

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

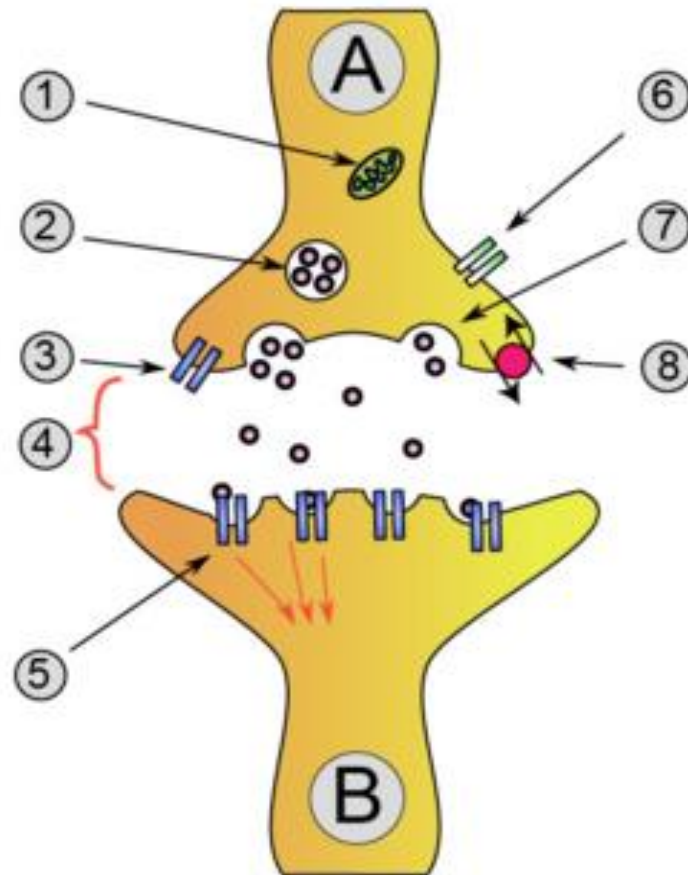
1. Neurotransmitters and the brain
2. Vitamins and minerals and the brain
3. Essential fatty acids and the brain

Part 1 Neurotransmitters and Vitamins And Minerals

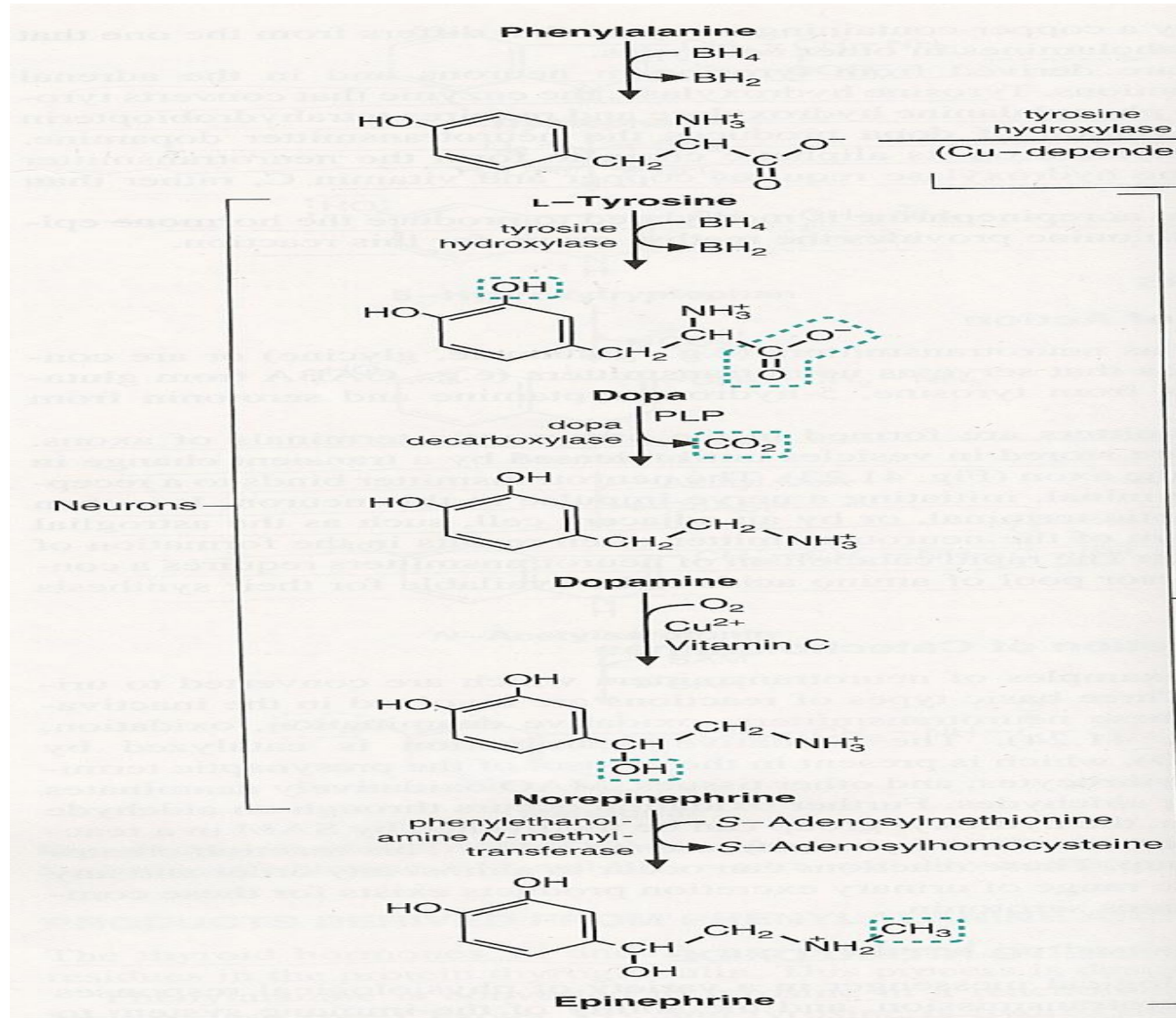
Brain cells make neurotransmitters that act like signaling agents from one nerve cell to the next (synaptic cleft), which are important in:

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

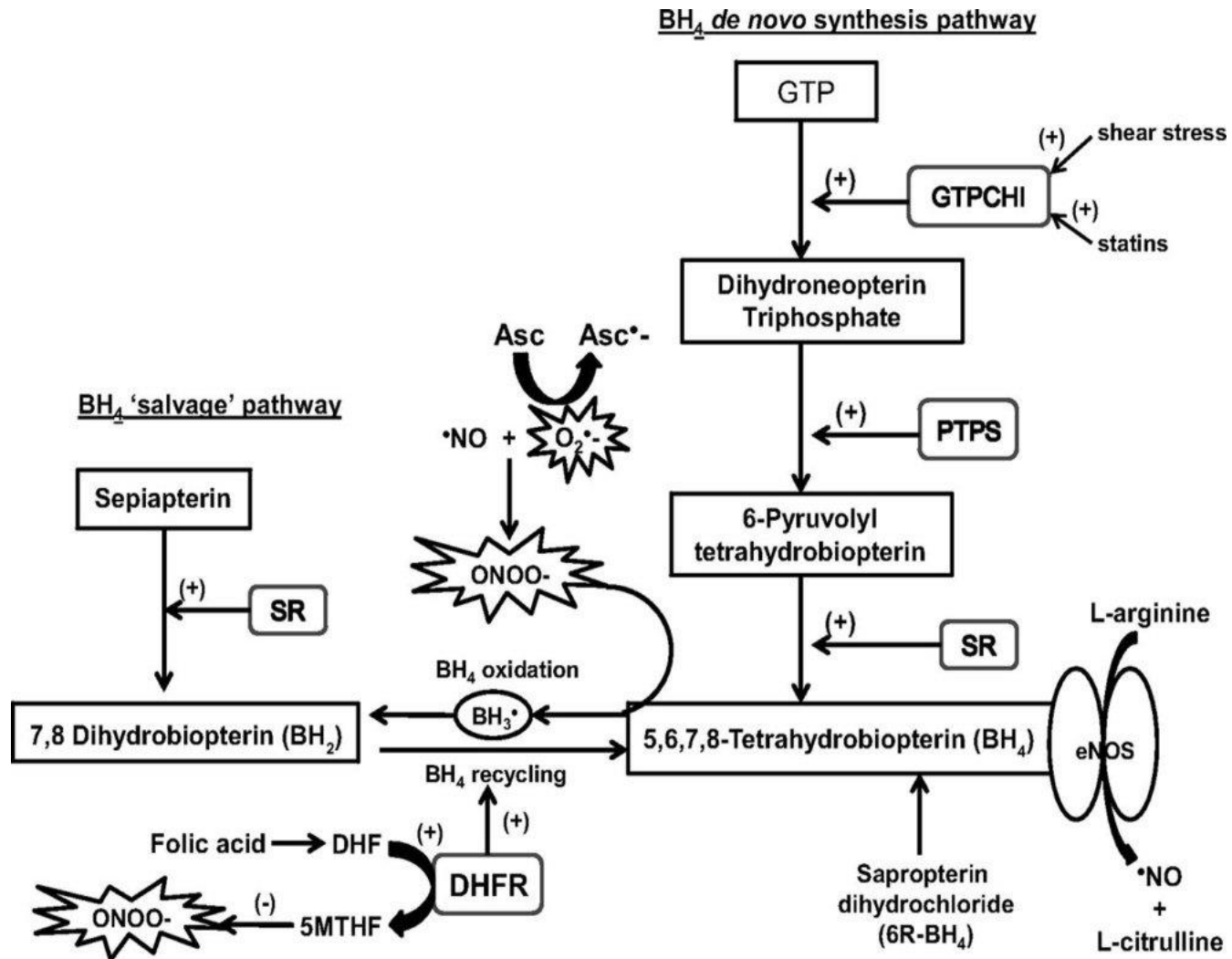
The Synaptic Cleft



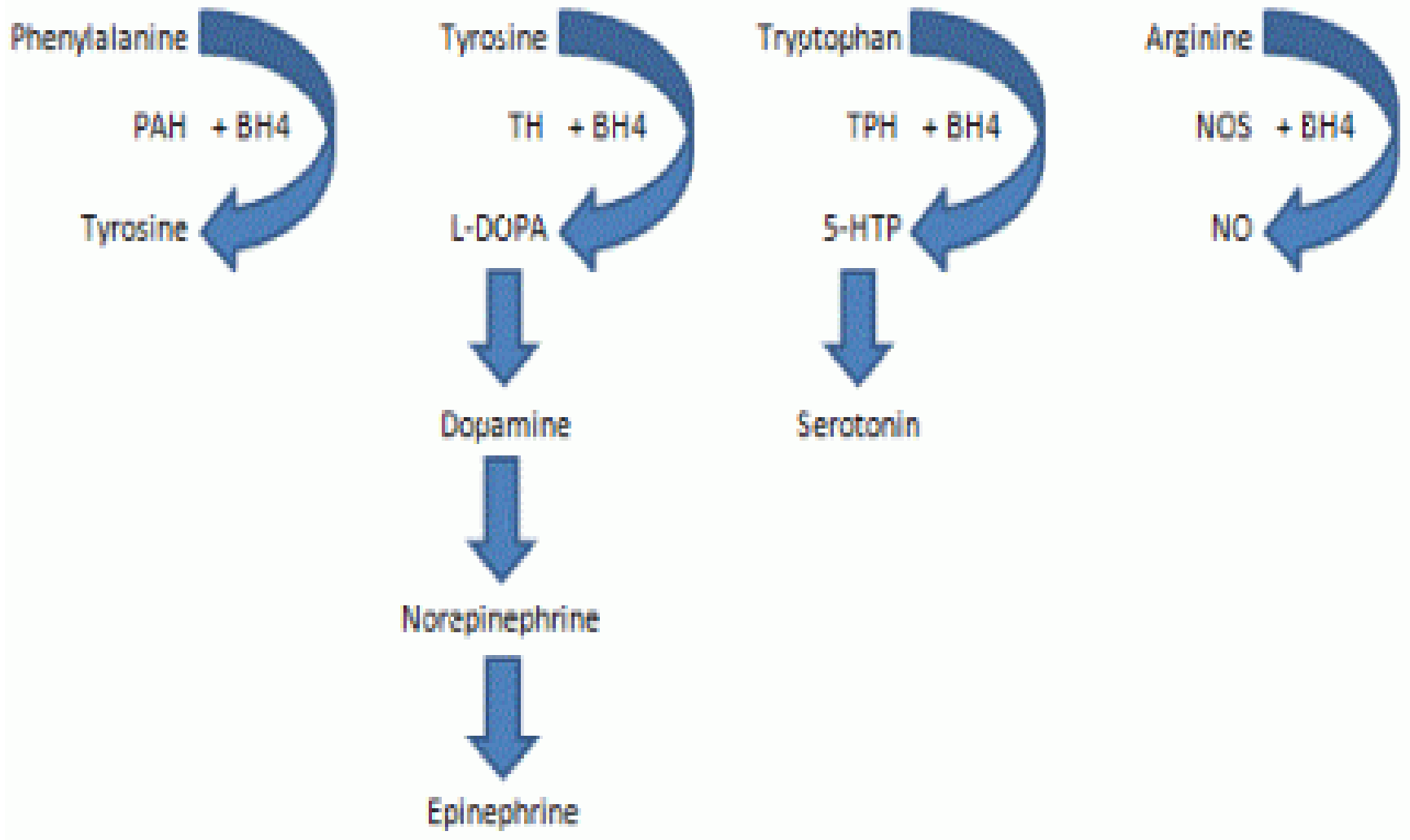
Synthesis of Dopamine, Norepinephrine and Epinephrine: Note dopa-decarboxylase



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 hyperkinesia: 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.

2006 Intervention Study (B6 and Mg in ADHD Trial)

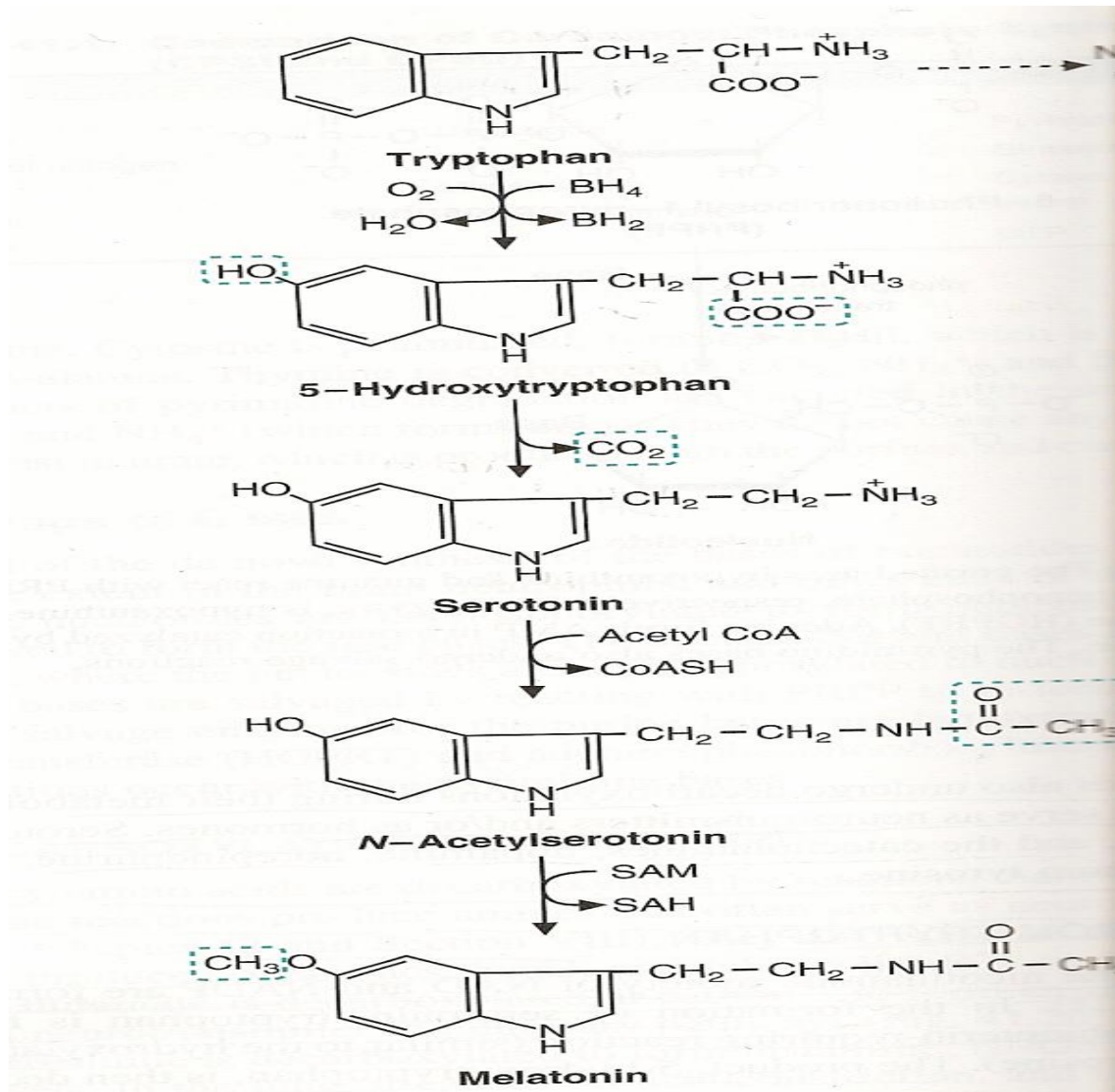
<http://europepmc.org/abstract/med/16846100>

- 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 Mg²⁺ (Erc-Mg) and blood ionized Ca²⁺ (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

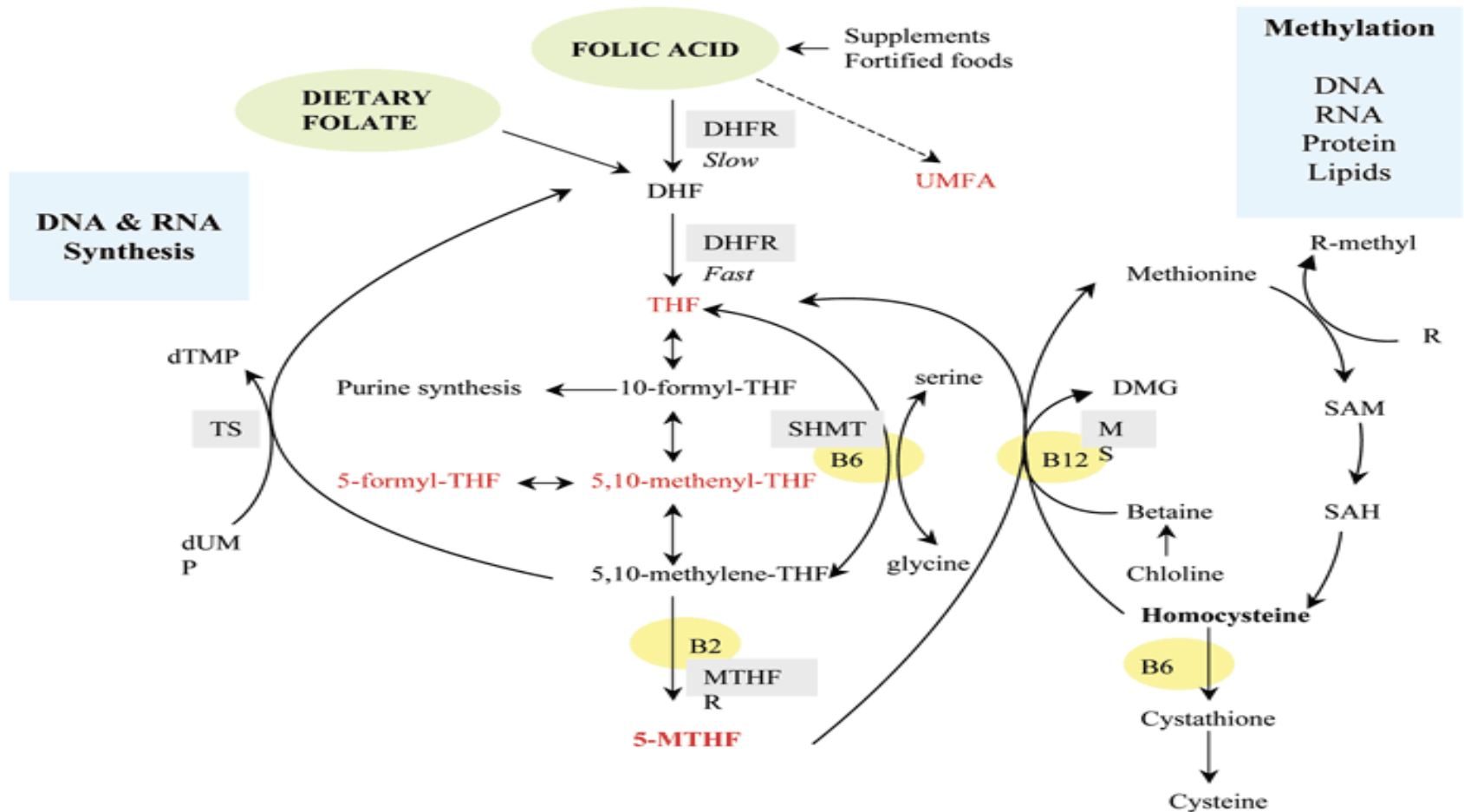
Interactions of B-Vitamins and Vitamin C

- 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

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-MTHFR) 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-MTHFR 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 switches 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 be provided in the form of methylfolate. The physician should monitor homocysteine levels 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)

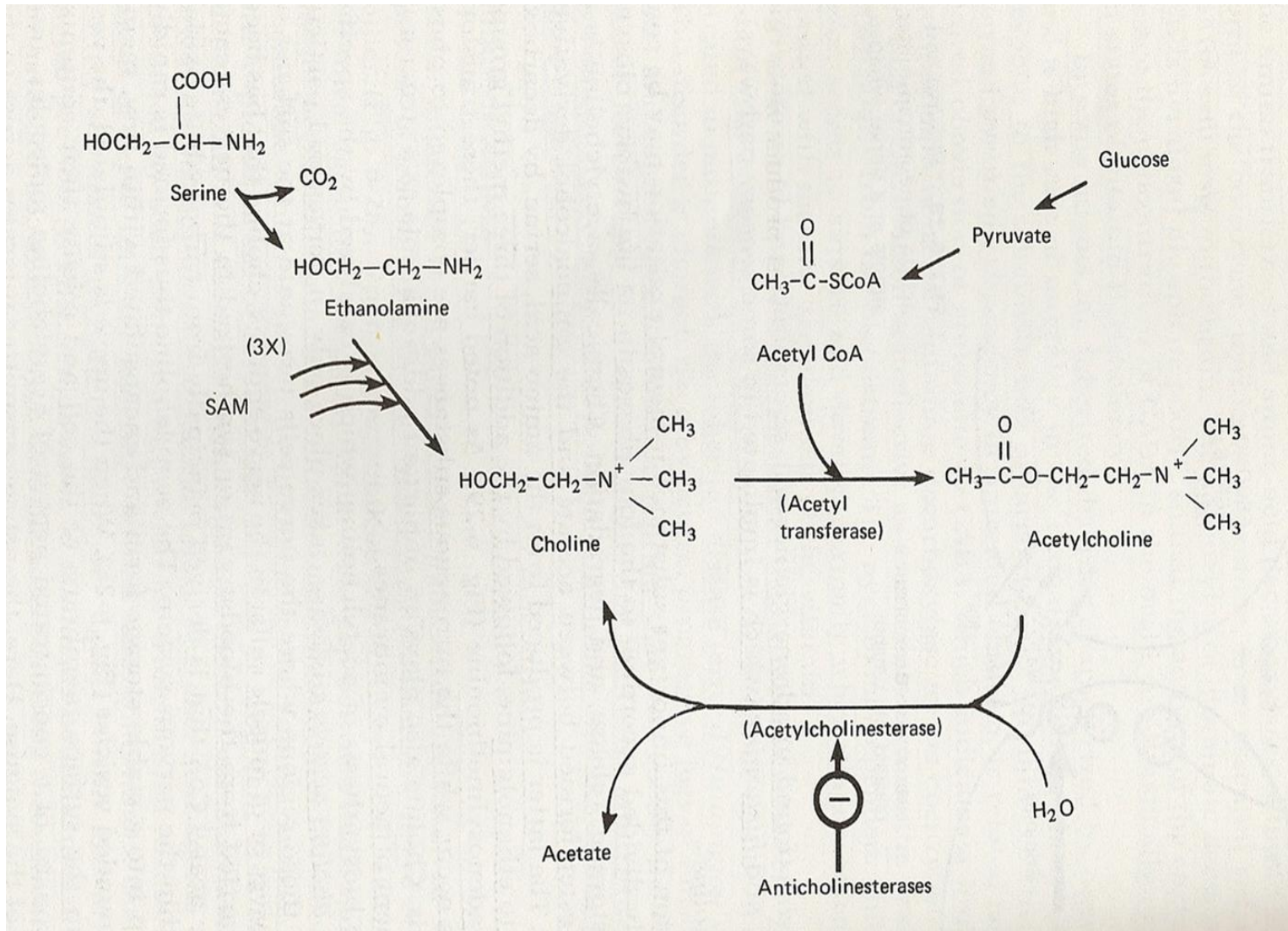
Amount per 4 Capsules

| <u>Example: Multiple Vitamin and Mineral</u> | | |
|---|--------------------------|--------------------|
| 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

| <u>Example: Multiple Vitamin and Mineral Continued</u> | | |
|---|--------------------------------|---------|
| 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

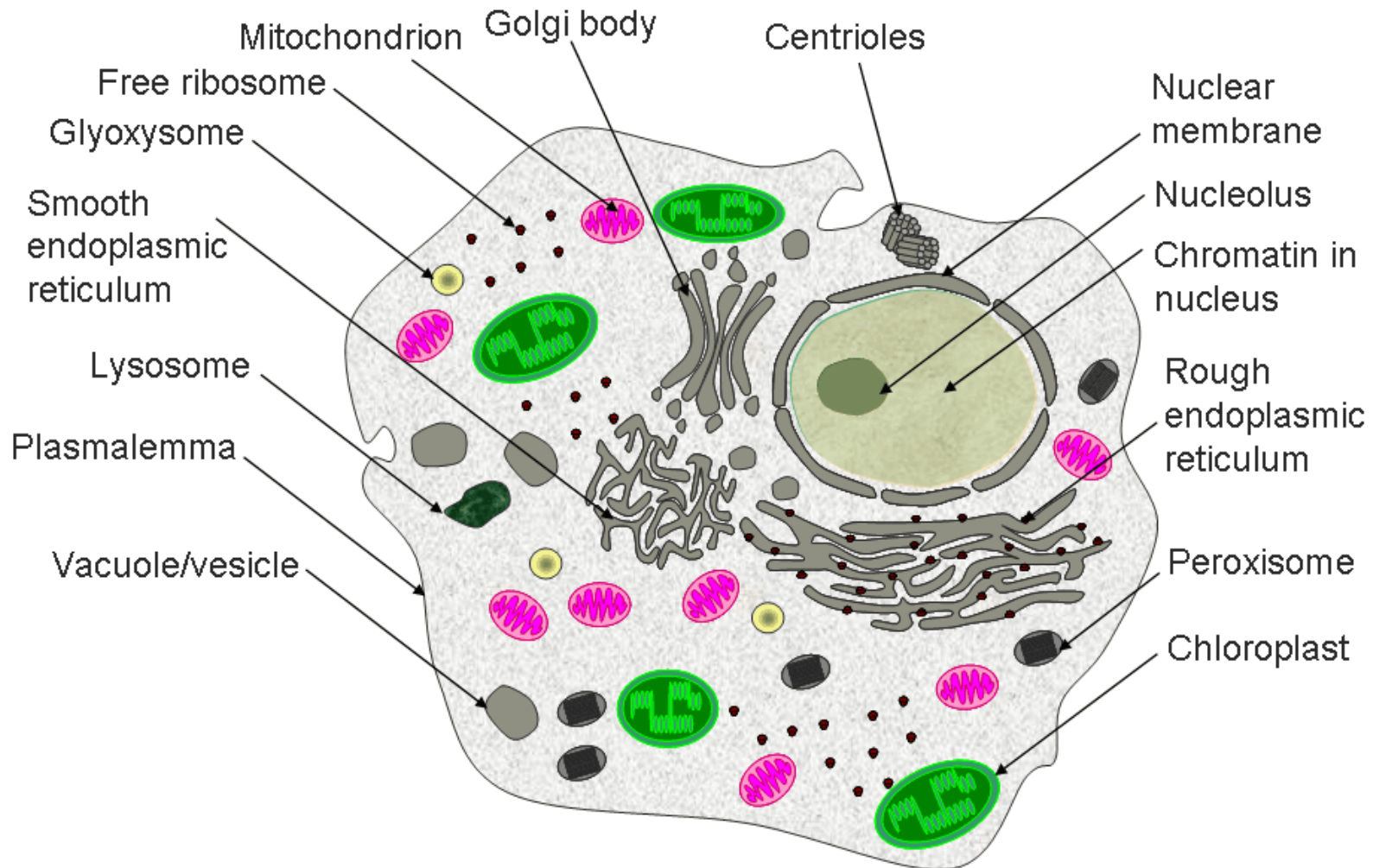
1. Most of the dry weight of the brain is lipid (fat)
2. The outer skin (membrane) of brain cells require EFA's for nerve conduction (electrical impulse transmission from nerve to nerve)
3. The brain particularly likes access to omega-3 fats. The brain has higher levels of DHA levels than most other 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

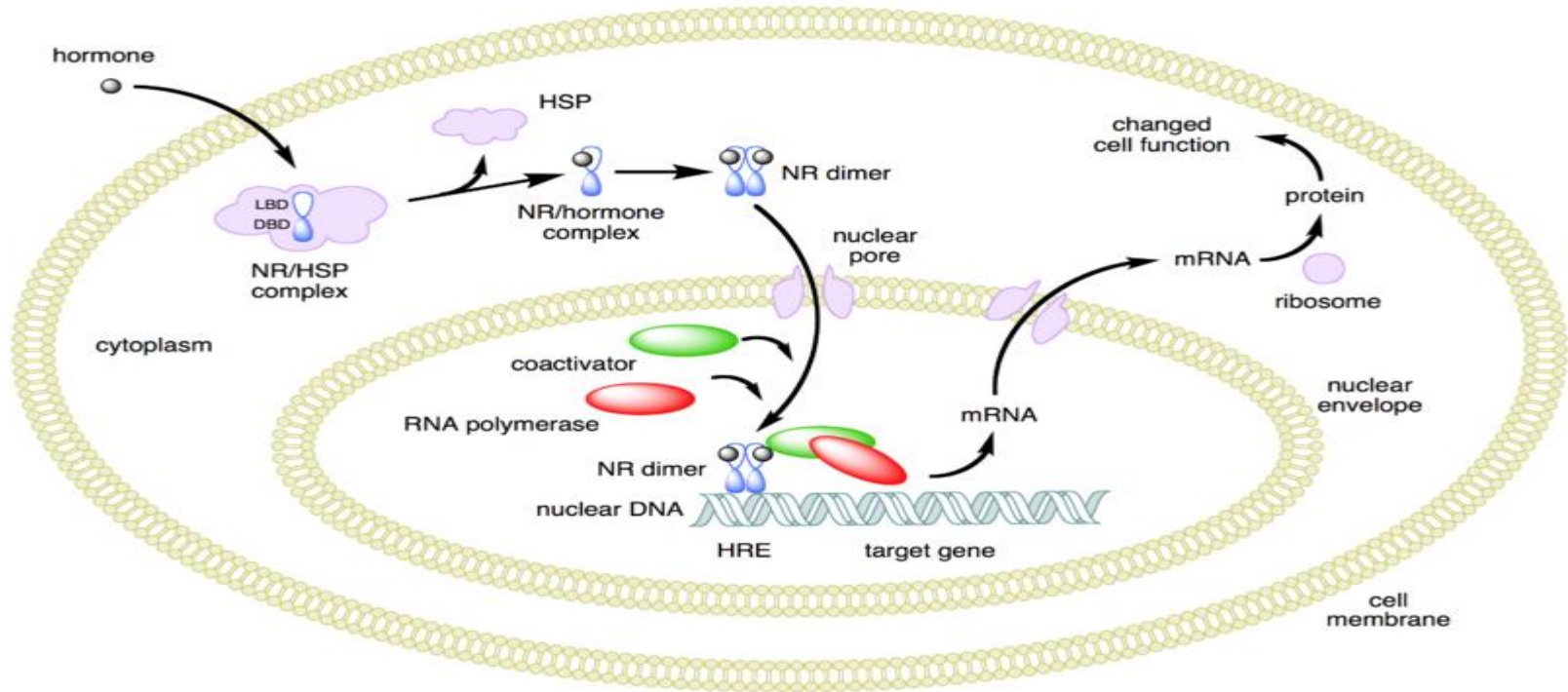
- Essential fatty acids are indispensable structural components of the cell membranes of all tissues.
- The brain, retina and other neural tissues are particularly rich in long-chain polyunsaturated fatty acids (LC-PUFA).
- Intracellular fatty acids or their metabolites (eicosanoids) regulate activation 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

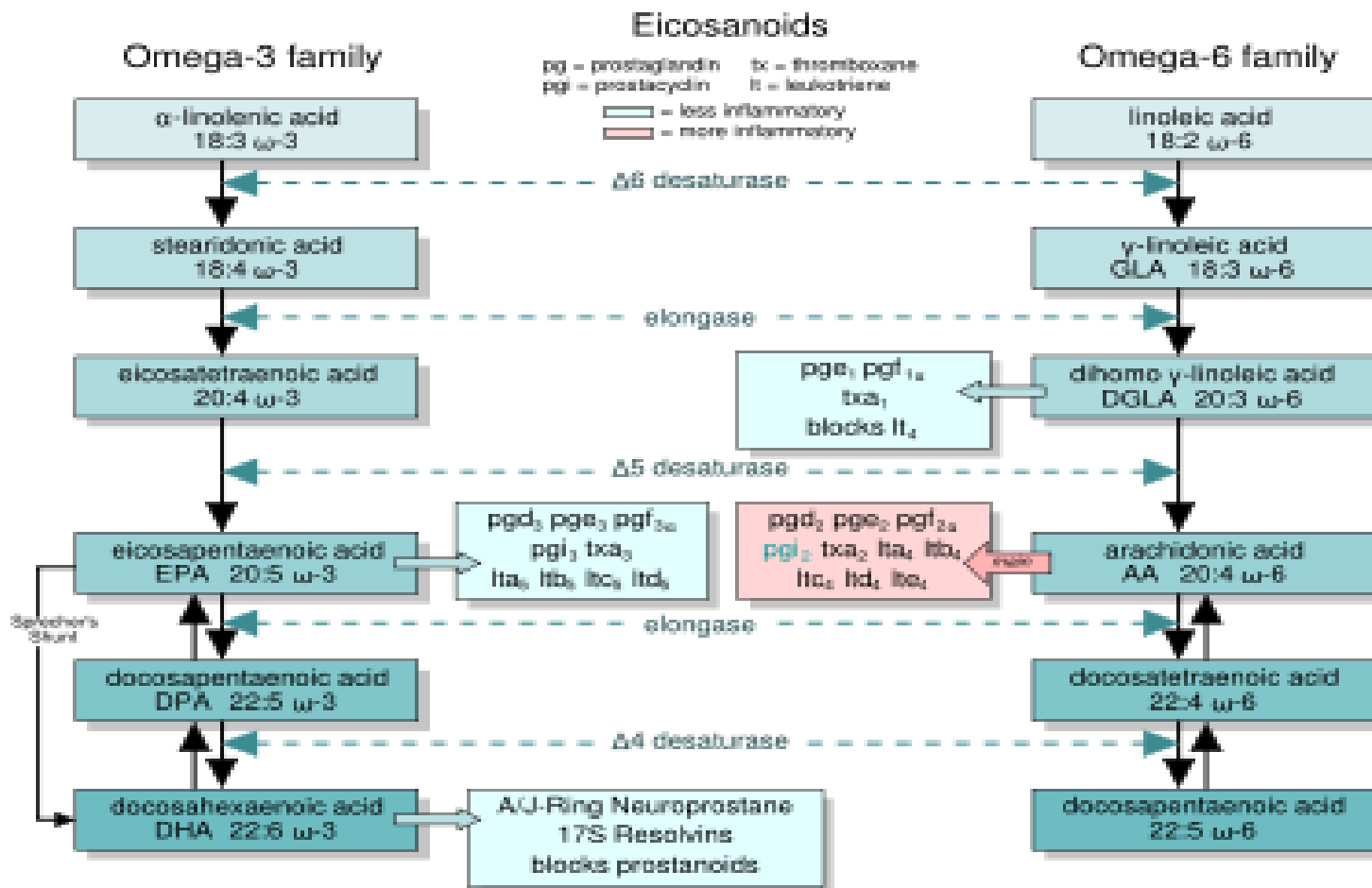
- The increase in brain size during the final three months of pregnancy is three fold, and this rapid growth in brain development requires appreciable amounts of DHA.
- The Fetal and infant brain (first three months of life) can not make sufficient DHA on its own, and is dependent on mother's body and 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)
4. Caspi A et al. Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. *Proceeding of the National Academy Of Sciences (North America)*. Nov 27, 104;47. 2007
5. Koeman M. EPA/DHA – The intelligence of fish oil. *Biocentials*. 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 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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- Jorgensen MH, Hernell O, Hughes E, Michaelsen KF. Is there a relation between docosahexaenoic acid concentration in mothers' milk and visual development in term infants? *J Pediatr Gastroenterol Nutr*. Mar2001;32(3):293-6
- Willatts P, Forsyth JS, DiModugno MK, et al. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet*. Aug1998;352(9129):688-91
- Uauy R, Mena P. Requirements for long-chain polyunsaturated fatty acids in the preterm infant. *Curr Opin Pediatr*. Apr1999;11(2):115-20

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 ϵ 4) gene on chromosome 19—does increase a person's risk. However, inheriting an APOE ϵ 4 allele does not mean that a person will definitely develop Alzheimer's. Some people with an APOE ϵ 4 allele never get the disease, and others who develop Alzheimer's do not have any APOE ϵ 4 alleles.

- The expression of genes (when particular genes are “switched” on or off) can be affected – positively or negatively – by 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

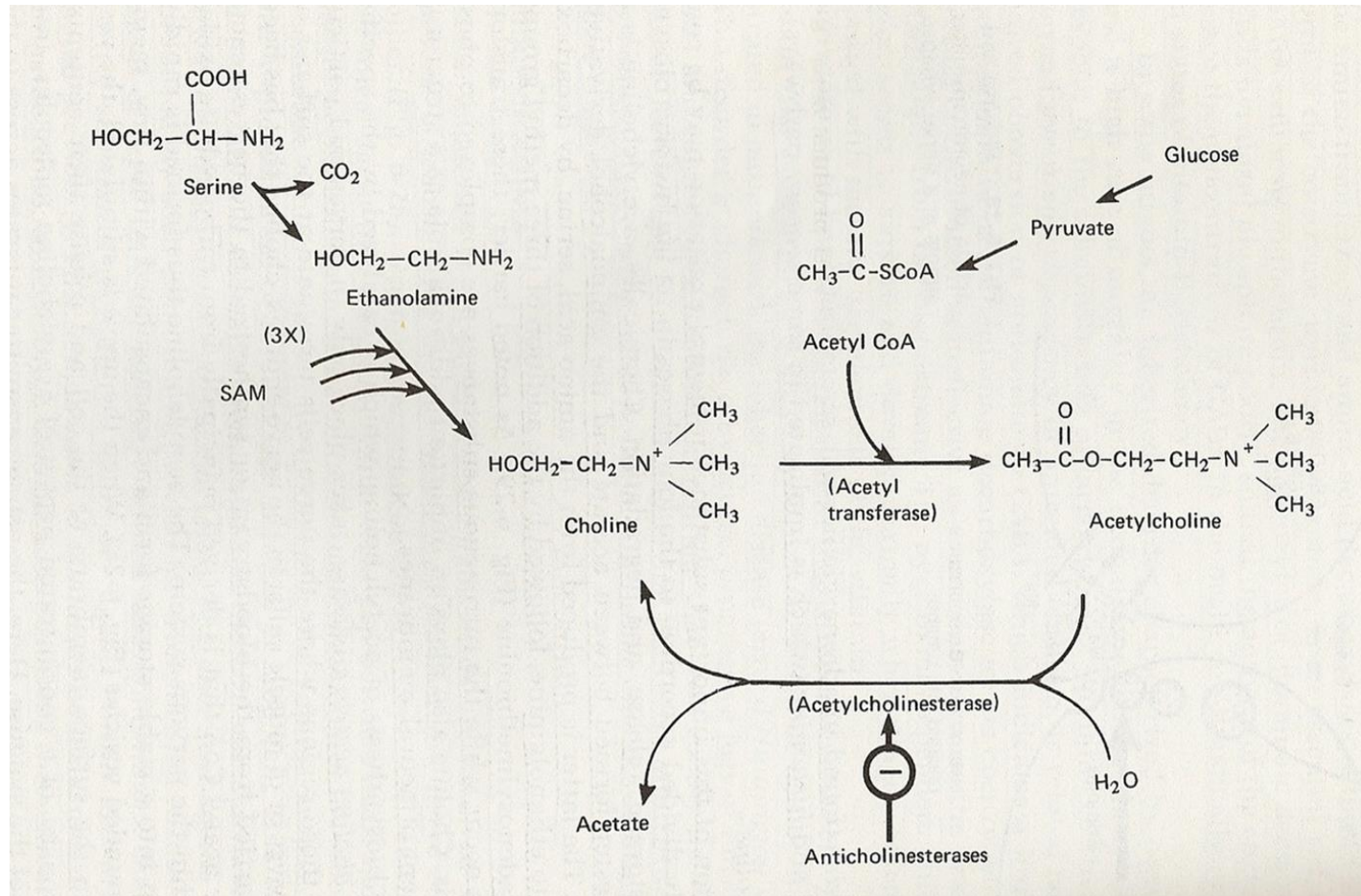
Causes (Three Hypotheses)

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.

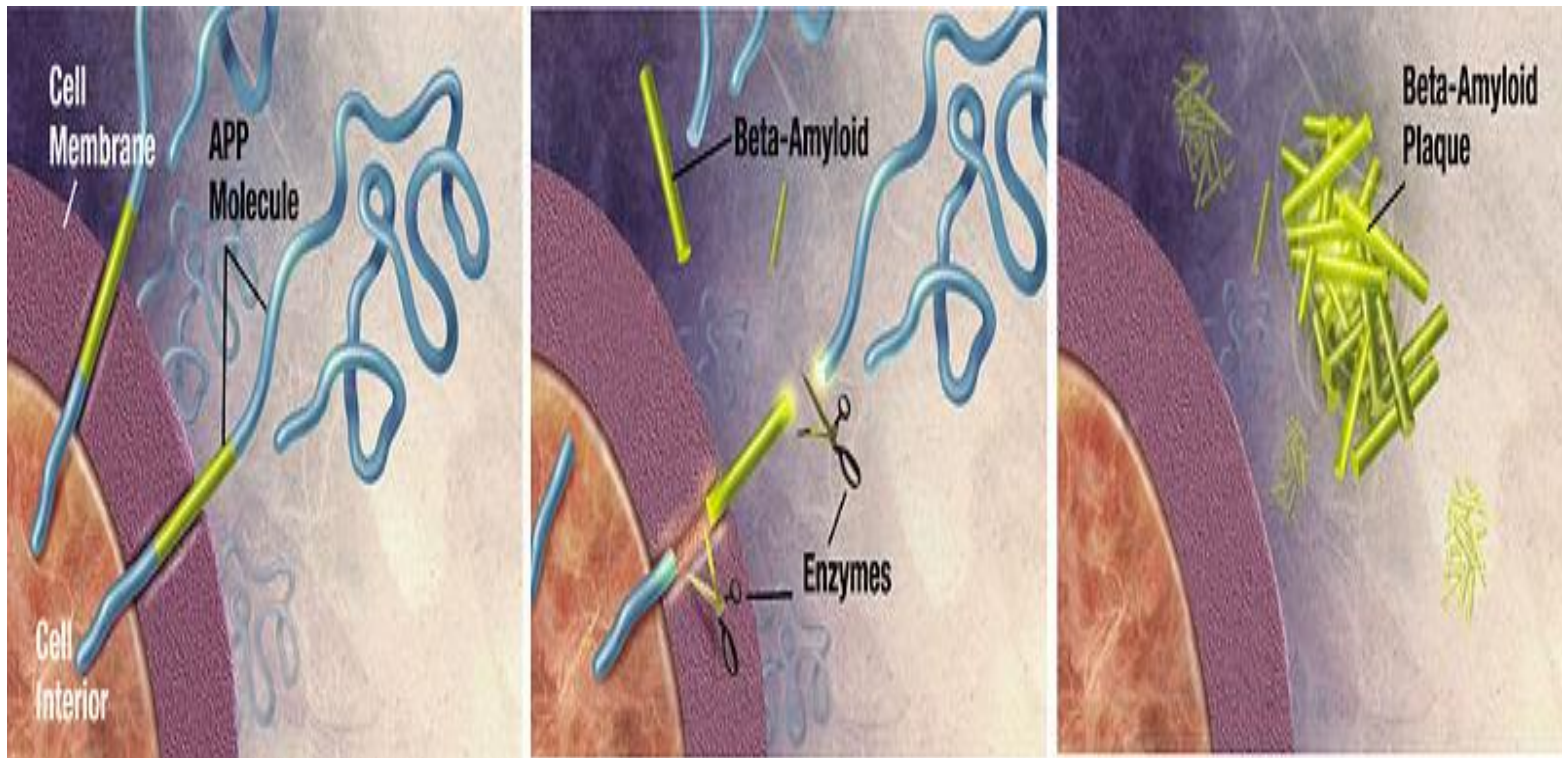
Amyloid Plaque and AD

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.

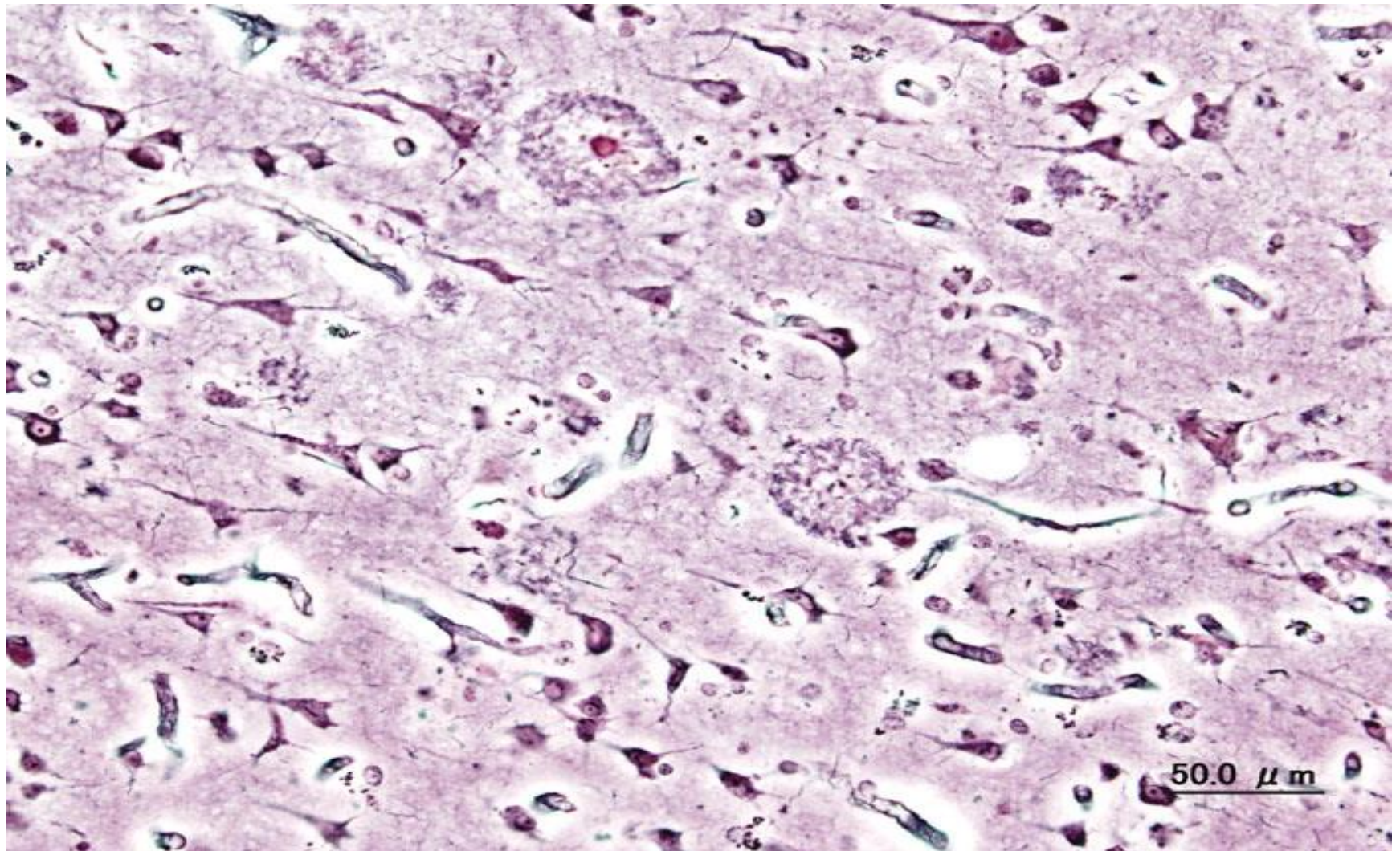
- **Also APOE4**, the major genetic risk factor for AD, leads to excess amyloid buildup in the brain before AD symptoms arise. Thus, beta amyloid protein deposition precedes clinical AD.
- Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop 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



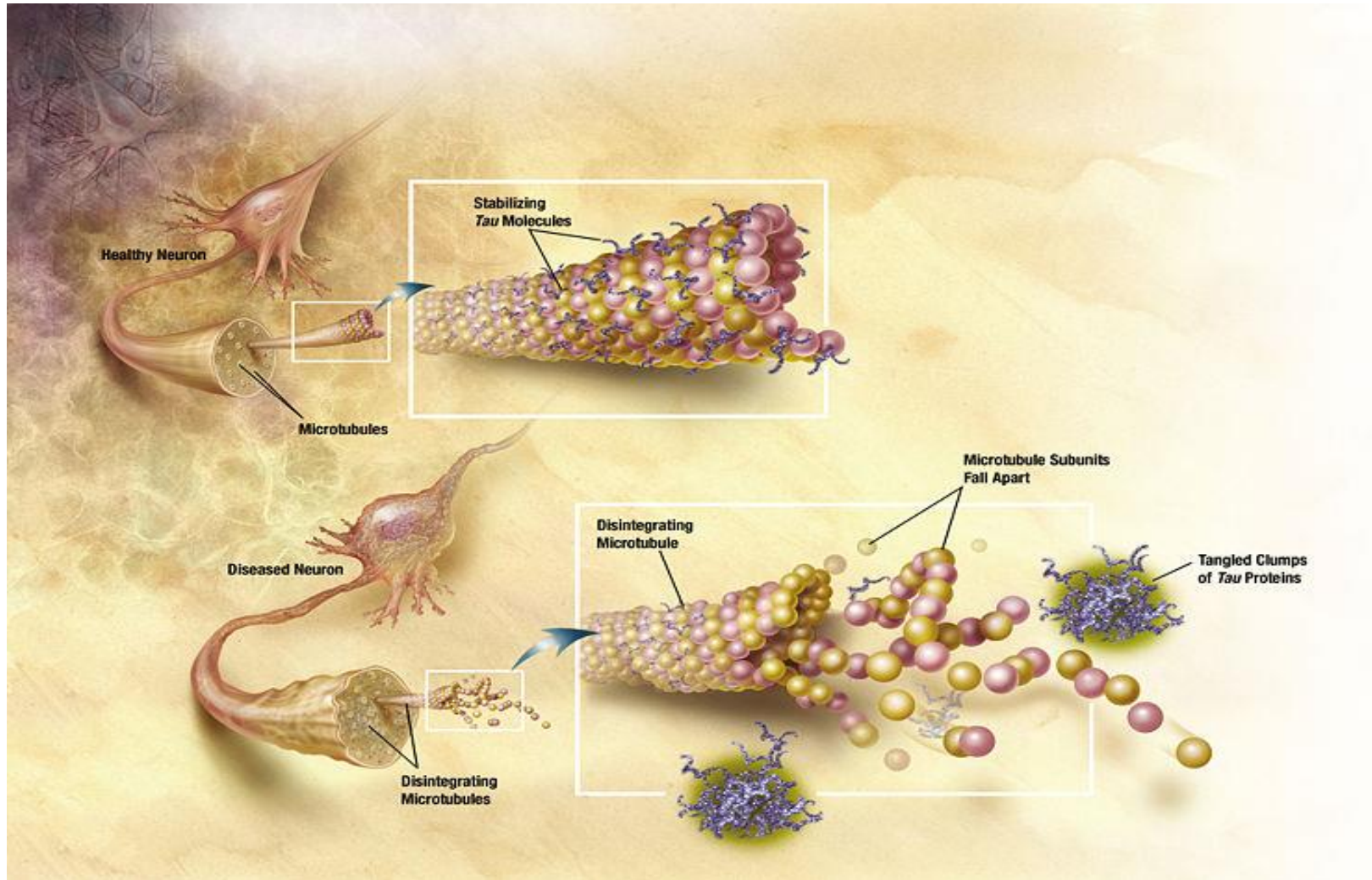
Senile plaques in cerebral cortex of person with Alzheimer's disease. (Silver impregnation)



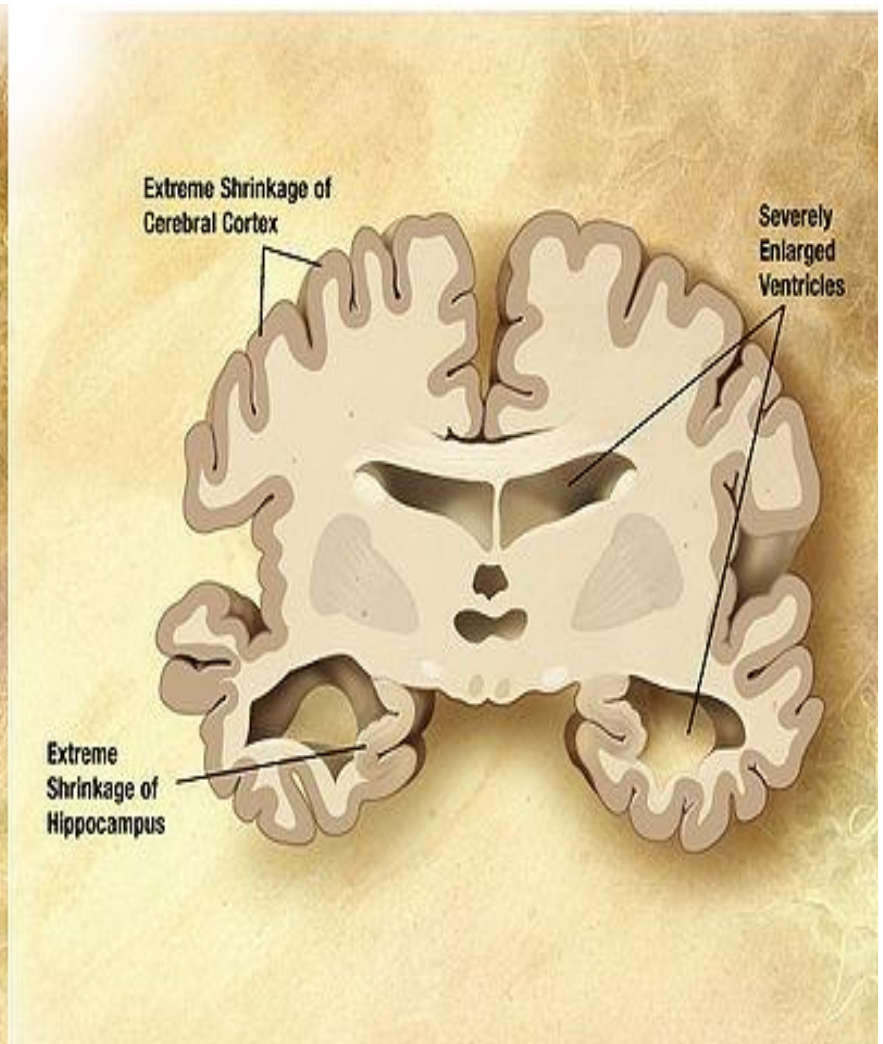
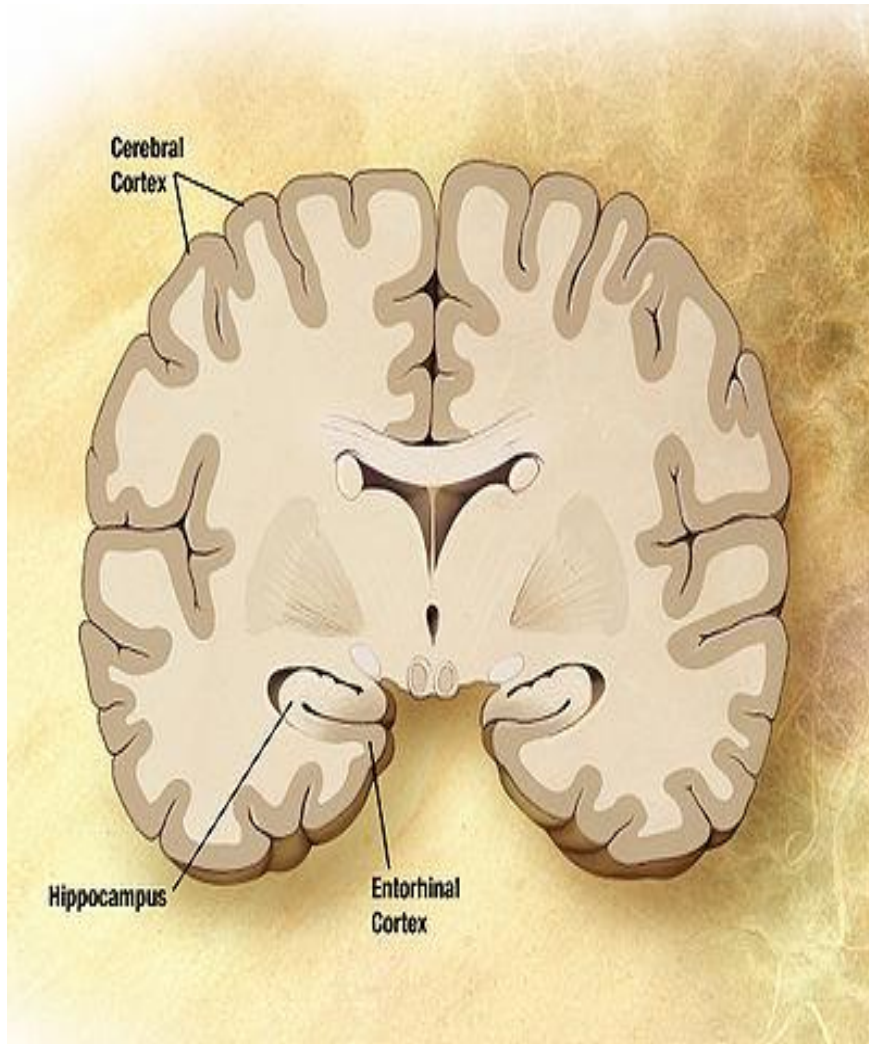
- 3. Tau Hypothesis** - tau protein abnormalities initiate AD, whereby hyperphosphorylated tau pairs with other threads of tau protein forming neurofibrillary tangles inside nerve cell bodies.
- When this occurs, the microtubules disintegrate, collapsing the neuron's transport system, resulting in malfunctions 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 abnormally with other tau protein threads, creating neurofibrillary tangles, which disintegrate the neuron's transport system.
- This eventually leads to cell death.

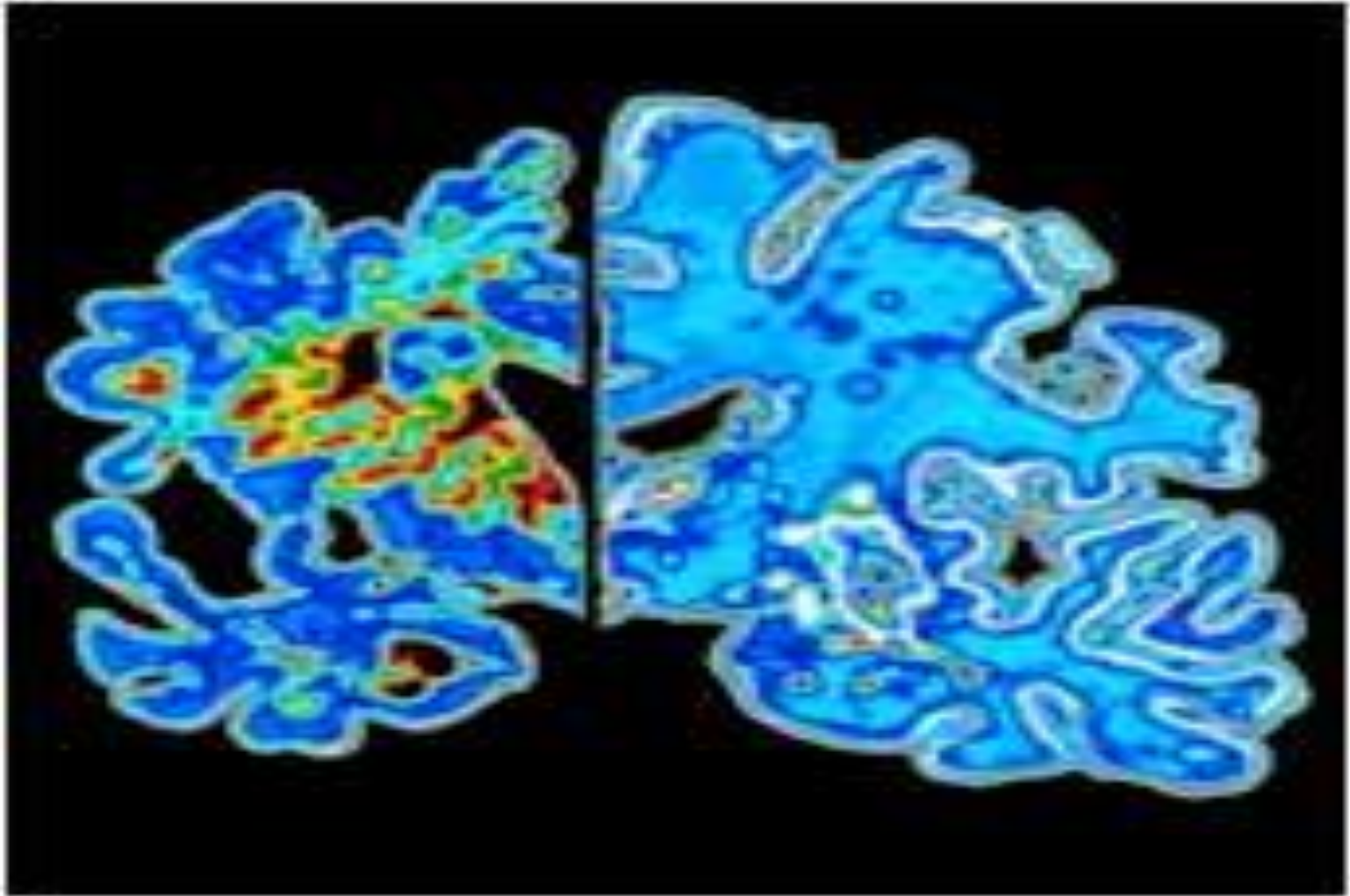
Changes in tau protein lead to neurofibrillary tangles in neurons and cell death



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