods that raise blood cholesterol

6. Fasting Blood Sugar – below 5.0mmol/L (90mg/dL)

Other:

- Avoid – Limit Alcohol consumption – kills nerve cells
- Avoid Recreational drugs
- Avoid Smoking
- Endurance Exercise – increases brain blood flow and appears to breakdown plaque (http://www.meschinohealth.com/blog/alzheimers-disease-and-cognition/2012/08/09/exercise-breaks-plaque-responsible-alzheimers-disease-study-shows)
- Adequate Sleep
- Avoid Head Injuries
- Supplementation with melatonin after 40-45
- ARB drugs in hypertension – block plaque build up and reduce risk of Alzheimer's in hypertensive patients (http://www.meschinohealth.com/blog/alzheimers-disease-and-cognition/2012/09/20/arb-drugs-reduce-risk-alzheimers-disease-patients-high-blood-pressure)
- Green tea recently shown to preserve hippocampus (http://www.meschinohealth.com/blog/alzheimers-disease-and-cognition/2012/09/06/egcg-green-tea-linked-memory)

Keep your mind active:
Learn new things – keeps nerve circuits intact:
Dance lessons
Ping pong (eye hand coordination and full body movement)
Badminton
Musical Instrument
Foreign language
Something outside your normal realm of knowledge

Recommended: Read the book by Dr Daniel Amen MD – Change Your Brain Change Your Life

Multiple Sclerosis

Vitamin B12 and MS

- A vitamin B12 binding and/or transport defect is suspected. Supplementing with methylocobalamin at **60 mg per day** was shown to improve both visual and brainstem auditory-evoked potentials by nearly 30 percent. Motor function did not improve, indicating a benefit to afferent not efferent nerve pathways.

- It is possible that the link between MS and vitamin B12 lies in defects of the transcobalamin transporter. In a study of 10 patients with MS, nine patients had hematologic abnormalities, but only two were anemic. All six patients examined had low erythrocyte cobalamin levels. Only two patients had pernicious anemia; in the remaining patients the vitamin B12 deficiency was unexplained. A vitamin B12 binding and/or transport defect is suspected. The nature of the association of multiple sclerosis and vitamin B12 deficiency is unclear but is likely to be more than coincidental (Arch Neurology 1991) http://www.ncbi.nlm.nih.gov/pubmed/1898255

- Many studies indicate MS patients have normal blood levels of B12. Japanese researchers have found that in MS patients, there is a **decrease in the binding capacity of B12, thus inhibiting the transport of B12 into the cells**, even in patients with normal levels in their blood. Even so, they were able to achieve some improvement with high-dose supplementation.

- As such, defects in the transcobalamin transporter may be overcome with high dose treatments of vitamin B12. This may explain the improvement in MS symptoms that has been reported with vitamin B12 injections in the presence of already normal vitamin B12 serum levels.

- Data suggests that patients given vitamin B12 supplements have experienced clinical improvements in their symptoms (Kidd 2001). For example, in the United Kingdom, researchers investigated the effects of 6 months of vitamin B12 (1 mg/week injection) on 138 patients with MS. The researchers concluded that the clinical course of patients with MS improved after beginning vitamin B12 treatment (Wade 2002).

Vitamin D and MS

- Numerous studies show that low levels of vitamin D in the blood are strongly linked to increased risk of developing multiple sclerosis (MS) and that MS patients with low blood levels of vitamin D (25-hydroxycholecalciferol) are more likely to have greater disability and more disease activity.

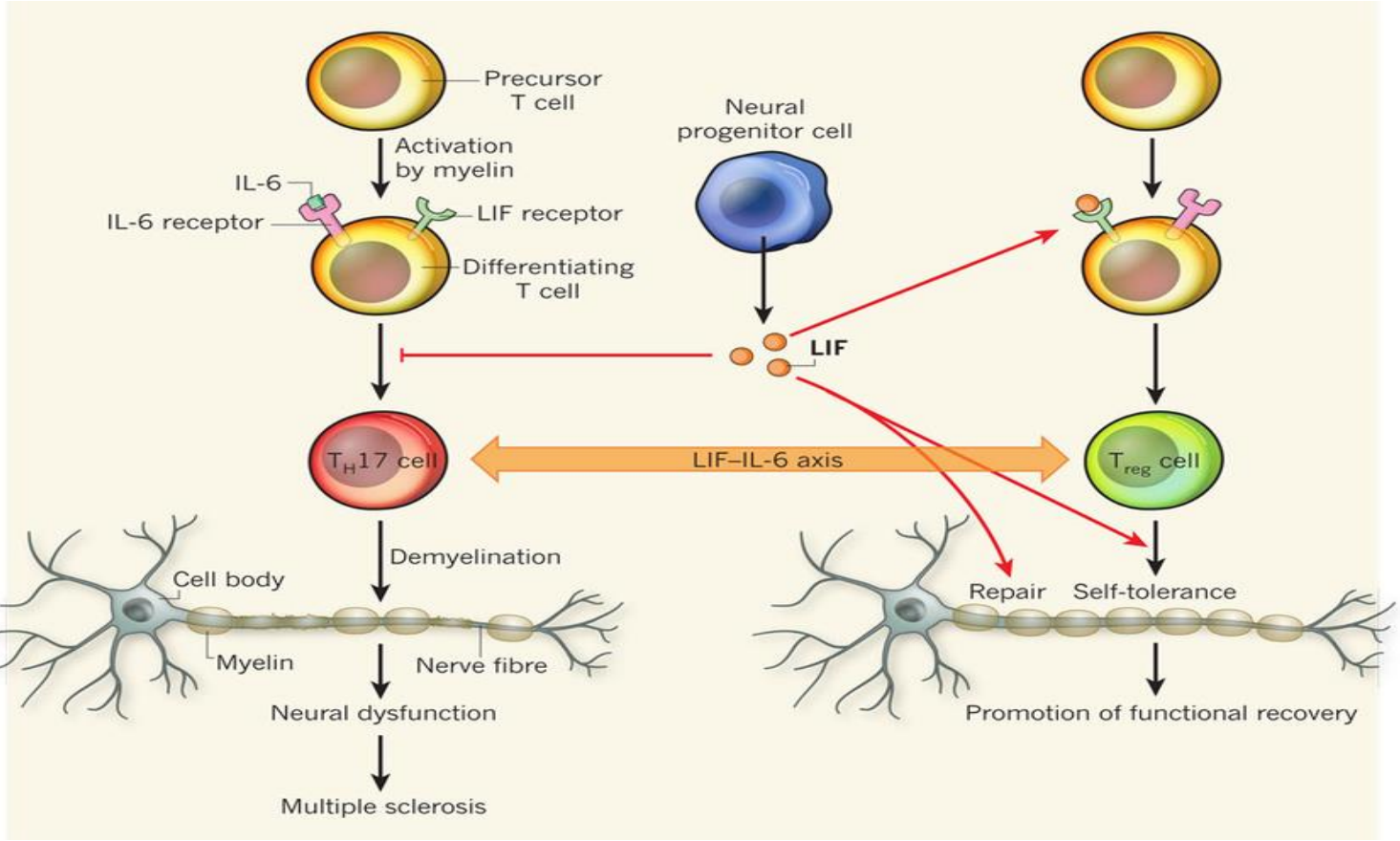
- The ground breaking study by E. S. Sotirchos et al, published in the journal *Neurology* in December 2015, showed that MS patients administered high-dose vitamin D (10,400 IU per day) supplementation, over a six month period, had a reduction in the percentage of inflammatory T cells related to MS severity - specifically IL-17+CD4+ and CD161+CD4+ cells.

- The study included 40 people with relapsing-remitting MS.

- Patients in the control group, who were given 800 IU per day of vitamin D, did not show a reduction in these MS inflammatory markers.

- For the patients ingesting 10,400 IU of vitamin D per day, when the increase in vitamin D levels in the blood over base line levels was greater than 18 ng/ml (45 nmol/L) every additional 5 ng/ml (12.5 nmol/L) increase in vitamin D led to a 1 percent decrease in the percentage of IL-17+CD4+ T cells in the blood.

TH-17 cell activity produce demyelination in MS.



- The people taking the low dose did not have any noticeable changes in the percentages of their T cell subsets.

- With respect to optimal vitamin D blood levels for MS patients, researchers are still working to determine what range is most beneficial. At the present time the range of 40 to 60 ng/ml has been proposed as a target.

- This is equivalent to 100 – 150 nmol/L. Participants taking the high-dose vitamin D protocol reached levels within the proposed target, whereas the group taking the low-dose (800 IU) did not reach the target. It is noteworthy that patients with severe vitamin D deficiency were not included in the study.

Inflammatory Markers in Multiple Sclerosis

- Multiple sclerosis is the most common neurological disease of young adults, afflicting hundreds of thousands of people worldwide. Until recently researchers had highlighted the role of type 1 and type 2 cytokines in the etiology of MS.

- The general notion was that a type 1 response (with CD4 T cells of helper type 1, TH1 cells) was associated with a pro-inflammatory, destructive immune reaction, whereas a type 2 response (with TH2 cells) reflected a modulatory, non-pathogenic immune reaction, which may even protect against autoimmune disease caused by TH1-dependent mechanisms.

- More recently it has been shown that IL-23 is an upstream modulator of a very important pathogenic signaling pathway way in MS. IL-23 is crucially involved in the expansion of cells producing IL-17, and that IL-17 is produced by TH cells that are distinct from the traditional TH1 and TH2 cell subsets, and have thus been designated as TH17 cells. This rapidly emerging evidence clearly demonstrates that TH17 cells are indeed a T-helper cell subpopulation distinct in differentiation and function from the TH1 and TH2 subsets described previously.

- Of great clinical significance is the fact that a systematic analysis of IL-17-positive cells in the brains of MS patients revealed a significant increase in the number of IL-17^{+} T cells in the active rather than the inactive areas of MS lesions.

- Another critical finding was the fact that IL-17 immunoreactivity could also be detected in astrocytes and oligodendrocytes in active areas of MS plaques. All of these findings have made it increasingly clear that IL-17 is an essential player in MS, and that IL-17 is likely an important target for future therapeutic interventions to improve MS progression and outcomes. (2) As such, the discovery that high-dose vitamin D supplementation can down regulate the release of IL-17 in MS patients is of great significance. (1)

Understanding Interleukin-17: A key cytokine in MS

- IL-17 is a signature cytokine of Th17 (T-helper 17) cells and plays critical roles in host defence against bacterial and fungal infections, as well as in the pathogenesis of autoimmune diseases. IL-17 is highly up-regulated at sites of inflammatory tissues of autoimmune diseases and amplifies the inflammation through synergy with other cytokines, such as TNF (tumour necrosis factor) α. Although IL-17 was originally thought to be produced mainly by Th17 cells, a newly defined T-cell subset with a specific differentiation program and tight regulation, several other cell types (especially innate immune cells) are also found as important sources for IL-17 production.

- Mouse genetic studies have demonstrated a critical role for IL-17 in the pathogenesis of variety of inflammatory autoimmune diseases, such as RA (rheumatoid arthritis) and MS (multiple sclerosis). Importantly, promising results have been shown in initial clinical trials of monoclonal antibodies against IL-17 or its receptor (IL-17R) to block IL-17-mediated function in treating autoimmune patients with psoriasis, RA and MS. (3) Human studies have also shown that IL-17 is over expressed in patients with Crohn's disease and that IL-17 induces a pro-inflammatory response in this condition. (4)

Other Vitamin D Studies In MS Patients and Summary

- Presenting at the American Academy of Neurology in 2009 Dr. Jodie Burton reveled the results of a vitamin D trial in MS patients. This study showed that high doses of vitamin D (14,000 IU per day for one year) dramatically cut the relapse rate in people with multiple sclerosis compared to those given only 1000 IU per day of vitamin D over the same time period.

- More specifically 16% of 25 MS patients in the high-dose vitamin D group suffered relapsed during the one year period, compared to 40% in the low-dose vitamin D group, which was comprised of 24 MS patients. As well, people taking high-dose vitamin D suffered 41% fewer relapses than the year before the study began, compared with 17% of those taking typical doses (1000 IU – the amount typically recommended to MS patients by neurologists). Also encouraging was the fact that patients taking high doses of vitamin D did not suffer any significant side effects. (5)

- Compelling evidence has linked low vitamin D levels with increased risk for MS, and progression of MS in patients suffering from MS. Our understanding of the importance of Vitamin D in immune system modulation continues to unfold with each passing year. Most recently we have learned that vitamin D is capable of down-regulating the over expression of IL-17, a highly implicated cytokine in the pathophysiology of multiple sclerosis.

- We have preliminary evidence that high-dose vitamin D supplementation (approx. 10,000-14,000 IU per day) can reduce IL-17 levels and significantly reduce relapses in MS patients. This is indeed encouraging, and thus, neurologists may want to reconsider their usual recommendation of 1000 IU vitamin D per day for MS patients by increasing this amount to 10,000-14,000 IU per day, for at least the first year. In these cases monitoring of vitamin D blood levels (25-hydroxycholecalciferol) should be undertaken to ensure that a range of 40-60 ng/ml (100-150 nmol/L) is achieved, while avoiding vitamin D toxicity, which typically can occur at vitamin D blood levels nearing 100 ng/ml (250 nmol/L). Complementary health practitioners should also be encouraged to discuss these findings with their MS patients and to follow the results of future clinical trials involving vitamin D administration to MS patients.

Vitamin D and MS References:

1. Sotirchos E. S., Bhargava P, Eckstein C, Van Haren K, Baynes M. Ntranos A et a**l.**Safety and immunologic effects of high- vs low-dose cholecalciferol in multiple sclerosis**.** *Neurology*, 2015 (http://www.neurology.org/content/early/2015/12/30/WNL.0000000000002316)

2. Gold R, Luhder F. Interleukin-17—Extended Features of a Key Player in Multiple Sclerosis. Am J Pathol. 2008;172(1):8-10

3. Zhu S, Qian Y. IL-17/IL-17 receptor system in autoimmune disease: mechanisms and therapeutic potential. Clin Sci (Lond). 2012;122(11):487-511.

4. Siakavellas SI, Bamias G. Role of the IL-23/Il-17 axis in Crohn's disease. 2012;14(77):253-62

5. http://www.webmd.com/multiple-sclerosis/news/20090428/high-doses-vitamin-d-cut-ms-relapses

Cannabis and MS

Cannabis active ingredients (CBD and THC) shown to exert several positive effects in MS patients:

1. Decrease inflammation
2. May promote neurogenesis
3. Decrease Pain
4. “Has enabled some patients to walk and function on temporary basis, primarily by reducing spasm and rigidity”. (THC inhibits acetylcholine release in presynaptic motor neurons breaking spasm cycle)
5. Improved digestion and bowel control
6. Improve sleep

References:

- https://www.nap.edu/read/24625/chapter/6
- https://herb.co/2016/07/28/marijuana-and-ms/

Amyotrophic Lateral Sclerosis (ALS) – Lou Gehrig's disease

Superoxide Dismutase (SOD): It quenches superoxide anion. Three forms of superoxide dismutase are present in humans:

SOD1 is located in the cytoplasm – requires **copper and zinc**

SOD2 in the mitochondria – requires mn (**manganese**)

SOD3 is extracellular – requires **copper and zinc**

Mutations in SOD1 can cause Familial Amyotrophic Lateral Sclerosis (ALS) and evidence also shows that wild-type SOD1, under conditions of cellular stress, is implicated in a significant fraction of sporadic ALS cases, which represent 90% of ALS patients.

Melatonin and Lou Gehrig's

- A 2013 animal study has now shown that melatonin also blocks key steps in the development of Lou Gehrig's disease (also known as Amyotrophic Lateral Sclerosis or ALS), a disease that causes progressive muscle weakness and eventual death due to the failure of respiratory muscles.

- After screening more than a thousand FDA-approved drugs several years ago, a research team determined that melatonin is a powerful antioxidant that blocks the release of enzymes that activate programmed cell death of nerve cells involved in the development of ALS.

- They later followed up using a transgenic mouse model of ALS, demonstrating that melatonin injections delayed symptom onset and reduced mortality from ALS in mice. In this model mice were bred to carry the gene that encourages the development on Lou Gehrig's disease.

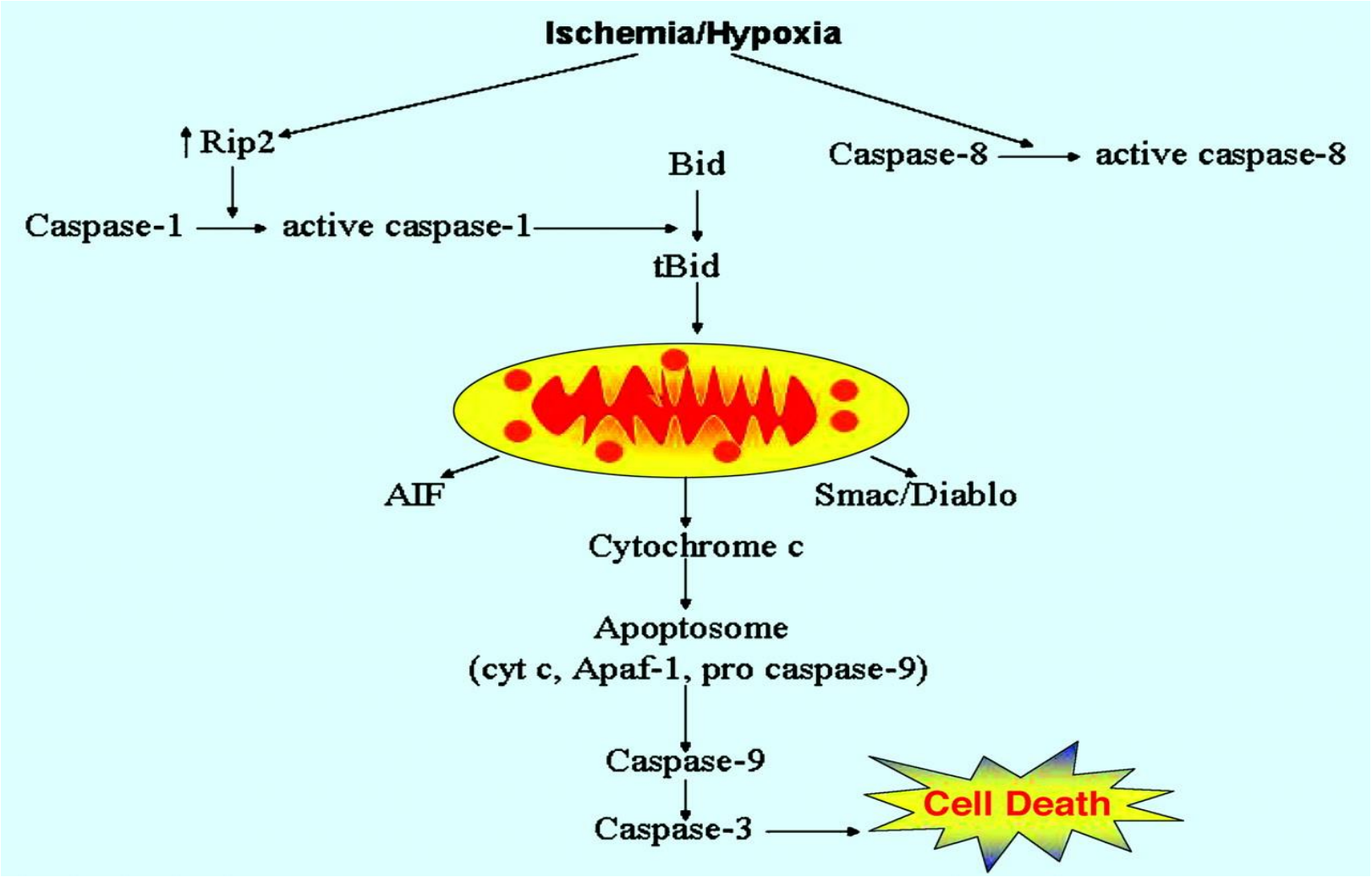
How Has Melatonin Been Shown To Inhibit ALS

- The researchers stated, “We demonstrate that melatonin significantly delayed disease onset, neurological deterioration and mortality in ALS mice”.

- More specifically melatonin was shown to inhibit nerve degeneration and nerve cell death of the motor nerves involved in ALS. These nerves are the motor nerves in the ventral horn of the spinal cord, which supply life-force energy to the muscles of the body, including respiratory muscles. When these nerve cells die muscles become paralyzed and unable to function.

- Melatonin was shown to block nerve cell death in the ventral horn motor nerves by **inhibiting several key pathways within these nerve cells that otherwise cause nerve cell death in ALS. These pathways include inhibiting the Rip2/caspase-1 pathway, blocking the release of mitochondrial cytochrome *c*, and reducing the over expression and activation of caspase-3.**

Caspase-3 Apoptosis in ALS



- The researchers went on to state that, “moreover, for the first time, we determined that disease progression was associated with the loss of both melatonin and the melatonin receptor 1A (MT1) in the spinal cord of ALS mice”.

- One of the study researchers, Dr. Friedlander, explained that they saw similar results in a Huntington's disease animal model in an earlier project, whereby melatonin injections inhibited the same nerve cell death pathways when injected into animals bred to be genetically predisposed to Huntington’s disease.

Reference:

- Yi Zhang, Anna Cook, Jinho Kim, Sergei V. Baranov, Jiying Jiang, Karen Smith, Kerry Cormier, Erik Bennett, Robert P. Browser, Arthur L. Day, Diane L. Carlisle, Robert J. Ferrante, Xin Wang, Robert M. Friedlander. **Melatonin inhibits the caspase-1/cytochrome c/caspase-3 cell death pathway, inhibits MT1 receptor loss and delays disease progression in a mouse model of amyotrophic lateral sclerosis**. *Neurobiology of Disease*, 2013; 55: 26 DOI: 10.1016/j.nbd.2013.03.008

Parkinson’s Disease

- A degenerative condition of the central nervous system
- The motor symptoms of Parkinson's disease result from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain
- The causes of cell death are poorly understood.
- **Early in disease** course see: movement-related problems, including: shaking, rigidity, slowness of movement and difficulty with walking and gait
- **Later in disease** course see: problems with thinking and behavioral problems (with dementia and depression commonly occurring in the advanced stages).
- Parkinson's disease is more common in older people, with most cases occurring **after the age of 50**; but becoming more common in younger adults in recent yrs.

General Considerations

Parkinson's disease (PD), the most common movement disorder and the second most common neurodegenerative disease after Alzheimer's disease, is characterized primarily by the loss of dopaminergic neurons in the substantia nigra leading to a dopamine deficit in the striatum.

Nerve cells in the substantia nigra produce the neurotransmitter dopamine and are responsible for relaying messages that plan and control body movement.

Dopamine administration reduces resting tremor by potentiating inhibitory mechanisms in a cerebellar nucleus of the thalamus (ventral intermediate nucleus).

This suggests that altered dopaminergic projections to the cerebello-thalamo-cortical circuit have a role in Parkinson's tremor - https://www.ncbi.nlm.nih.gov/pubmed/28073788

50,000 new cases in the US per year (1 million US citizens over 60) and increasing incidence as population ages

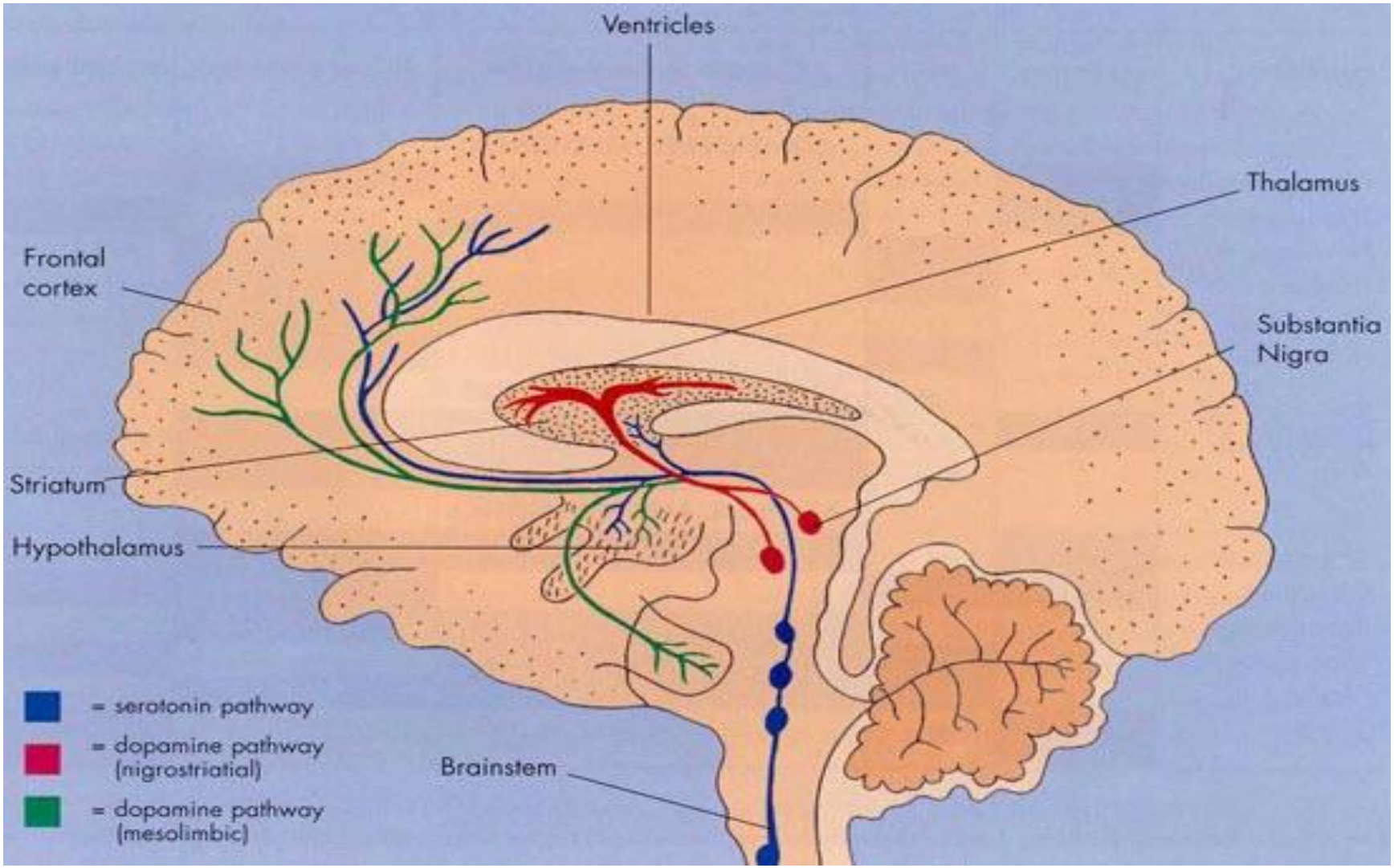
Signs and Symptoms in PD

The consequent dysregulation of basal ganglia circuitries accounts for the most prominent motor symptoms, including:

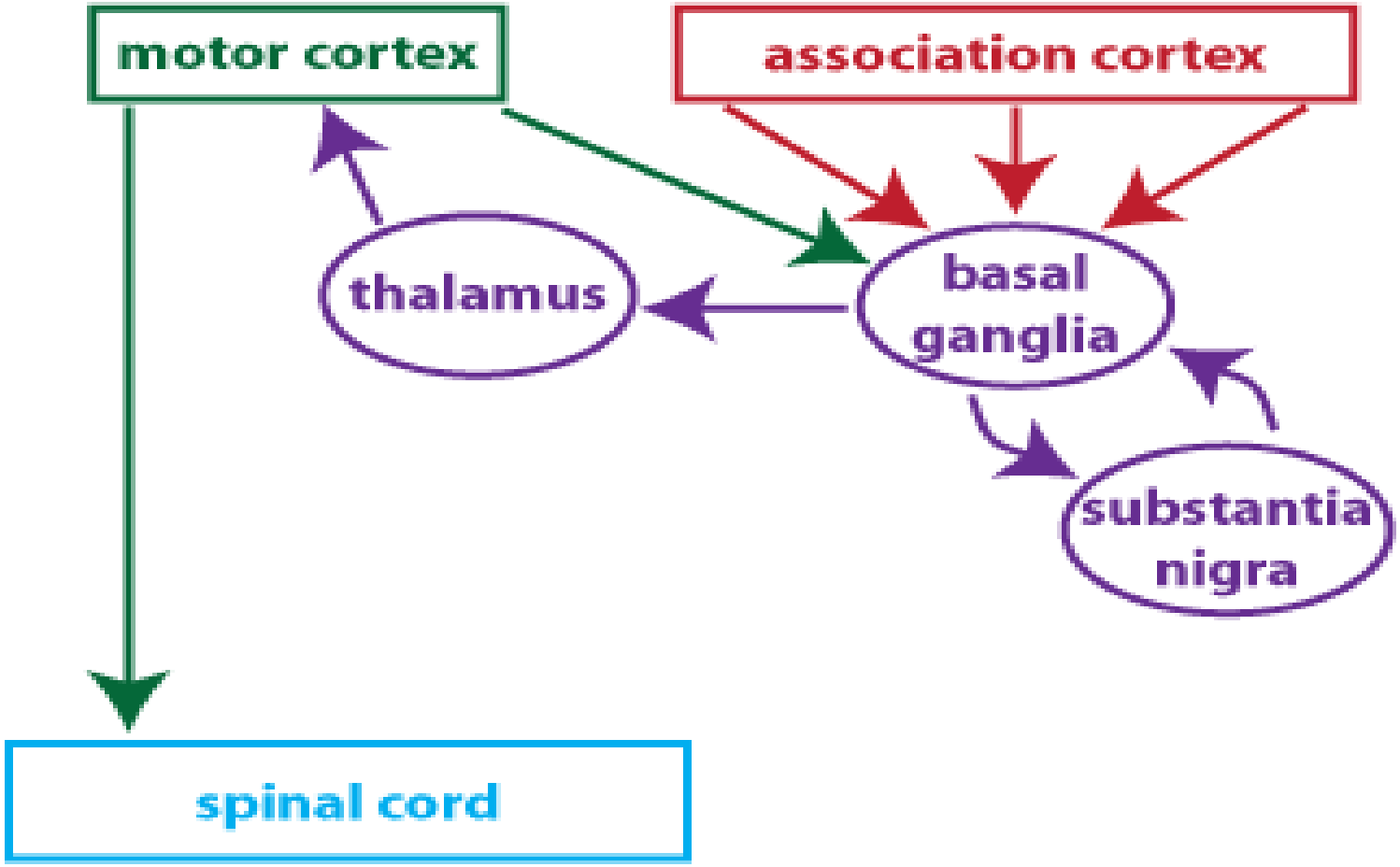
- Bradykinesia – slow movement
- Hypokinesia - partial or complete loss of muscle movement
- Rigidity
- Resting Tremor and postural instability.

In addition to motor symptoms, various non-motor features may develop, such as **autonomic dysfunction, sleep disturbances, depression and cognitive impairment**, indicating a more widespread degenerative process.

Note: Dopamine pathway from Substantia Nigra to Striatum



Link btw Basal Ganglia, Substantia Nigra and Motor Cortex



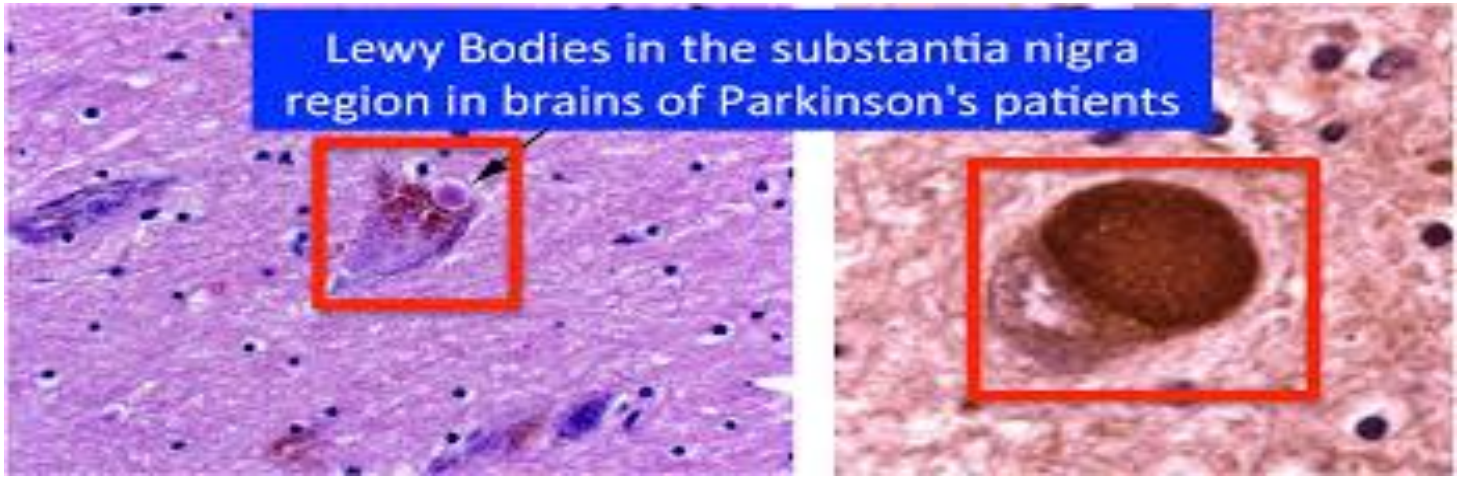
By the time PD motor symptoms are clinically recognized, 60% of dopaminergic neurons and 80% of putamen dopamine have been lost.
The **putamen** is a large structure located within the brain. It is involved in a very complex feedback loop that prepares and aids in movement of the limbs

PD is also associated with the presence of ubiquitin- and **α-synuclein**-positive cytoplasmic inclusions known as **Lewy bodies** within surviving dopaminergic neurons.

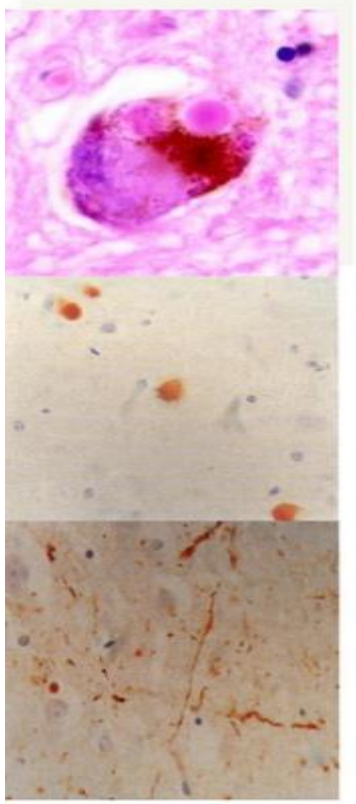
α-synuclein has been shown to damage nerve cells via various mechanisms

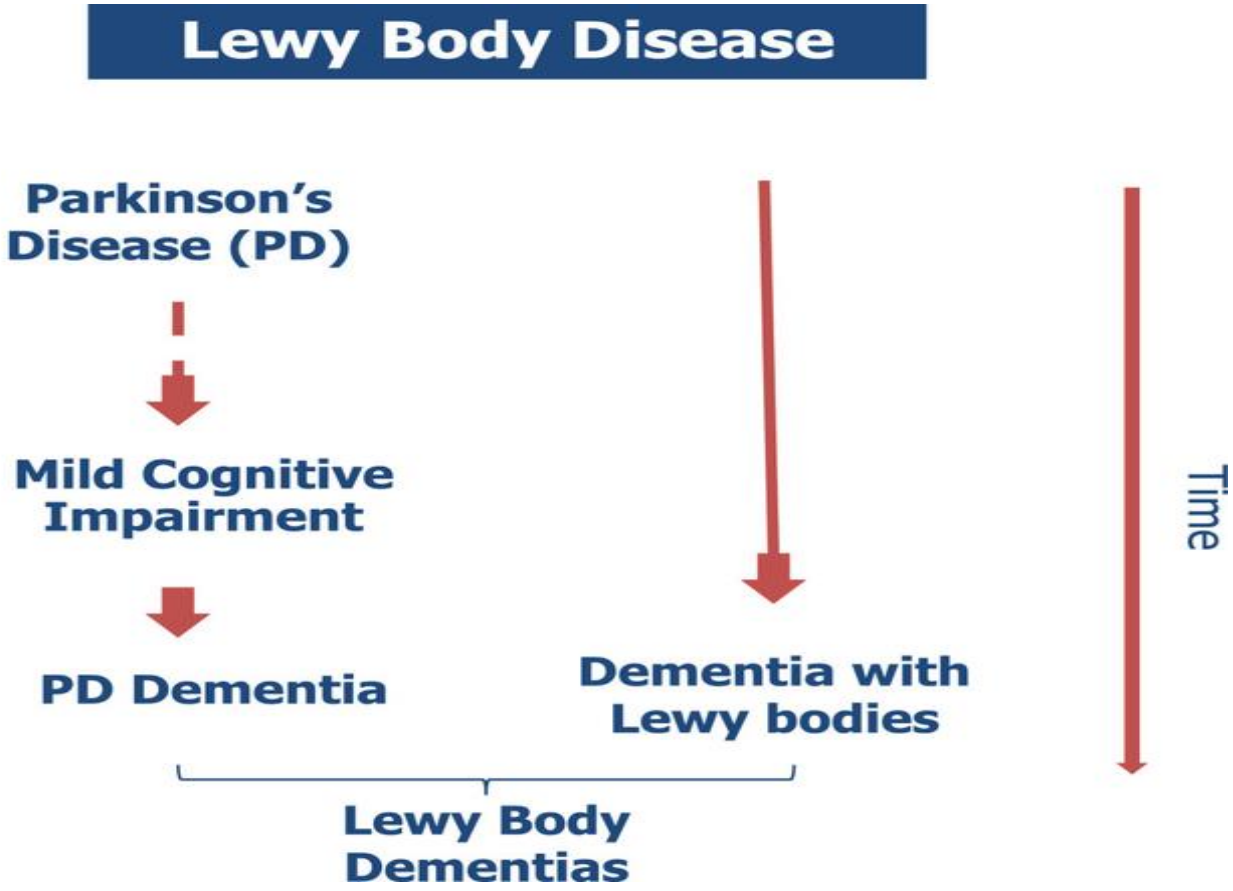
Lewy Bodies and Lewy Body Dementia

A pathological hallmark of sporadic PD is the presence of proteinaceous deposits within neuronal cell body (Lewy bodies) and processes (Lewy neurites), mainly composed of α-synuclein, ubiquitin, neurofilaments and molecular chaperones



Lewy Body Dementia





Lewy Body Dementia

Dementia with Lewy Bodies

- **Definition: clinically defined by the presence of dementia, prominent hallucinations and delusions (yet sensitive to antipsychotic medications), fluctuations in alertness, and gait/balance disorder** (McKeith et al., Neurology 1996;47:1113-1124)
- **Accounts for up to 20-30% of degenerative dementias** (Hansen et al., Neurology 1990;40:1-8)
  - **Second in occurrence behind AD**

Sporadic PD (90%) vs Inherited PD (10%)

- The most common **sporadic form** of PD seems to be a complex multifactorial disorder with variable contributions of environmental factors and genetic susceptibility.

- Aging is the most important risk factor, thus with increasing average life expectancy the incidence and prevalence of PD will rise considerably in the next future.

- Inherited Gene Mutations account for 10% of PD cases, and most of these gene mutations are linked to defects in mitochondrial integrity (Loss-of-function mutations in the genes encoding parkin, PINK1, and DJ-1 account for autosomal recessive PD. Mutations in the genes encoding α-synuclein and LRRK2 (leucine-rich repeat kinase 2) are responsible for autosomal dominant forms of PD, presumably by a gain-of-function mechanism).

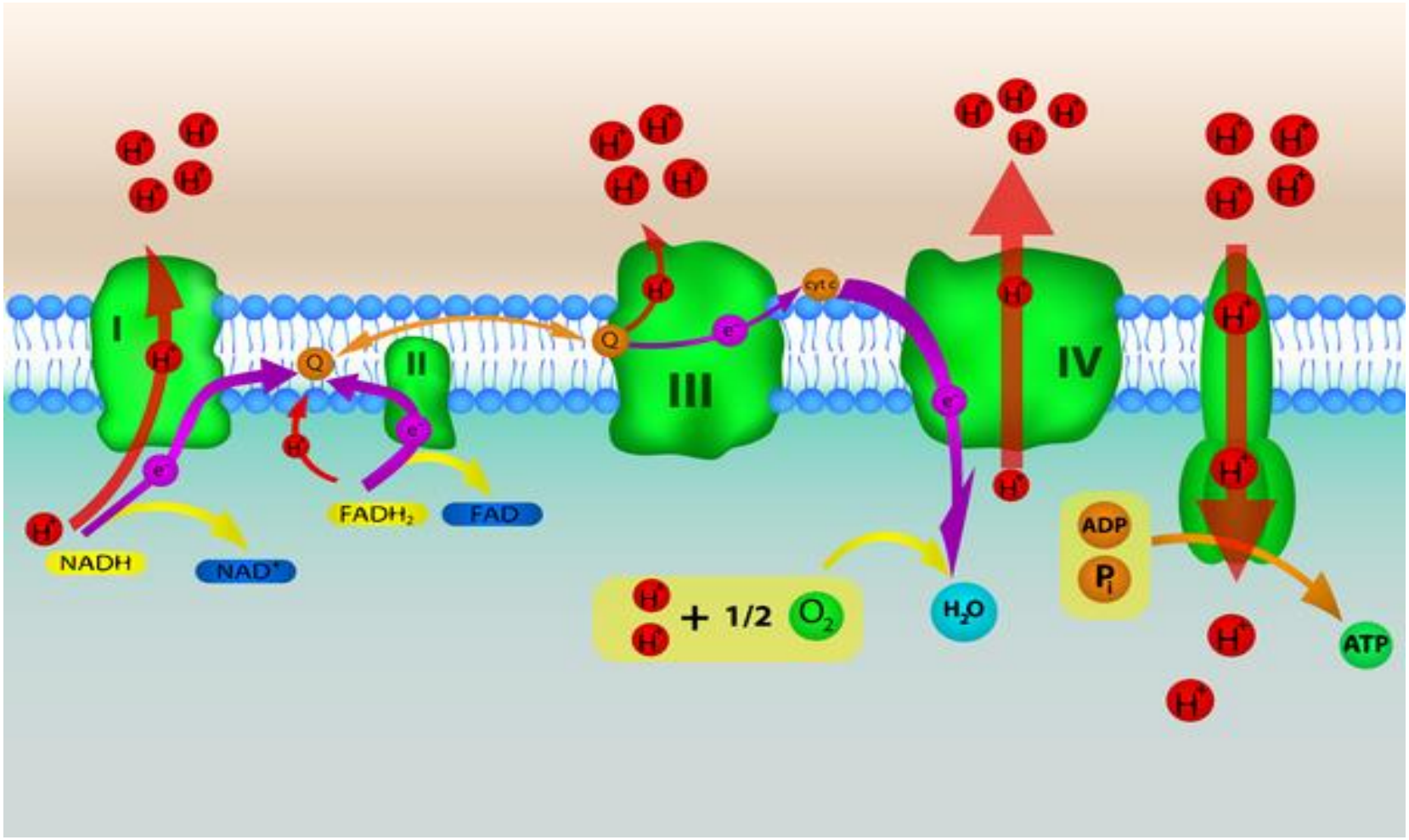
Sporadic (Environmental-Aging) PD

Causes Linked to:

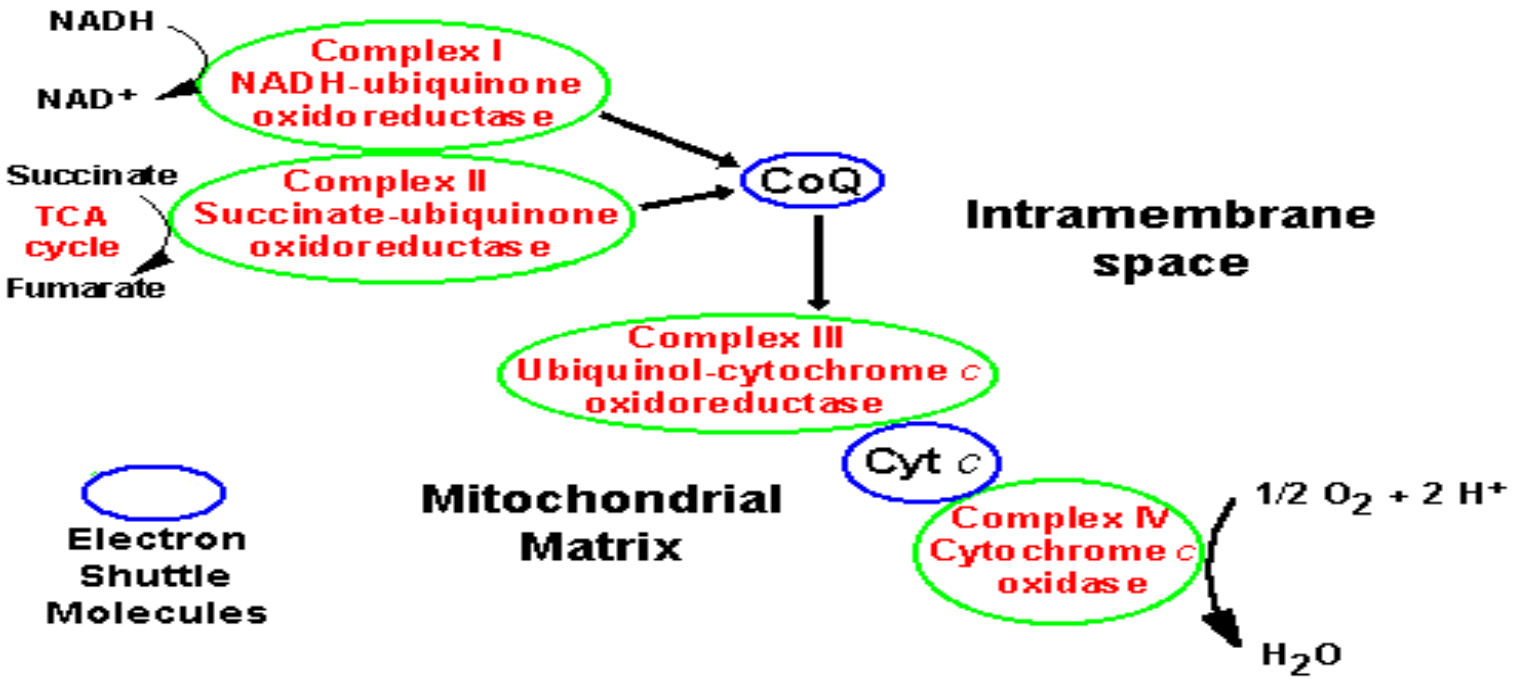
1. Defective Complex I Cytochrome function in Mitochondria in Substantia Nigra- resulting in decreased ATP production (to synthesize dopamine) and increased ROS due to leakage of electrons out or mitochondrial membrane.

2. Cumulative Mitochondrial DNA damage (mtDNA) – with aging get increased mtDNA damage from ROS. mtDNA has less efficient DNA repair mechanisms and absence of protective histones. Proximity to respiratory chain makes it vulnerable to ROS damage with resulting DNA mutations = decreased ATP and dopamine synthesis

Note: Cytochrome I - III



CoQ10 –electron shuttle Complex I-II



Complex I and to a lower extent complex III of the ETC are considered to be the **main sites of ROS** production which results from the transfer of a single electron to oxygen to generate the superoxide anion.

Decline in CoQ10 synthesis in aging increases ROS production and decreases ATP production.

Medical Treatment in PD

- Dopamine replacement therapy, i.e., levodopa administered orally or stimulation of dopamine receptors, has been the most widely used treatment option for PD, but the beneficial effects of dopaminergic therapy wear off over time and its clinical efficacy gradually declines as the disease advances

Reference:

Mitochondrial Dysfunction in Parkinson's disease BBA-Molecular Basis of Disease Vol 1820 issue 1, January 2010 http://www.sciencedirect.com/science/article/pii/S0925443909001963

Nutritional Medicine Research in PD

- Convincing evidence from post-mortem brain tissue, cell culture and animal models of PD and the analysis of human genetics support the involvement of oxidative stress and mitochondrial dysfunction in PD pathogenesis.

- Mitochondrial dysfunction due to oxidative stress, mitochondrial DNA deletions, altered mitochondrial morphology and the interaction of pathogenic proteins with mitochondria all result in dopaminergic neurodegeneration.

- Thus, therapeutic approaches targeting mitochondrial dysfunction and related oxidative stress may hold great promise of a cure for PD.

- One potential approach to ameliorating complications arising from PD is to suppress mitochondrial reactive oxygen species (ROS) generation with specific antioxidants. Several small antioxidant molecules, such as ubiquinol and creatine, have shown promising neuroprotective effects in different models of PD

- ROS can be generated within mitochondria in several sites of mitochondrial electron transport chains (ETC), in particular on Complexes I and III, where electrons occasionally leak to oxygen and form a superoxide anion ($O_2\bullet^-$), the predominant ROS in mitochondria.

- In fact, mitochondria are the major sites of cellular ROS production, with approximately 1-3% of mitochondrial oxygen consumption being converted to ROS.

- In addition to formation from incomplete reduction of oxygen in ETC, a number of enzyme systems also generate superoxide, including the tricarboxylic acid cycle (TCA) enzymes α-ketoglutarate dehydrogenase and aconitase, the non-TCA cycle enzymes pyruvate dehydrogenase, dihydroorotate dehydrogenase, and glycerol-3-phosphate dehydrogenase, and the mitochondrial outer membrane proteins such as methemoglobin reductase

- Mitochondria contain a series of well-defined and tightly controlled antioxidant defense systems, which work synergistically to intercept ROS, thereby minimizing oxidative damage.

- Disruption of these antioxidant defenses may result in extensive oxidative damage to mitochondria. There are two main types of mitochondrial antioxidant defense systems: enzymatic and nonenzymatic:

1. Enzymatic antioxidants involve SOD, GPx, catalase, and TPx (thioredoxin reductase), all of which are encoded by the nuclear genome and are subsequently imported into the mitochondria.

- Once oxidized, GSH can be regenerated by the action of glutathione reductase using NADPH as its electron donor.

- In addition, GSH serves as a nonenzymatic antioxidant, scavenging hydroxyl radical and singlet oxygen directly and maintaining vitamin C and E in their reduced forms.

2. Other nonenzymatic antioxidants include α-tocopherol (vitamin E), ascorbic acid (vitamin C), coenzyme Q_{10} (CoQ_{10}), β-carotene, flavonoids, and α-lipid acid.

- **Vitamin E** is lipid-soluble, and therefore, is widely distributed in mammalian cell membranes. Of the different forms of vitamin E, α-tocopherol is the most biologically active form. As a lipid-soluble antioxidant, vitamin E acts as a scavenger of peroxyl radical, peroxynitrite, and hydroxyl radical by preventing the propagation of the radical chain, thus effectively inhibiting lipid peroxidation.

- During the antioxidant reaction, α-tocopherol is converted to α-tocopherol radical, which gets reduced to its original α-tocopherol form.

- **Vitamin C** – is a water-soluble, making it able to work in the body's aqueous environments. Vitamin C functions in association with vitamin E to regenerate α-tocopherol from α-tocopherol radical.

- **CoQ_{10} -** is an essential component of the ETC, where it accepts electrons from Complexes I and II. It is also a coenzyme for Complex III and acts as a lipid-soluble antioxidant as well.

- The antioxidant activity of CoQ_{10} arises from its capacity to exchange two electrons in a redox cycle between its oxidized (ubiquinone) and its reduced form (ubiquinol). Ubiquinol is a very effective chain-breaking antioxidant that not only inhibits lipid peroxidation and protein and DNA oxidation, but also directly quenches oxidants such as superoxide and peroxyl radicals.

- Despite the presence of elaborate defense systems to counteract oxidative damage, it seems that cellular ROS levels are not perfectly under control. Indeed, oxidative damage due to excessive ROS production may accumulate during both normal and stressful conditions. Oxidative stress accumulation and concomitant mitochondrial dysfunction have been implicated in PD pathogenesis.

- Postmortem studies have consistently shown high levels of oxidation of lipids, proteins, and nucleic acids in the substantia nigra of sporadic PD brains Also, significant alterations of the antioxidant defense system, in particular reduced glutathione, were found in the substantia nigra of PD patients.

- In addition to mitochondria, the auto-oxidation of dopamine, a reaction known to generate superoxide and hydrogen peroxide, as well as reactive dopamine quinones, specifically contribute to cellular ROS in dopaminergic neurons. **This dopamine-dependent oxidative stress is believed to partially explain the selective vulnerability of dopaminergic neurons in PD.**

Conclusion

- Considerable evidence exists suggesting a role for mitochondrial dysfunction in PD pathogenesis

- Mutations in mitochondrial DNA (mtDNA) play a role in the demise of dopaminergic neurons. Indeed, high levels of somatic mtDNA point mutations in elderly PD patients have also been reported.

Antioxidants Protect Mitochondria and Decrease Free Radical Damage

Coenzyme Q10 – fat soluble antioxidant operating in region of mitochondria. Acts as electron shuttle between complex I-III to optimize ATP production. With aging, Co10 synthesis declines leading to decreased ATP production and increased ROS damage to mtDNA.

Animal studies show that CoQ10 administration can prevent PD in animals engineered to develop the disease.

Human intervention studies show that CoQ10 can slow progression of PD in dose-dependent manner (more details shortly).

Vitamin C and E

- The observational data in humans suggest that the combined administration of high-dose vitamin E and vitamin C supplements was associated with a reduced progression of PD.

- Results of double-blind, randomized controlled trials have been disappointing, where vitamin E showed no benefits in PD. But need vitamin C to regenerate vitamin E

Creatine

- Creatine also possesses antioxidant properties and can be an effective inhibitor of mitochondrial permeability transition pore opening and mitochondrial iron accumulation.

- Preclinical studies in various models have demonstrated its potential role as a neuroprotective agent.

- In early clinical studies, two grams daily creatine administration improved behavioral difficulties in a clinical trial of 200 subjects who were within 5 years of a PD diagnosis.

- In an additional follow-up study, creatine continued to show neuroprotective efficacy 18 months after creatine administration.

- Although a 2-year placebo-controlled study of 60 subjects demonstrated that creatine had no effect on PD scores or dopamine transporter imaging, improved mood behavior (a non-motor symptom of PD) was noticed in those patients.

- A phase III clinical trial has been started by the NIH, where creatine is administered with a dose of 10 g in a large long-term study of PD targeting 1720 participants with the disease. This study involving 52 medical facilities is expected to be completed in 5-7 year

Next Generation of Antioxidants in PD Rx:

Mitochondrial-targeted antioxidant therapy is on horizon- delivering higher concentrations of antioxidants to mitochondria via conjugation with a lipophilic cation, such as triphenylphosphonium (TPP)- acting as chaperone molecule:

MitoQ

MitoE etc.

Reference:

- MITOCHONDRIA-TARGETED ANTIOXIDANTS FOR TREATMENT OF PARKINSON'S DISEASE: PRECLINICAL AND CLINICAL OUTCOMES. BBA 2014 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3961561/

Alpha -lipoic acid

- Reactive oxygen species are thought to be involved in a number of types of acute and chronic pathologic conditions in the brain and neural tissue. The metabolic antioxidant α-lipoate is a low molecular weight substance that is absorbed from the diet and crosses the blood–brain barrier.

- α-Lipoate is taken up and reduced in cells and tissues to dihydrolipoate, which is also exported to the extracellular medium; hence, protection is afforded to both intracellular and extracellular environments.

- Both α-lipoate and especially dihydrolipoate have been shown to be potent antioxidants, to regenerate through redox cycling other antioxidants like vitamin C and vitamin E, and to raise intracellular glutathione levels.

- Thus, it would seem an ideal substance in the treatment of oxidative brain and neural disorders involving free radical processes.

- Examination of current research reveals protective effects of these compounds in cerebral ischemia-reperfusion, excitotoxic amino acid brain injury**, mitochondrial dysfunction**, diabetes and diabetic neuropathy, inborn errors of metabolism, and other causes of acute or chronic damage to brain or neural tissue.

- Very few neuropharmacological intervention strategies are currently available for the treatment of stroke and numerous other brain disorders involving free radical injury. We propose that the various metabolic antioxidant properties of α-lipoate relate to its possible therapeutic roles in **a variety of brain and neuronal tissue pathologies**: thiols are central to antioxidant defense in brain and other tissues. **The most important thiol antioxidant, glutathione, cannot be directly administered, whereas α-lipoic acid can. In vitro, animal, and preliminary human studies indicate that α-lipoate may be effective in numerous neurodegenerative disorders.**

Reference

- Neuroprotection by the metabolic antioxidant alpha-lipoic acid. Free Radical Biology and Medicine vol 22 issues 1-2 1997 (pages 359-378) http://www.sciencedirect.com/science/article/pii/S0891584996002699

N-Acetyl Cysteine (NAC)

- Measurement of malondialdehyde (MDA) showed that NAC reduced glutamate-induced elevations in levels of lipid peroxidation by-products.

- Oxidative stress plays an important role in neuronal cell death associated with many different neurodegenerative conditions such as cerebral ischemia and **Parkinson's disease.**

- **Elevated levels of glutamate are thought to be responsible for CNS disorders** through various mechanisms causing oxidative stress induced by a nonreceptor-mediated oxidative pathway which blocks cystine uptake and results in **depletion of intracellular glutathione (GSH**).

- The newly designed amide form of *N*-acetylcysteine (NAC), *N*-acetylcysteine amide (NACA), was assessed for its ability to protect PC12 (neural crest)cells against oxidative toxicity induced by glutamate. NACA was shown to protect PC12 cells from glutamate (Glu) toxicity, as evaluated by LDH and MTS assays

Reference
http://www.sciencedirect.com/science/article/pii/S0006899305010735

Acetyl-L-Carnitine and Alpha-Lipoic Acid

- Although the mechanisms of neurodegeneration in Parkinson's disease are not fully understood, mitochondrial dysfunction, oxidative stress and environmental toxins may be involved.

- The current research was directed to investigate the protective role of two bioenergetic antioxidants, acetyl-L-carnitine and α-lipoic acid, in rotenone-parkinsonian rats.

- Treatment with acetyl-L-carnitine or α-lipoic acid improved the motor performance and reduced the level of lipid peroxides in rat brains as compared to rotenone group.

- Further, **ATP production was enhanced** along with acetyl-L-carnitine treatments. Taken together, our study reinforces the view that acetyl-L-carnitine and α-lipoic acid are promising candidates for neuroprotection in Parkinson's disease.

Reference: http://www.sciencedirect.com/science/article/pii/S0091305711003091

Supplementation

1. **Coenzyme Q10** – A breakthrough study in the Archives of Neurology (October, 2002) - early-stage Parkinson's disease patients supplemented with 300, 600, or 1,200 mg of CoQ10 per day for 16 months showed significantly less impairment than did the group given the placebo.

- Patients given highest dosage achieved best results.

2. **Antioxidants (Vitamin E and Vitamin C)** – free radicals contribute to the progression and, possibly, the cause of Parkinson's disease and other neurodegenerative diseases

- 10-year study of early-stage Parkinson's disease patients given 750 mg of Vitamin C and 800 IU of Vitamin E four times/d (totaling 3,000 mg of Vitamin C and 3,200 IU of Vitamin E per day).

  Results – antioxidant supplementation significantly delay the need for drug therapy by average of two and half years, compared to placebo group

3. Creatine Monohydrate – supplementation with creatine monohydrate has been shown to improve and help stabilize symptoms in various neuro-degenerative diseases, including Parkinson's disease. Creatine monohydrate supplementation increases energy production within nerve cells, enabling them function more normally, synthesize more of their own dopamine, and favorably affect DNA repair and nerve cell survival mechanisms. The usual dosage is 5000 mg, twice daily (creatine monohydrate is a powder that is typically mixed into juices, such as grape juice, cranberry juice etc).

4. CDP-choline – supplementation with CDP-choline has been shown to improve symptoms and slow progression in Parkinson's disease patients. CDP-choline is a vital nerve cell membrane phospholipid that affects nerve cell function, nerve transmission, and is a source from which nerve cells synthesize a key nerve chemical known as acetylcholine. Acetylcholine is also the main nerve chemical (neurotransmitter) involved in memory consolidation. The typical dosage is 500-1000 mg per day of CDP-choline. In addition to CDP-choline, many experts also advise ingesting additional lecithin each day, which provides additional choline and phosphatidylcholine, required for brain cell function and acetylcholine synthesis.

5. **Additional Vitamin D** (2000-5000 IU) – low levels of vitamin D are associated with an increased risk of Parkinson's disease and preclinical studies show that vitamin D helps to regenerate new nerve cells in key areas of the brain. As such, some experts suggest supplementing with addition vitamin D to help optimize brain cell function

Complementary Management Of Parkinson's Disease

1. Protein at Dinner – Some evidence shows that the action of L-dopa can be greatly enhanced by consuming most of the day's protein intake at dinner, while limiting protein through the day. Possibly other amino acids from food compete with L-dopa to cross blood-brain barrier.

2. Consume Fava Beans (Vicia faba) – Fava beans contain additional L-Dopa. However, over-consumption may cause an L-dopa overdose. Thus, patients should speak to their doctor before adding substantial amounts of fava beans (broad beans) to their diet.

Overall Supplement Considerations In Parkinson's Disease

1. *Coenzyme Q10: 300-1,200 mg per day, taken in divided doses with meals*

2. *CDP- Choline – 500- 1000 mg per day*

3. Phosphatidylserine: 100 mg, three times per day until mood and cognitive function improve, followed by a maintenance dosage of 100 mg, one to three times daily based upon patient response. (Take with meals)

4. *Creatine Monophosphate – 5,000 mg, twice daily*

5. Vitamin C: 500 mg, 3-4X daily with food

6. Vitamin E: 800 IU, 3-4X daily with meals

7. High Potency Multi-Vitamin: antioxidant enriched and B-50 complex (B-vits boosts neurotransmitter synthesis)

Continued on Next Page

8. Combination Flaxseed and Fish Oil: a supplement containing at least 400 mg per capsule each, of flaxseed and fish oil (30% EPA, 20% DHA). 2- 3 caps per day

9. Alpha-lipoic acid- 75 mg, twice daily

10. N-acetylcysteine – 600 mg, twice daily

11. Acetyl-L Carnitine – 1000-2000 mg per day

12. Maintain serum Vitamin D at minimum 85nmol/L (34ng/ml)

The ones in *italics* have best supporting evidence

Other Considerations:

1. Urinary Organic Acids Testing – assess mitochondrial dysfunction, dysbiosis leading to gut endotoxins disrupting dopamine synthesis.

2. Heavy Metal Detoxification – chelation therapy. We will explore nutritional medicine detoxification in next section of course.

Addendum to Parkinson's disease Subject Matter

Decline in Dopamine and Dopamine Receptors in CNS in Aging

- An overwhelming number of studies have reported age-related changes in dopamine synthesis, binding sites, and number of receptors.
- Studies using positron emission tomography (PET) in living human subjects have shown **a significant age-related decline in dopamine synthesis,** notably in the striatum and extrastriatal regions (excluding the midbrain).
- Significant age-related **decreases in dopamine receptors D_1, D_2, and D_3** have also been highly reported.
- Post-mortem studies also show that the number of D_1 and D_2 receptors decline with age in both the caudate nucleus and the putamen.
- The loss of dopamine with age is thought to be responsible for many neurological symptoms that increase in frequency with age, such as decreased arm swing and increased rigidity.
- Changes in dopamine levels may also cause age-related changes in cognitive flexibility – "hardening of the attitude".

Reference: https://medicalxpress.com/news/2015-06-age-related-cognitive-decline-dopamine.html

Mucuna pruriens - a tropical legume known as **velvet bean** found in Africa, India and the Caribbean

- Contains L-DOPA. The L-DOPA content increases when extracts are prepared. Also contains some serotonin and 5HTP.

- Mucana pruriens has been used traditionally for:

1. Parkinson's disease
2. Sexual Dysfunction
3. Antidepressant

In large amounts (e.g. 30 g dose crude herb) it has been shown to be as effective as pure levodopa/carbidopa in the treatment of Parkinson's disease

The mature seeds of the plant contain about 3.1–6.1% L-DOPA

Example of Typical Supplement:

Now Brand – 800 mg capsules, standardized to 15% L-dopa (120 mg L-dopa per capsule): Dosage – 2 caps per day

J Neurol Neurosurg Psychiatry. 2004. Dec;75(12):1672-7.

Mucuna pruriens in Parkinson's disease: a double blind clinical and pharmacological study.

Katzenschlager R, Evans A, Manson A, Patsalos PN, Ratnaraj N, Watt H, Timmermann L, Van der Giessen R, Lees AJ.

National Hospital for Neurology and Neurosurgery, London, UK.

Eight Parkinson's disease patients were challenged with single doses of 200 / 50 mg L-dopa / carbidopa, and 15 and 30 g of Mucuna pruriens preparation in randomised order at weekly intervals.

Compared with standard L-dopa / carbidopa, the Mucuna preparation led to a considerably faster onset of effect, reflected in shorter latencies to peak L-dopa plasma concentrations.

No significant differences in dyskinesias or tolerability occurred. The rapid onset of action and longer time without concomitant increase in dyskinesias on Mucuna seed powder formulation suggest that this natural source of L-dopa might possess advantages over conventional L-dopa preparations in the long term management of Parkinson's disease.

Selegiline hydrochloride:

- Drug that inhibits MAO-B (monoamine oxidase –B) enzyme in the CNS.

- MAO-B activity increases with age – breaking down dopamine, NE etc.,

- Selegiline increases dopamine in striatum- prevents age-related memory and learning decline in humans and preserves ejaculate ability in rats (PD patients live longer on selegiline, which should start asap, not waiting for l-dopa Rx)

Reference: https://www.ncbi.nlm.nih.gov/pubmed/1634730

Endurance Exercise – A large 2017 meta-analysis study showed that endurance exercise slows the progression of PD and helps to preserve mobility.
https://www.ncbi.nlm.nih.gov/pubmed/28870627

Strength Training Exercise - Studies show strength training improves mobility, fatigue, quality of life, and disease progression among people with PD
http://pennstatehershey.adam.com/content.aspx?productId=107&pid=33&gid=000123

The Brain's Way of Healing (Dr. Norman Doidge, M.D.) – Chapter Two – A Man Walks Off His Parkinson's Symptoms (by recruiting other brain centres to preserve normal function and mobility) – Penguin Books