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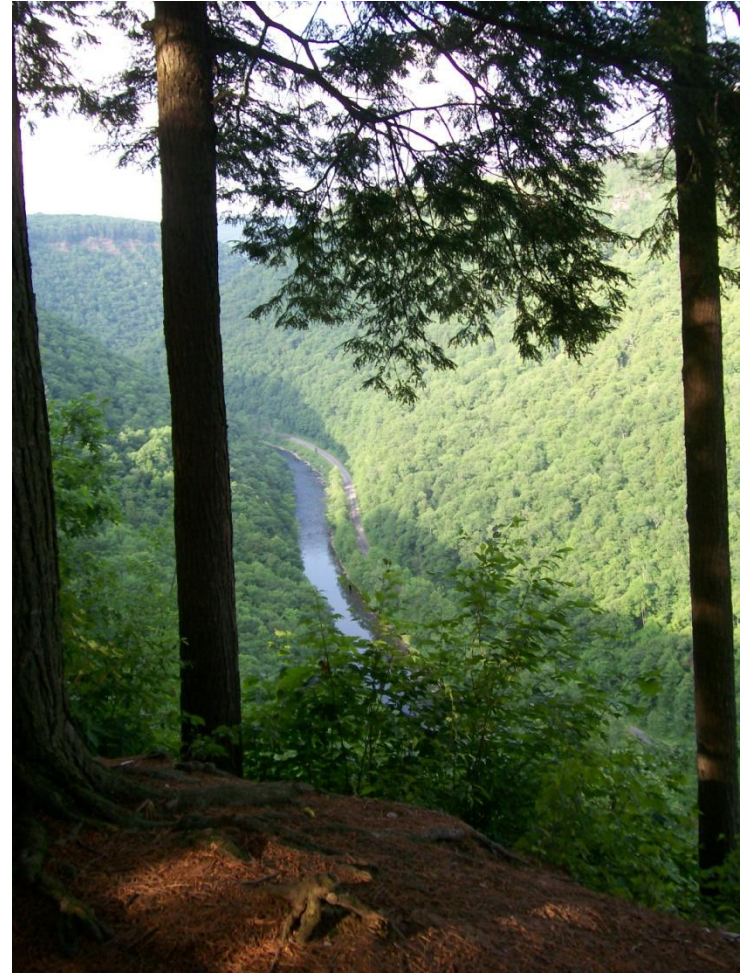


Systemic Nutrition: What's YOUR Gut Reaction?

First Things First...



What An Honor for a Small Town Pennsylvania Girl...



Transplanted from Wellsboro...

TO PITTSBURGH, PA



THEN TO GREENVILLE, NC



To Receive the Cooper Lecture Award!!

Thank you:

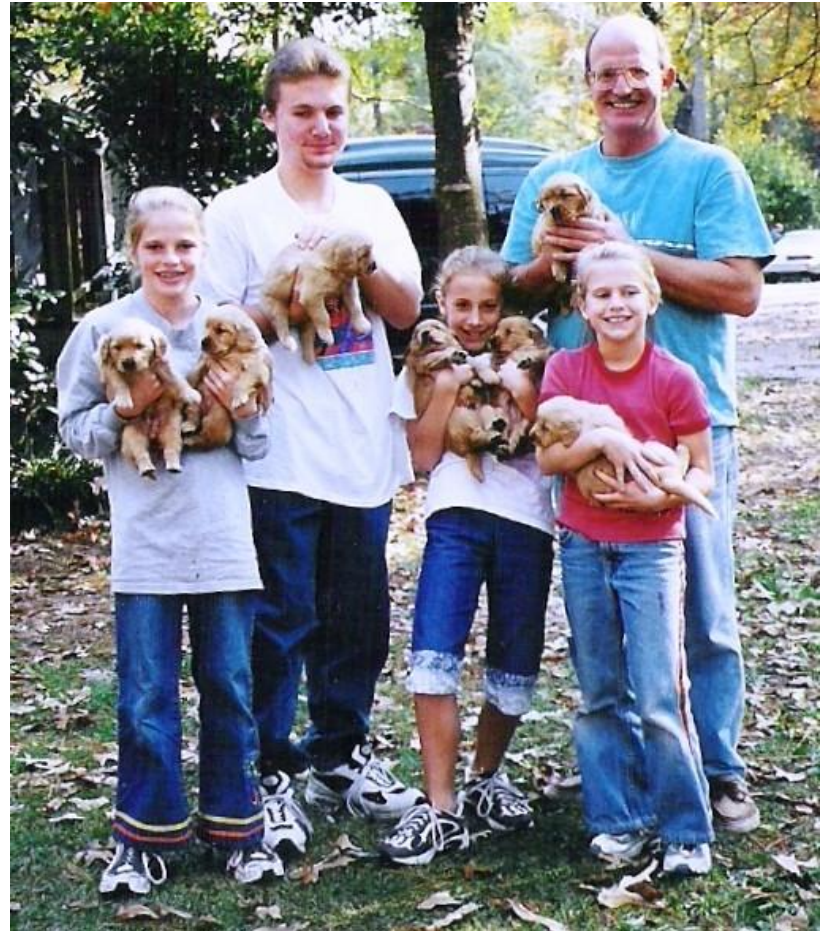
- Suzanne Cryst and **CDHCF** for the award nomination
- Judy Dodd, Sara Parks and many friends for constant support and mentoring
- Will Forsythe, PhD, ECU Department Chair

■ Colleagues who supported this Award:

- Tracy Bates (NCDA)
- Pete Beyer
- Ann Childers (CNM)
- Melani Duffrin
- Becky Dorner
- Marion Franz
- Linda Snetselaar
- Sandy Spann

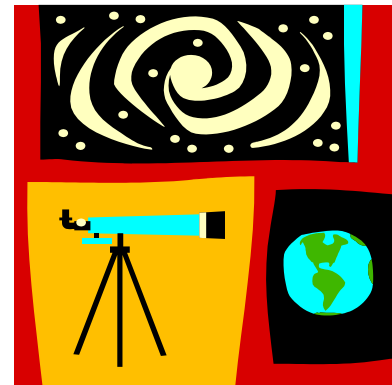
Family, colleagues, students and interns

- My husband and 2 children... who tolerate my writing, traveling and volunteer time.
- Students, interns and colleagues at ECU.

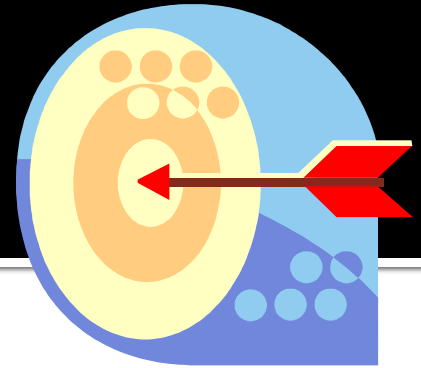


Lenna Frances Cooper

- Lenna Frances Cooper and Lulu Graves established the American Dietetic Association in Cleveland, OH in 1917.
- *Thank you, dear pioneers who forged the way for our bright futures.*



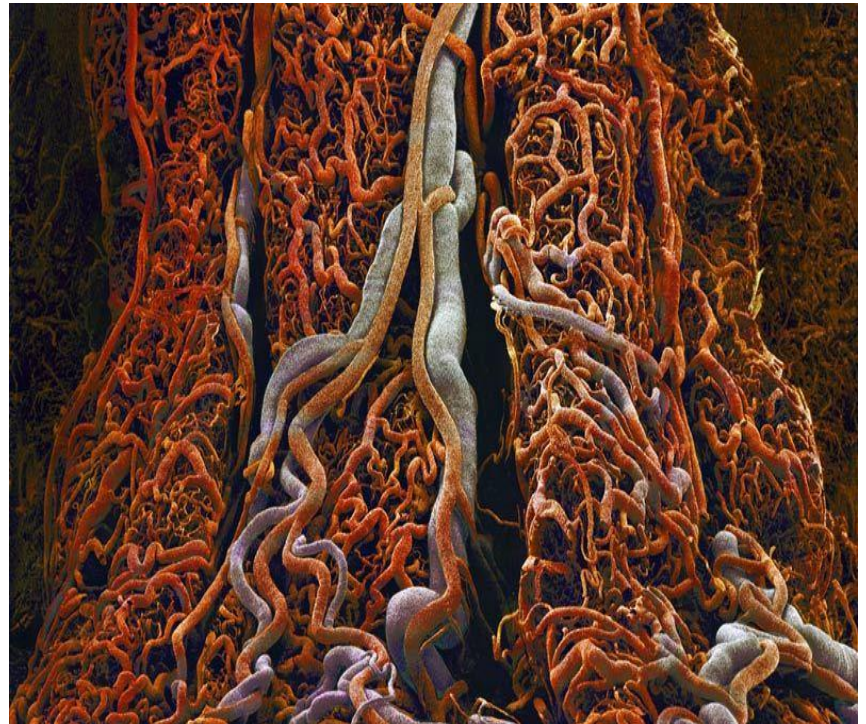
Lecture Objectives



- Participants will be able to name 3 conditions in which the MTHFR deficiency requires **L-methylfolate**.
- Participants will be able to describe how specific nutrients help to maintain or improve health (e.g., **choline, betaine, omega-3 fatty acids, methionine, cysteine, methylated vitamin B-12, tryptophan.**)
- Further define our role in managing issues related to **nutritional genetics**.

Why “Systemic Nutrition”?

- *The brain and the gut, along with other organs, work synergistically.*



Systemic Nutrition

- A new way of approaching the role dietetics professionals play in comprehending the onset and in managing chronic diseases

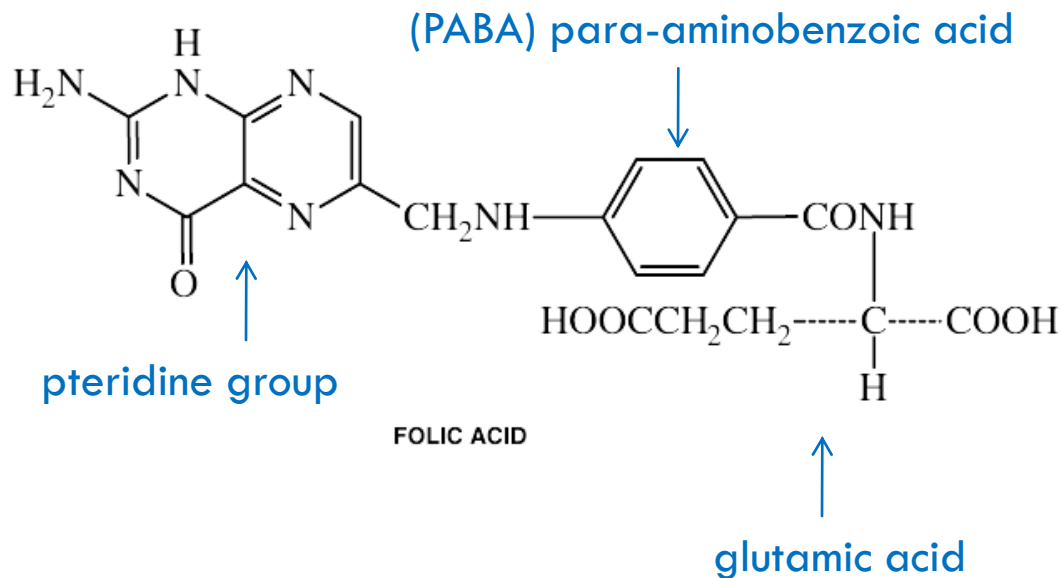


Classic Nutrient Deficiency States

<u>Disease</u>	<u>Vitamin Deficiency</u>
Beriberi	Thiamin
Pellagra	Niacin
Megaloblastic anemia	Folic acid, B ₁₂
Pernicious Anemia	Vitamin B ₁₂
Scurvy	Vitamin C
Rickets	Vitamin D
Goiter and cretinism	Iodine
Iron-deficiency anemia	Iron

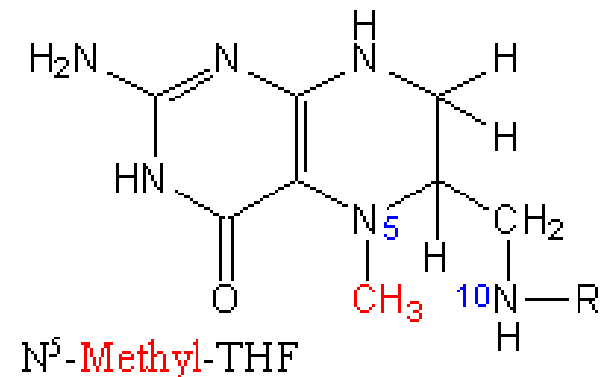
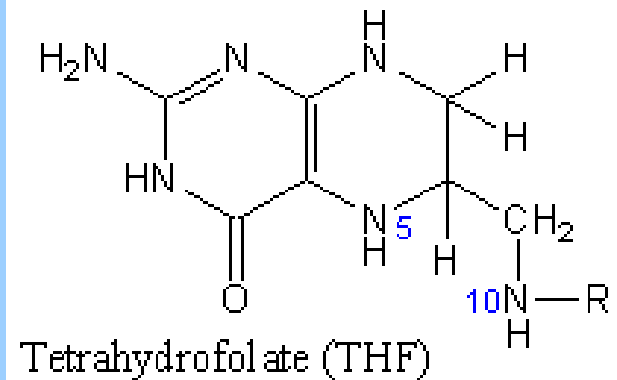
Folic Acid Structure and Forms

- Folic acid



- Coenzyme forms:

- THF, Methyl-THF, MethyleneTHF

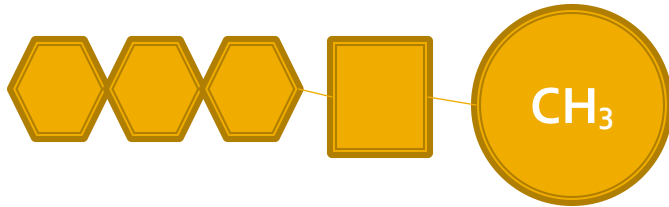


Folic Acid (Folate)

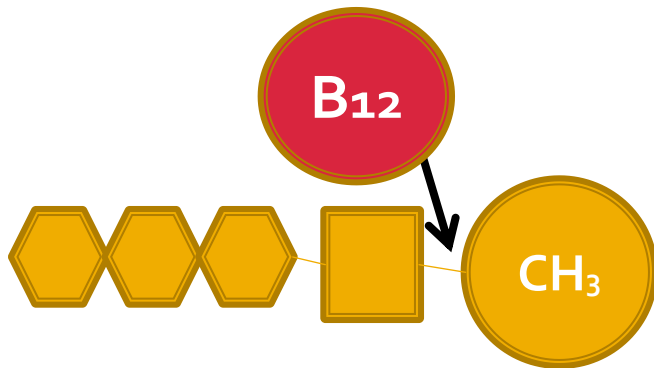
- Folate absorption occurs in the proximal jejunum.
- Folate enters the enterohepatic circulation, loosely bound to albumin.
- Serum folate levels reflect very recent dietary ingestion as opposed to total body folate stores.
 - A normal serum folate does not reflect a potential cellular deficiency.
- Once taken up by cellular folate receptors, 5-methyl THF is converted to **tetrahydrofolate (THF)** by the vitamin B₁₂ dependent enzyme, methionine synthase.

Folate and Vitamin B₁₂

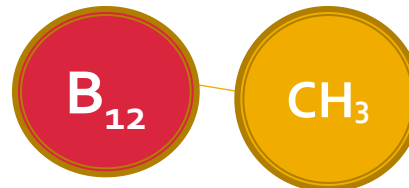
□ The two vitamins work together



In the cells, folate is trapped in its inactive form.



To activate folate, vitamin B_{12} removes and keeps the methyl group, which activates vitamin B_{12}



Once folate and vitamin B_{12} are active, they are available for DNA synthesis

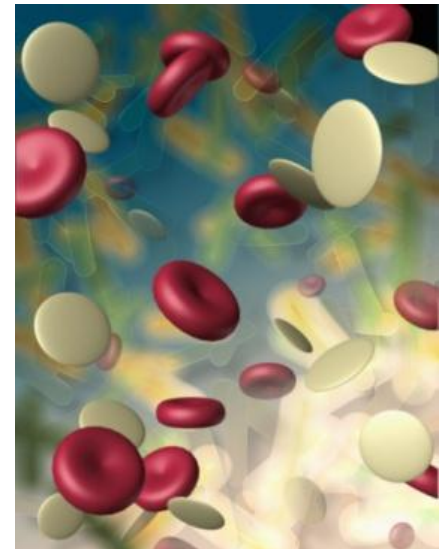
Role of Folate in Health

- Folate is necessary for the production and maintenance of new cells.



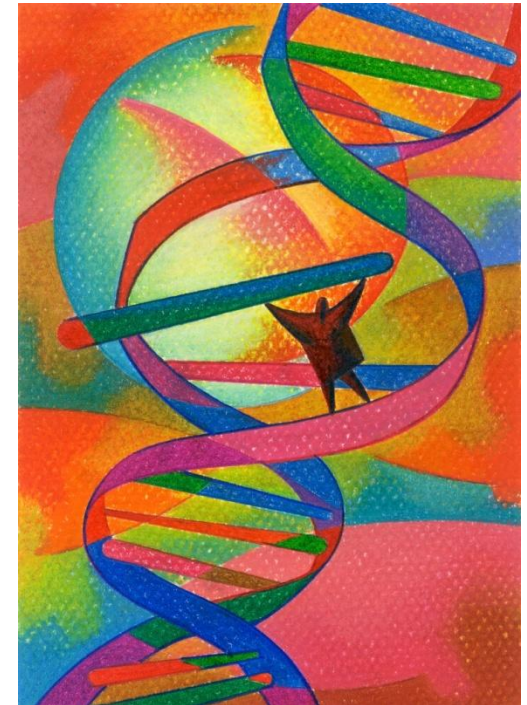
Folate and DNA

- Folate is needed to replicate DNA. Thus **folate deficiency hinders DNA synthesis and cell division**, affecting most clinically the bone marrow, a site of rapid cell turnover.
- Megaloblastic anemia can occur



Folate Biochemistry

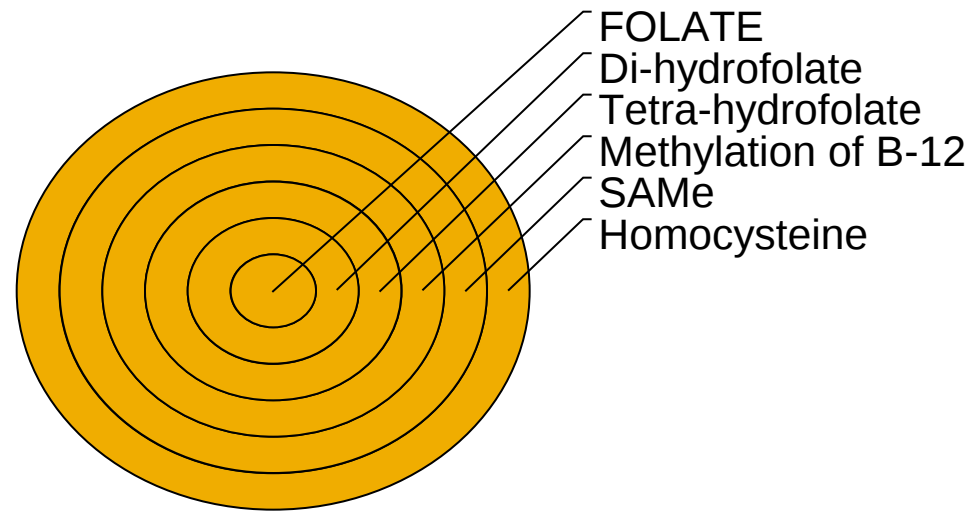
- As **tetrahydrofolate compounds**, folate derivatives are
 - substrates for single-carbon-transfer reactions
 - active in the synthesis of deoxythymidine and deoxyuridine



Folate Biochemistry

Folate (F) is reduced to dihydrofolate (FH_2)

- then to **tetrahydrofolate** (FH_4)...the biologically active form.



- **Dihydrofolate reductase** catalyses both steps.

MTHFR Deficiency Symptoms

- Congenital abnormalities such as cleft lip or palate
 - Developmental delay
 - Gait abnormality
 - Gastric cancer (Boccia et al, Am J Epid 3/1/08; Dong et al, JAMA, 5/28/08)
 - Homocystinuria (rare)
 - Infertility or miscarriage
 - Mental retardation
 - Pediatric stroke (Biwas, *Annals Hematol* 10/4/08)
 - Psychiatric manifestations
 - Seizures
- Inborn Error of Metabolism:
 - Chromosome 1



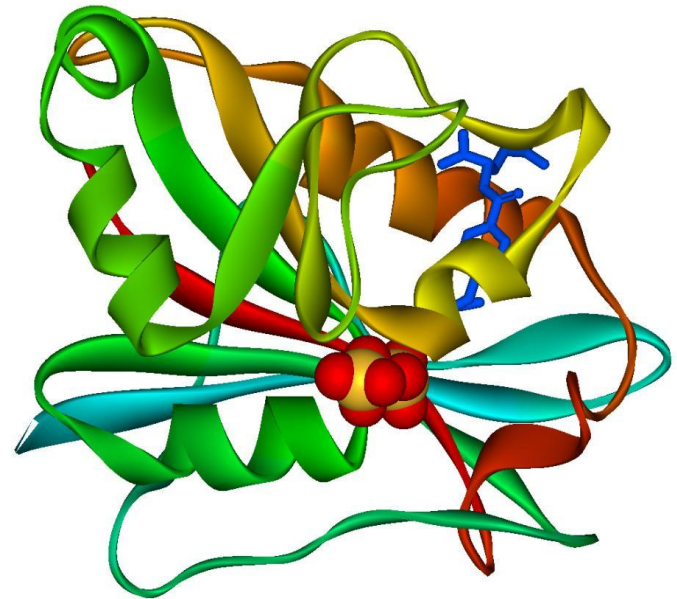
More on Genomics

- Check out www.cdc.gov/genomics
- *JADA* September 2008 issue

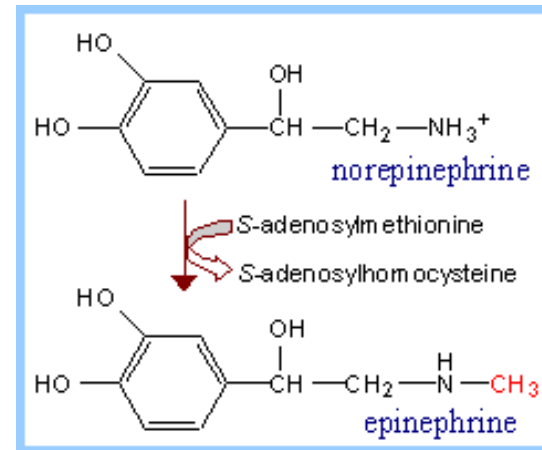
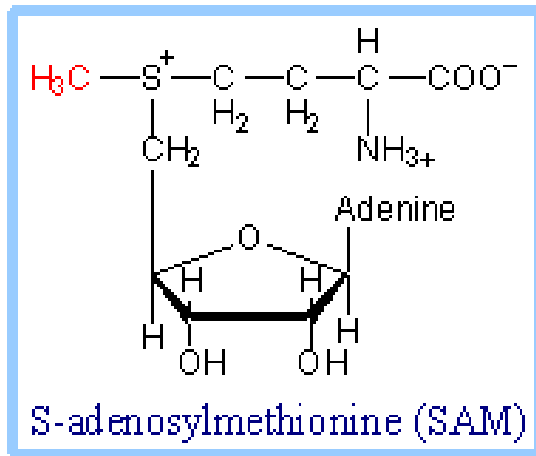


Methylene tetrahydrofolate (CH_2FH_4)

- **Methylene tetrahydrofolate:** formed from tetrahydrofolate by the addition of methylene groups from carbon donors:
- *formaldehyde, serine or glycine.*



Methylation



- **Methionine** is converted to **S-Adenosylmethionine (SAM)** by an ATP-dependent reaction.
- **SAM** serves as a methyl group donor in various synthetic reactions....such as changing norepinephrine to epinephrine.

Methylation Dependent Activities

- DNA synthesis and repair
- Silencing of genes: viruses, cancer genes
- Myelination and pruning
- Conversion of tryptophan to serotonin
- Conversion of serotonin to melatonin

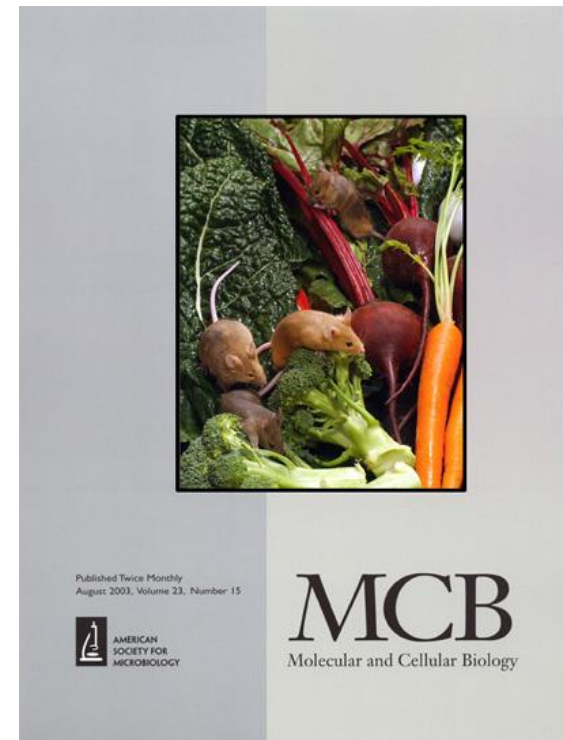
■ Schneider, 2007

Randy Jirtle, PhD – Duke U.

- Maternal nutrition affects the phenotype of viable yellow agouti offspring by influencing the degree of methylation at the agouti locus. - 2003

“This research will define genomic targets that couple maternal nutrition during pregnancy to adult susceptibility to cancer, autism, bipolar disease and schizophrenia.”

<http://cmb.duke.edu/faculty/jirtle.html>



DNA Sequence Variations



- Single nucleotide polymorphisms (SNPs)
 - Nucleotides (sugar, phosphate plus an adenine, cytosine, guanine or thymine base...A-C-G-T)
- DNA coding changes can occur
 - Altered amino acid placement in the genome, leads to changes in enzyme or cellular function and metabolism.
 - Kauwell, 2008

If We Are What We Eat...



Then We Are What Our Ancestors Ate!



FOLATE TRIVIA



Click for Question



**1 μg food folate = how many μg folic acid
from supplements and fortified foods?**



0.6 μg

Click for: Answer and next Question

© S. Escott-Stump

What is the average daily intake of folate from unfortified foods?



200 μg

Click for: Answer and next Question

© S. Escott-Stump

When does the spinal column close in the fetus?



Days 17-28

Click for: Answer and next Question

© S. Escott-Stump

Pregnant women need how much folate?



600 mcg

Click for: Answer and next Question

Breastfeeding women need how much folate?



500 mcg

Click for: Answer and next Question

© S. Escott-Stump

What is the UL for folic acid?



**1 mg
(1000 mcg)**

Click for: Answer and next Question

Dietary Folate Equivalents

1998 Dietary Reference Intakes:

Dietary folate equivalents ("DFEs") measure the differences in the absorption of naturally occurring food folate and more bioavailable synthetic folic acid.

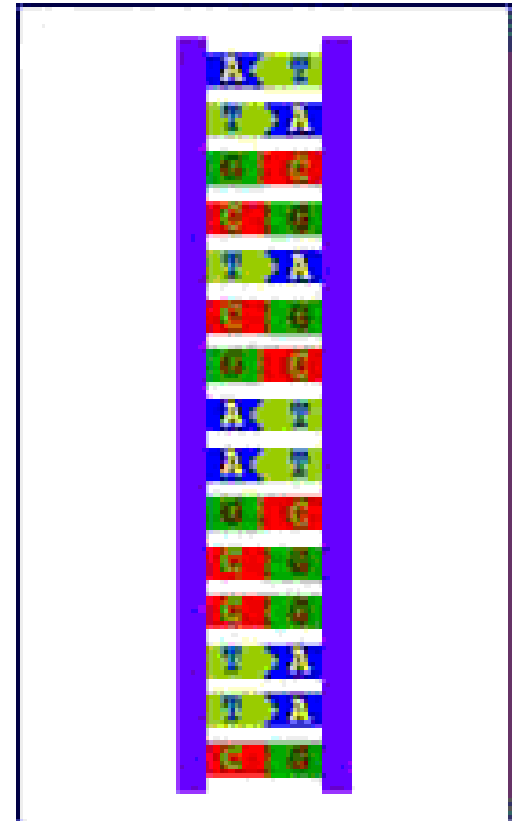
Methylene-tetrahydrofolate-reductase Polymorphism

- Methylene-tetrahydrofolate-reductase (MTHFR) polymorphisms
 - 10% of the world's population
 - Common in the United Kingdom
 - At least 8 known MTHFR alterations



Two Most Common Genetic Polymorphisms of Folate

- MTHFR enzyme is responsible for creating the circulating form of folate
- *Methyltetrahydrofolate reductase mutations*
 - C677T (Cytosine>>Thymine)
 - A1298C (Adenine>>Cytosine)



MTHFR C677T (C>T) Allele

- 21% of US Latinos
 - 20% of Italians
 - 13% of British Caucasians
 - 11% of Irish Caucasians
 - 10-14% of other Caucasians
 - 11% of Asians
 - 8% of German Caucasians
 - <1% of African Americans
- Schneider, 2007



MTHFR C677T (C>T) Allele

- Homocysteine levels may be ↑
- Increased risk of arsenic-related cancers
- Increased risk of heart disease; ↑ cholesterol
- ↑ Diabetes and insulin resistance
- ↑ Inflammatory bowel disease
- Autism: MTHFR levels only 40-50% of normal
- Anencephaly and spina bifida; more often in males.

NOTE: Rates of spina bifida are highest in Ireland and Wales and their descendents around the world.

▪ Schneider, 2007

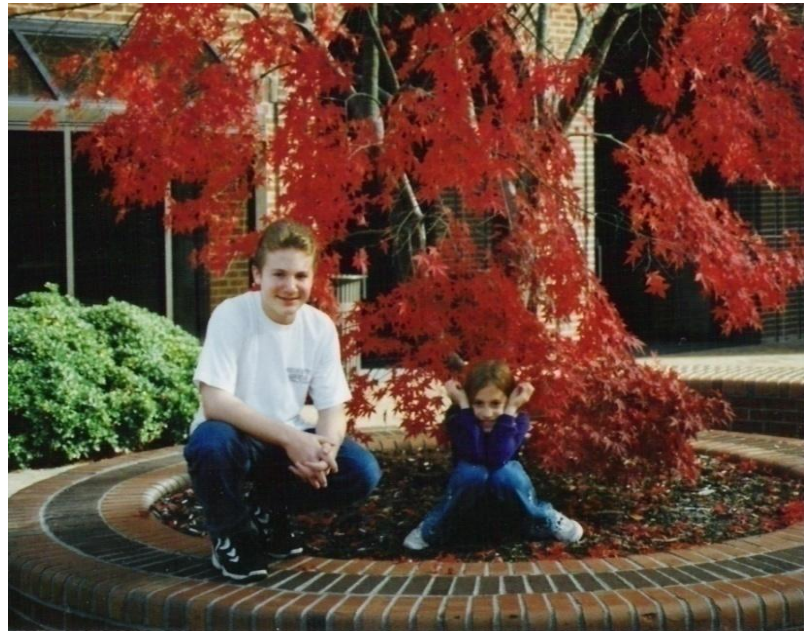
MTHFR A1298C (A>C) Allele

- Not relevant for heart disease risk
- Relevant in autism, pediatric stroke, schizophrenia
- Facilitates conversion of dihydrobiopterin (BH₂) to tetrahydrobiopterin (BH₄,)
 1. production of serotonin
 2. neutralization of ammoniathrough the action of dihydrofolate reductase.

Schneider, 2007

Why did I start studying the issue?

■ *My Family Tree...*



Putting the Puzzle Together...

I was tested for MTFHR:

altered allele (A1298C);
Normal C677T.

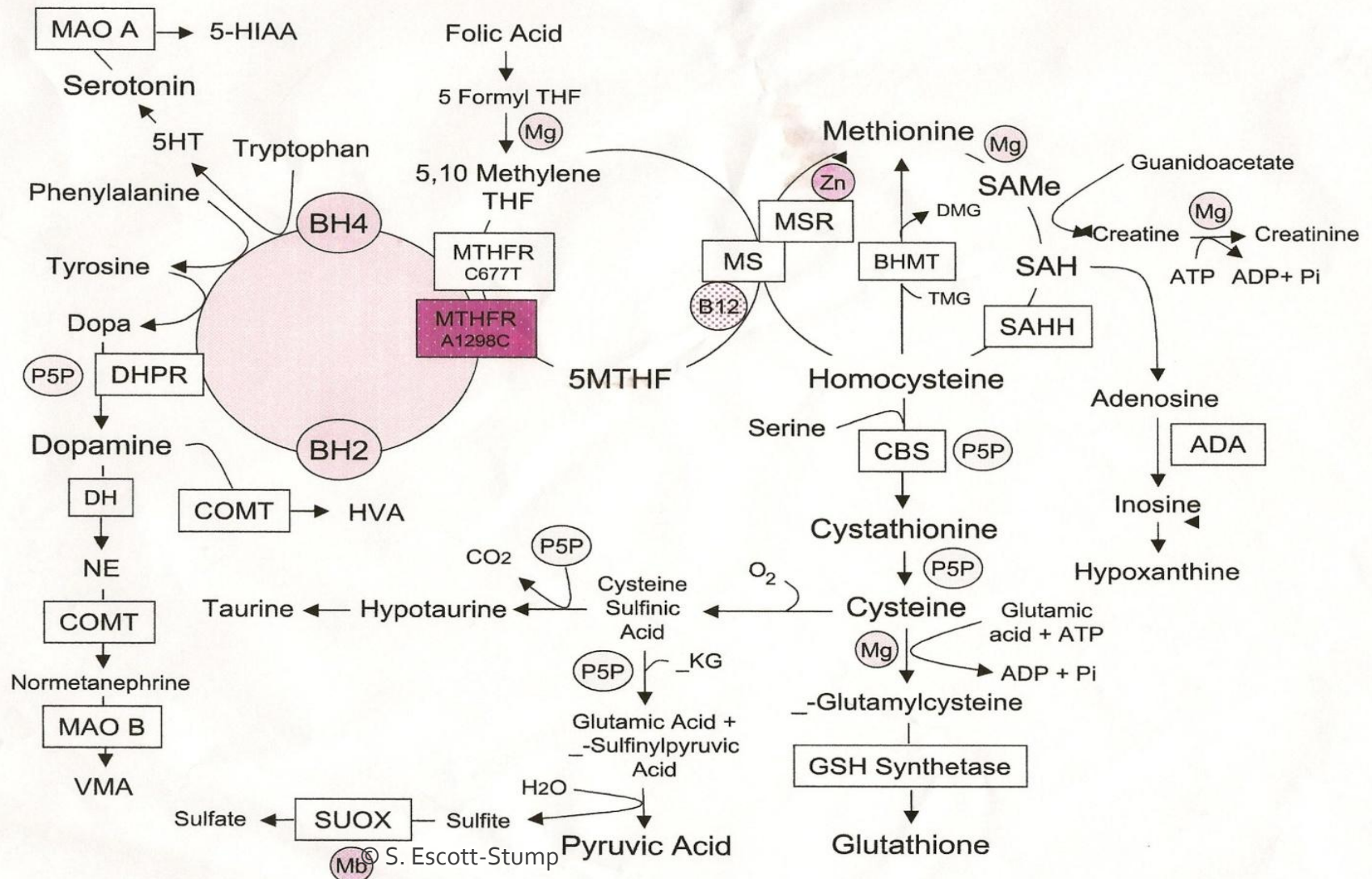
My mother has the same
allele. She has gait
abnormalities; essential
HTN.

My daughter has **two** copies
of the A1298C (from both
parents); she has ulcerative
colitis (proctitis, 6 inches.)

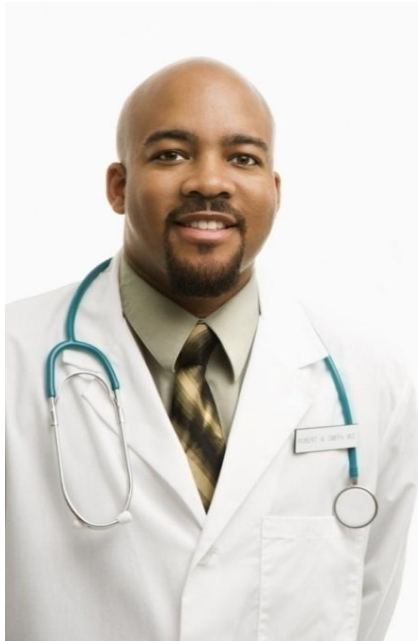
- My son also has **two** copies
of the A1298C allele; he has
spina bifida occulta and
schizophrenia.



The MTHFR Alleles



Literature Review



Crossing the Blood Brain Barrier

- *Unmetabolized folic acid:*
 - unable to cross the blood brain barrier (BBB)
 - may become bound to receptors (folate binding proteins) on the membrane, thereby blocking the absorption of L-methylfolate.

* Zajecka, 2007 (Rush)

Note the Competition!

- Dietary folate and folic acid supplements compete with L-methylfolate at the blood-brain barrier



Disorder Implications

- MTHFR
- Homocysteine
- Other nutrients

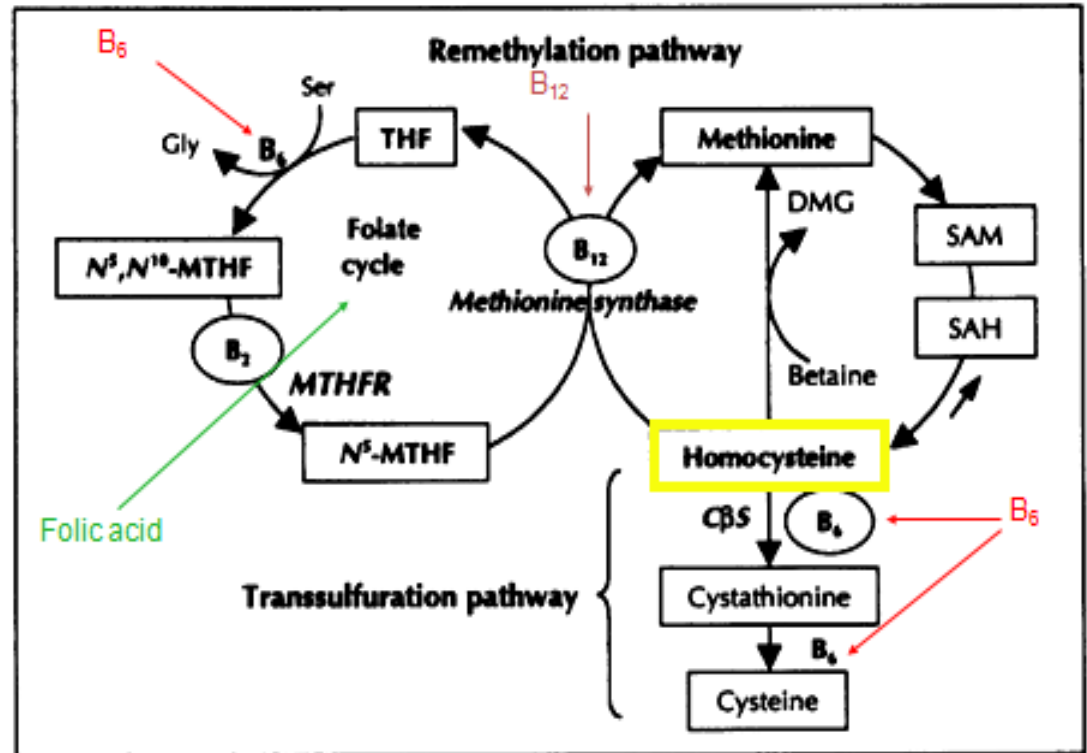
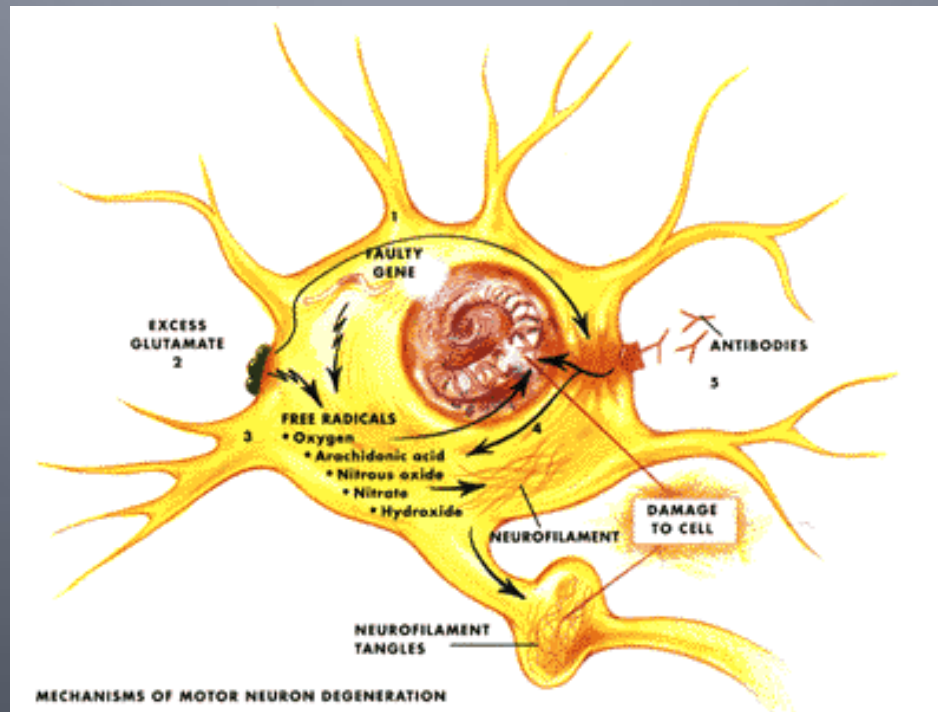


Fig. 1: Biochemical pathways of homocysteine metabolism. Ser = serine; Gly = glycine; MTHF = methylenetetrahydrofolate; MTHFR = N^5, N^{10} -methylenetetrahydrofolate reductase; THF = tetrahydrofolate; SAM = S-adenosylmethionine; SAH = S-adenosylhomocysteine; DMG = dimethylglycine; CBS = cystathionine- β -synthase.

Amyotrophic Lateral Sclerosis

ALS and Homocysteine



ALS and Homocysteine

- Study involving 62 ALS patients and 88 age-matched controls
 - Homocysteine (Hcy) may be directly involved in the damage of motor neurons and in several pathways implicated in amyotrophic lateral sclerosis (ALS) pathogenesis.
- *SO WHAT?* Higher Hcy may be linked to faster progression of ALS.
 - *Zoccolella et al, 2008.*

Autism

Methylation??



Genes Studied in Autism

- Methionine Synthase (MS)
- Methionine Synthase Reductase (MSR)
- **MTHFR C677T and A1298C**
- Cystathionine -B-Synthase (CBS)
- Catecholamine-O-Methyltransferase (COMT)
- Adenosine Deaminase (ADA)
- MET Receptor Tyrosine Kinase (MET)
- Reelin
- Paraoxonase (PON₁)

■ Schneider, 2007

Folate and Autism

- Plasma methionine and the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH), an indicator of methylation capacity: significantly  in autistic children .
- Relevant genes:
 1. reduced folate carrier (RFC 80G > A)
 2. transcobalamin II (TCN2 776G > C)
 3. catechol-O-methyltransferase (COMT 472G > A)
 4. methylenetetrahydrofolate reductase (MTHFR C677 T and A1298C)
 5. glutathione-S-transferase (GST M1).
- *SO WHAT?* Increased vulnerability to oxidative stress (endogenous or environmental) may contribute to the development and clinical manifestations of autism
 - James 2007

Cerebral Folate Deficiency

- A 6-year-old girl with developmental delay, psychomotor regression, seizures, mental retardation, and autistic features associated with low CSF levels of 5-methyltetrahydrofolate.
 - Folate and B12 levels were normal in peripheral tissues, suggesting cerebral folate deficiency.
 - Treatment with folinic acid corrected CSF abnormalities and improved motor skills.
- *SO WHAT?* Cerebral folate deficiency may be involved in autism.

Moretti et al, 2005

Environmental Toxins in Autism



- Oxidative stress
- Total heavy metal, chemical, viral burden
- Streptococcal infection
- Gender/age/timing
- Nutritional status
- Genetic capacity to clear toxins or repair damage

Immune Issues in Autism

- IgA deficiency is common
- NK cell # and function is decreased
- TNF is produced in response to infection or exposure to casein, gluten, or soy
- Antibodies against serotonin receptors have been found



BONE DISEASE

Elevated Homocysteine



Homocysteine (tHcy) and Bone Turnover



- Cysteine (Cys) is formed from tHcy
 - Involved in bone metabolism via incorporation into collagen and cysteine protease enzymes.
 - Thiols: metabolically linked with homocysteine (tHcy)
- *So what?* Hyperhomocysteinemia is a risk factor for developing osteoporosis.
 - Baines et al, 2007

CANCER

Genetics and Gene Expression



Epigenetics: Regulation of Gene Expression

- Epigenetics in cancer pathogenesis:
Normally, oncogenes are silent because of DNA methylation.
- *SO WHAT?* Loss of methylation can induce the aberrant expression of oncogenes, leading to cancer pathogenesis.



Epigenetics, continued



- Known mechanisms of epigenetic change:
 - DNA methylation
 - Methylation/acetylation of histone proteins bound to chromosomal DNA at specific locations
 - van Vliet et al, 2007
- Medications: [HDAC inhibitors](#) and [DNA methyltransferase inhibitors](#) can re-regulate the epigenetic signaling in the cancer cell.

Folate and Colon Cancer

- Folate helps prevent changes to DNA that may lead to cancer.
- However, with folate added to grain foods, there has been a reduction in neural tube defects, but an **increase in colon cancer**...Is there a relationship???
- “Be mindful that more folate is not better in all circumstances.”
Ulrich, 2007
- *SO WHAT?* Individuals with the polymorphism need the **right form of L-methyfolate**.

Alcohol + Methylation of Folate

- Alcohol redirects use of folate toward serine synthesis ; interferes with thymidine synthesis, a critical function of methylenetetrahydrofolate.
- Inhibition of methionine synthase also creates a "methylfolate trap," as in that which occurs in vitamin B12 deficiency.
- *SO WHAT?* Chronic alcohol ingestion produces hypomethylation of DNA in the colonic mucosa, a feature of early colorectal neoplasia.
 - *Mason and Choi, 2005.*



MTHFR Polymorphisms in Colorectal Cancer

- Individuals having at least one mutant allele have a **higher risk of colorectal cancer**
 - distant metastases more often



So what? There is increased colorectal cancer prevalence in patients with one of the MTHFR gene mutations.

Osian et al, 2007

- Inadequacies of other 1-carbon vitamins (riboflavin , B6 and B12) may **amplify aberrations of the p53 gene** induced by folate depletion alone, which may lead to increases in colorectal cancer.
 - Liu et al, 2008.

MTHFR and Breast Cancer



MTHFR C677T and A1298C variant alleles were associated with **decreased** risk for breast cancer.

- Heterozygote and homozygote variants (C677C + TT and A1298C + CC) had **reduced risk among women with lower plasma folate levels.**

SO WHAT? These results support for the important role of folate metabolism in breast tumorigenesis.

- Chou et al, 2006

MTHFR Polymorphisms in Gastric Cancer (GC)



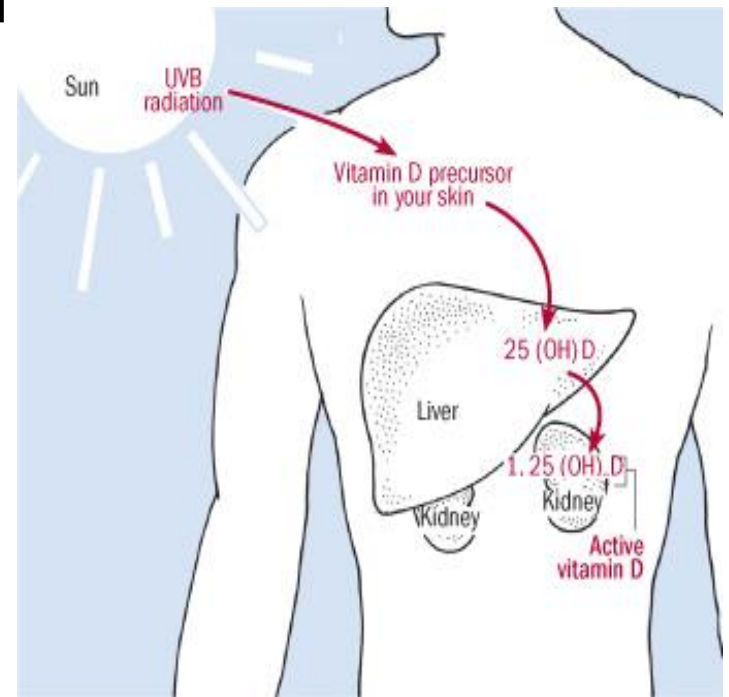
- Meta-analysis: influence of MTHFR C677T and A1298C polymorphisms on gastric cancer
 - 27% increase with the C677T allele compared with the A1298C allele.
 - *SO WHAT?* There is evidence of association between MTHFR polymorphisms and GC, mainly in East Asians.
 - Zintzaras, 2006a



Don't Forget Vitamin D₃...!

- Vitamin D deficiency is linked to colon cancer and more recently, to breast cancer.
 - Conflicting evidence with other forms of cancer.

*Associated with depression,
multiple sclerosis*



Summary: Diet and Cancer Risk

- Food components that increase or depress gene expression (**nutritional transcription**) may account for variable response to foods.



- ***So what?*** Variation in DNA methylation patterns and other epigenomic events influence the biological response to food components and vice versa.

CARDIOVASCULAR DISEASE

Homocysteine and MTHFR



Essential Hypertension

- Essential hypertension (EH) and cardiovascular disease:
 - influenced by multiple genes.
 - C677T genotypes: Homocysteine level is higher in TT genotypes in CAD patients compared with CC and CT genotypes ($p < 0.01$).
- *SO WHAT?* MTHFR gene polymorphism is an independent risk factor for EH but not for CAD.



Elevated Homocysteine (tHcy)

- Elevated tHcy levels: increased incidence of stroke (thrombosis), cardiovascular disease, MI and other cardiac effects.
- *SO WHAT?* tHcy > 6 $\mu\text{mol/L}$ = a warning sign.



Folic Acid and tHcy: NORVIT Trial

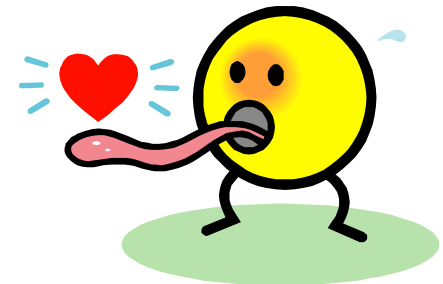


- Giving folic acid to reduce levels of homocysteine does not result in clinical benefit
 - In combination with B₁₂ may even increase some cardiovascular risks.
 - The NORVIT trial: folic acid supplements may do more harm than good.
http://www.rxpgnews.com/research/cardiology/myocardialinfarction/printer_2298.shtml/
- *So what?* Test for alleles; trials using L-methylfolate are needed.

Premature Cardiovascular Disease

- In deficit of MTHFR, cardiovascular risk is increased with hyperhomocysteinemia and hypomethionemia.
- C677T mutation :  Height, weight, body mass index, obesity index, arm circumference, fat mass, fat distribution, carotid IMT, homocysteine
 Folic acid levels than the normal genotype group.
- *SO WHAT?* MTHFR genotype may be useful in predicting the development of premature coronary artery disease in hypertensive adolescents.

- Koo et al, 2007



DEPRESSION

Genes and L-methylfolate



Depression

- Major depressive disorder (MDD)
 - High mortality
 - Lifetime risk of 10-25% in women, 5-12% in men
- Current treatments
 - SSRIs
 - Tricyclic antidepressants

MAJORITY OF PATIENTS WITH MDD never achieve symptom remission with first medication treatment



Folate in Depression

Only a minority of patients achieve full remission with antidepressants. Augmentation can improve the effects, but safety and tolerability are a concern.

So what?

Folate may further reduce symptoms in patients with depression when used in conjunction with an antidepressant.

- Safe and well tolerated.
- Typically be used in patients with low plasma or red blood cell folate levels.

■ Fava 2007



Emerging Augmentation Therapies for Depression

OTHER MEDS

- Dopaminergic Agents
- Pergolide
- Amantadine
- Pramipexole
- Stimulants
- Methylphenidate
- Amphetamines
- Modafinil
- Anticonvulsant
- Lamotrigine



OTHER TREATMENTS

Opioids

Dehydroepiandrosterone

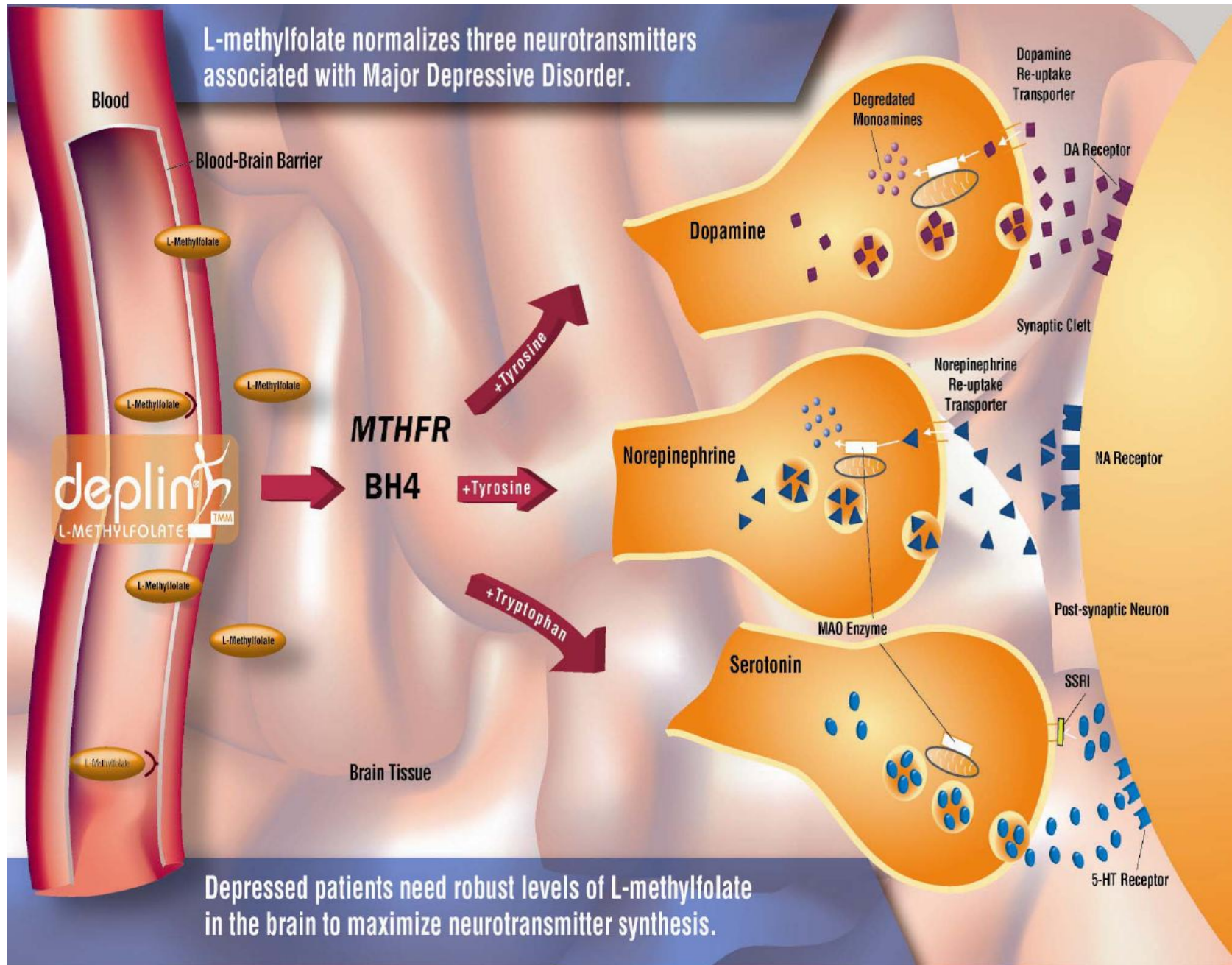
Methylfolate

Omega-3 fatty acids

- Shelton 2007

Vitamin D₃

L-methylfolate normalizes three neurotransmitters associated with Major Depressive Disorder.

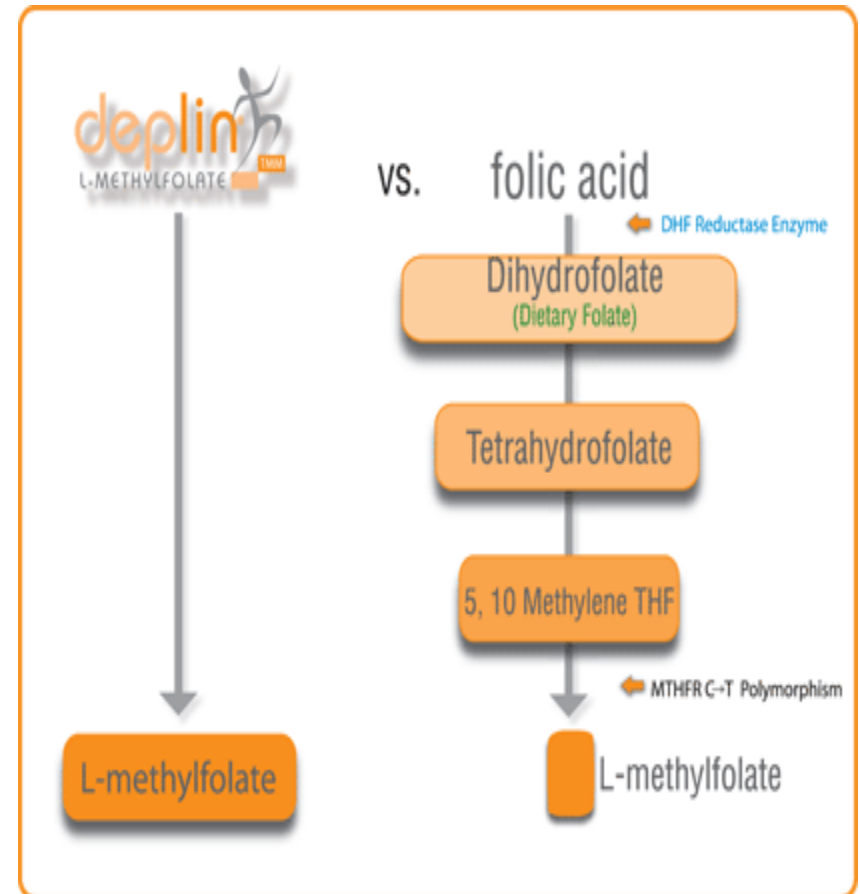


Depressed patients need robust levels of L-methylfolate in the brain to maximize neurotransmitter synthesis.

Link of severity of depressive episodes

Lower red blood cell folate levels – longer and more severe the episodes

- PamLabs, 2007
- After 4- week trial of Deplin, if patients are not feeling better, some doctors use **15 mg/day** instead of 7.5 mg
 - Zajecka (Rush)



Trials of L-methylfolate vs Folic Acid

- L-methylfolate 7.5 mg effective in managing depressive episodes (Deplin)



- *L-methylfolate UNMASKS vitamin B-12 anemia*

- Folic acid 52.5 mg equivalent from diet or supplements



- *Folic acid MASKS B-12 anemia*

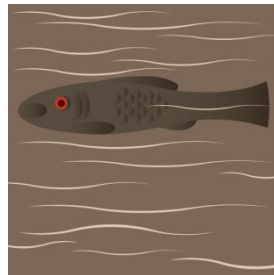
What about...

Other Nutrients???



Essential Fatty Acids

- Essential fatty acids (EFAs): cis-linoleic acid (LA) and alpha-linolenic acid (ALA) are essential for humans.
- Deficiency ?
 - rare in humans
 - easily available in diet.
- EFAs are metabolized to their respective long-chain metabolites:
 - dihomogamma-linolenic acid (DGLA), and arachidonic acid (AA) from LA
 - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA.



- Das, 2006

Inflammation vs. Anti-inflammation

Omega-6 Pathway



Alpha-Linoleic Acid



Gamma-Linoleic Acid



Arachidonic Acid



Docosapentaenoic Acid



Pro-inflammatory

Omega-3 Pathway



Alpha-Linolenic Acid



Stearidonic Acid



Eicosapentanoic Acid



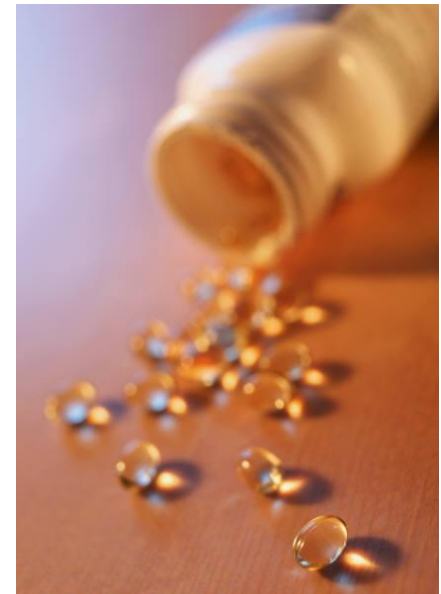
Docosahexaenoic Acid



Anti-inflammatory

Omega 3 Fatty Acids

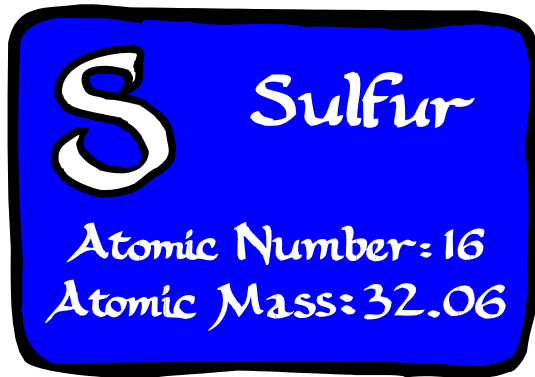
- Role: reduce the Inflammatory process



EFA Implications

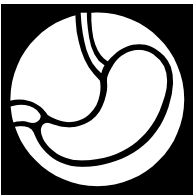
- Precursors to prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), lipoxins (LXs) and resolvins.
- *So what?* EFAs and their derivatives have significant clinical implications in obesity, hypertension, diabetes mellitus, coronary heart disease, alcoholism, schizophrenia, Alzheimer's disease, atherosclerosis, and cancer.
 - Das, 2006

Sulfur Amino Acids



Sulfur Amino Acid Metabolism

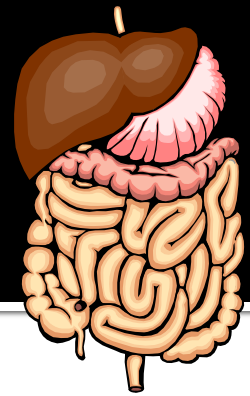
- Sulfur amino acid metabolism in gastrointestinal tissues may be linked to human health and gut disease.
- *So what?* The gastrointestinal tract metabolizes 20% of dietary methionine; metabolic fate is transmethylation to homocysteine and transsulfuration to cysteine.
 - Burrin and Stoll, 2007



Sulfur Amino Acid Metabolism

- The GI tract is a site of net homocysteine release.
- Production of homocysteine within the intestinal mucosa may contribute to the inflammatory response and endothelial cell dysfunction in patients with inflammatory bowel disease.
- *So what?* Availability of S-adenosylmethionine (SAM) as a precursor for methylation reactions and polyamines plays a key role in epigenetic DNA methylation, gene expression and colon carcinogenesis.
 - Burrin and Stoll, 2007

Folate and Cysteine



- Cysteine derived from the diet and methionine transsulfuration is a functional constituent of antioxidant systems .
 - Cysteine impacts redox status that regulate epithelial intracellular signaling, proliferation and survival.
- *So what? Need further studies:*
 - how local production of homocysteine, S-adenosylmethionine and antioxidants contributes to the development of gastrointestinal diseases
 - If dietary intervention with folate and cysteine is an efficacious approach to prevention and treatment.
- Burrin and Stoll, 2007

Sulfa Allergy???

dihydropteroate diphosphate + p-aminobenzoic acid (PABA)

dihydropteroate synthetase x ← **sulfonamides**

dihydropteroic acid

↓

dihydrofolic acid

dihydrofolate reductase x ← **trimethoprim**

tetrahydrofolic acid

DEMENTIA

Gene Expression, Homocysteine, N-acetylcysteine, Carnitine



NAC, Carnitine, SAM

Aggressive behavior, depression, and psychosis occur in Alzheimer's disease from imbalanced neurotransmitters.

N-acetyl cysteine (NAC): antioxidant and glutathione precursor that protects against A beta neurotoxicity

Acetyl-L-carnitine: raises ATP levels, protects mitochondria, and buffers A beta neurotoxicity

S-adenosylmethionine (SAM): facilitates glutathione usage and maintains acetylcholine levels

- *So what?* Administration of NAC, carnitine and SAM reduce aggressiveness in mouse models of aging and neurodegeneration.

Folate and Dementia

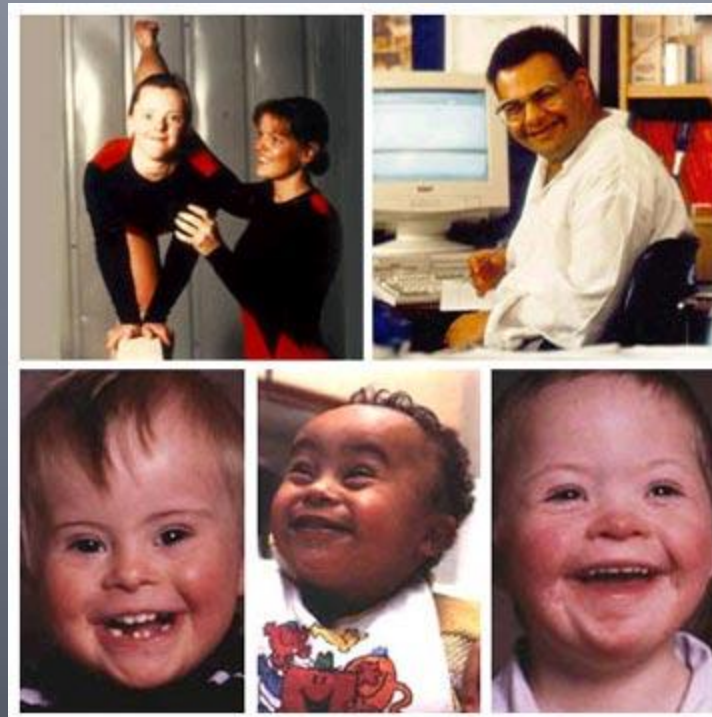
- Folate deficiencies:
 - increased risk of depression, poorer antidepressant treatment outcomes, increased risk of **cognitive impairment and dementia**.
- 1996, FDA mandated fortification of grain products with folic acid...vast reductions in folate deficiency.
- *Folate deficiencies may also be caused by improper absorption and utilization from genetic polymorphisms.*

So what? Supplementation with the active form of folate, methyltetrahydrofolate may be effective in the prevention and treatment of both depression and dementia.

- Mischoulon and Raab , 2007

Down Syndrome

Folate Alleles and Homocysteine



Down Syndrome

- Maternal risk for Down syndrome (DS):
 - Presence of 3+ polymorphic alleles increased the risk 1.74 times.
 - Elevated maternal risk for DS was also observed when plasma Hcy concentration > 4.99 micromol/L.
 - *So what? MTHFR and homocysteine markers are important*
 - Biselli et al, 2008

INFLAMMATORY BOWEL DISEASE

Gene Expression, Homocysteine



Homocysteine and Inflammatory Bowel Disease

- Moderate hyperhomocysteinemia is a trait commonly associated with IBD.
 - Consider folate and vitamin B12 deprivation and MTHFR polymorphisms
- *So what?* Screening and treating folate and vitamin B(12) deficiencies in IBD patients, especially
 - active disease
 - history of intestinal resection
 - treatment with methotrexate
 - Peyrin-Biroulet et al, 2007

NEURAL TUBE DEFECTS

Folate Receptor Deficiencies

If taken daily before becoming pregnant, folic acid can reduce the risk of an NTD affected pregnancy by up to 70%.

What about the other 30%???

Anencephaly & Spina Bifida



- **Anencephaly** : upper end of the neural tube fails to close. Brain either never completely develops or is totally absent.
- **Prognosis:** Spontaneous loss, Stillborn, Neonatal death

SPINA BIFIDA OCCURS BY THE 28TH DAY OF GESTATION

PHOTO: DAYS 23-28 WHEN THE LOWER END OF THE NEURAL TUBE FAILS TO CLOSE.



MTHFR Polymorphism



- Etiology of neural tube defects (NTDs) is multifactorial: environmental + genetic
- Folate supplementation prevents the majority of NTDs.
- *So what?* The MTHFR polymorphism is a genetic risk factor where diets deficient in folate do not influence the incidence or severity of NTDs.
 - Li et al, 2006

Folate and Neural Tube Defects

- Different populations provide different results:
 - Folate pathway genes + the environmental cofactor: **maternal folic acid supplementation.**
 - **Betaine-homocysteine methyltransferase** (BHMT rs3733890) was significantly associated. MTHFR was not a major risk factor in the population of this study.
- *So what?* Need to investigate **folate and methionine cycle genes for SNP genotyping** to identify variants and the effects of folate in the diet.
 - Boyle et al, 2007



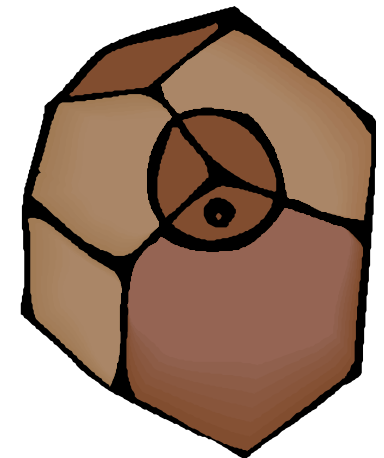
Betaine and Methylation

- Betaine: a methyl donor for transmethylation in the methionine cycle—primarily in the liver and kidney
- Widely distributed in animals, plants, and microorganisms.
 - Richest sources: seafood, wheat germ or bran, and spinach.



Betaine and Hypomethylation

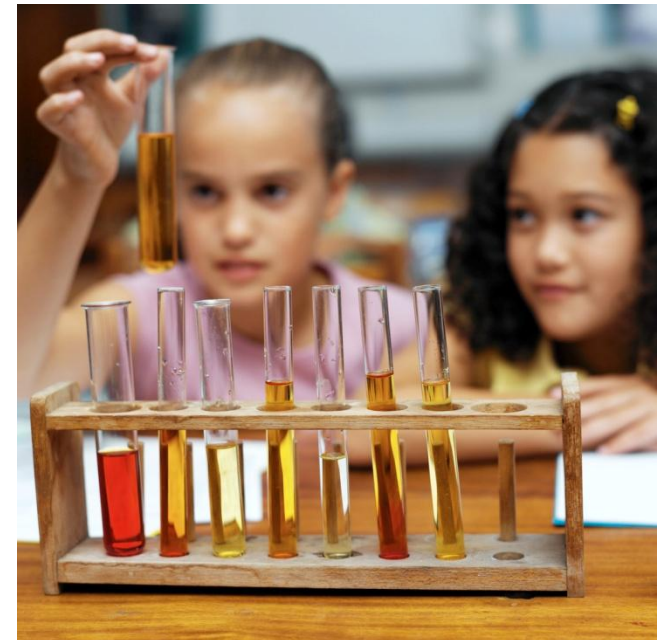
- Inadequate dietary intake of methyl groups leads to hypomethylation
 - disturbed hepatic **methionine** metabolism
 -  plasma **homocysteine** concentrations
 -  **S-adenosylmethionine** concentrations
 - inadequate hepatic fat metabolism...leading to **steatosis** and plasma **dyslipidemia**.



Liver Cell

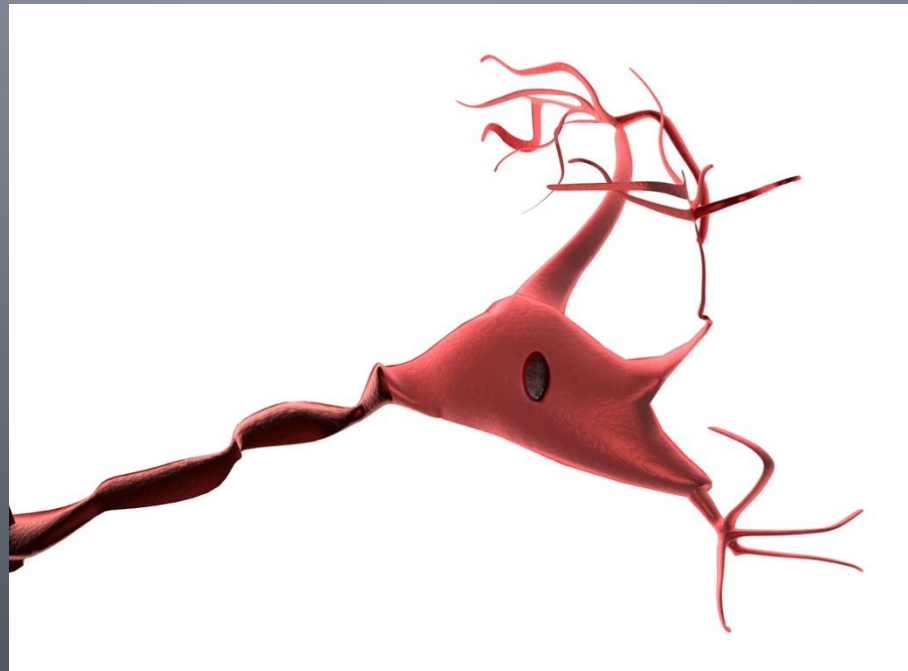
Choline

- Choline: also involved in one-carbon metabolism for methylation of homocysteine to methionine.
- *So what?* Inadequate choline may also contribute to NTD etiologies.
 - Shaw et al, 2004



NEUROPATHY

MTHFR??



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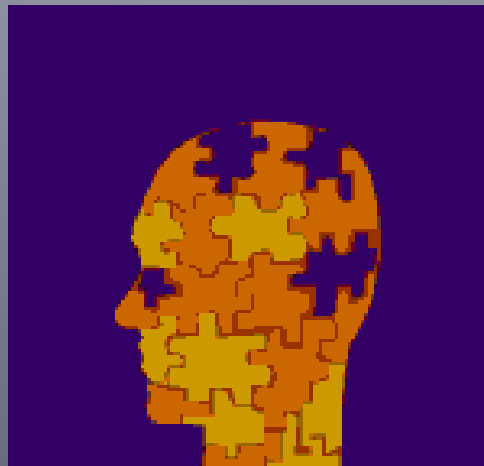
Diabetic Neuropathy



- Meta-analysis: studies investigating the association between **MTHFR C>T polymorphism and diabetic nephropathy (DN)**
 - Significant association in Caucasians and in persons with type 2 diabetes.
 - *So what?* Some evidence of association between MTHFR C677T gene polymorphism and DN; **need further and more rigorous studies.**
 - Zintzaras et al, 2007

PARKINSON'S DISEASE

HOMOCYSTEINE



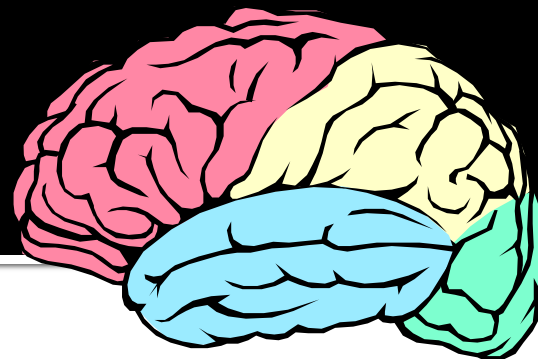
Homocysteine and Parkinson's

- Prospective, population-based cohort study
- 5,920 participants aged 55+
- TT variant of the MTHFR C>T polymorphism is associated with increased risk for Parkinson's disease in smokers.

So what? Increased plasma levels of homocysteine through direct neurotoxic effects might accelerate the selective dopaminergic cell death underlying Parkinson's disease. Homocysteine plays a role in the pathogenesis of PD.

- De Lau et al, 2005

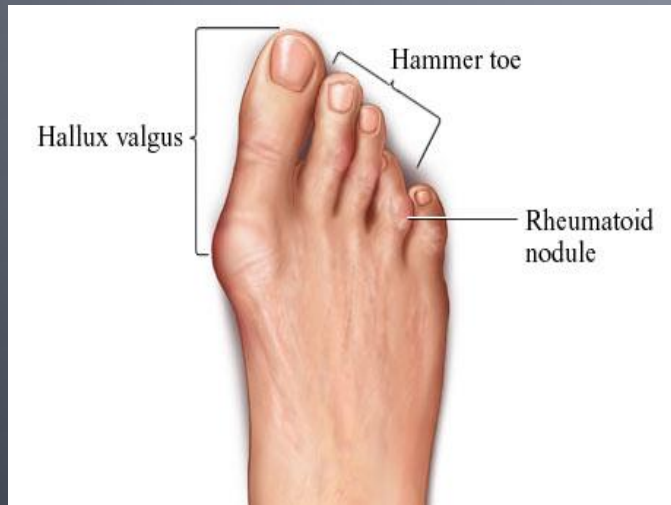
MTHFR C677T



- MTHFR - C677T genotype and levodopa treatment may give rise to elevated serum homocysteine levels in Parkinsonian patients.
- *SO WHAT?* MTHFR C677T genotype is a significant factor for hyperhomocysteinemia in patients with PD, levodopa-untreated and even more in levodopa-treated PD patients.
 - Todorovic et al, 2006

Rheumatoid Arthritis

Methotrexate

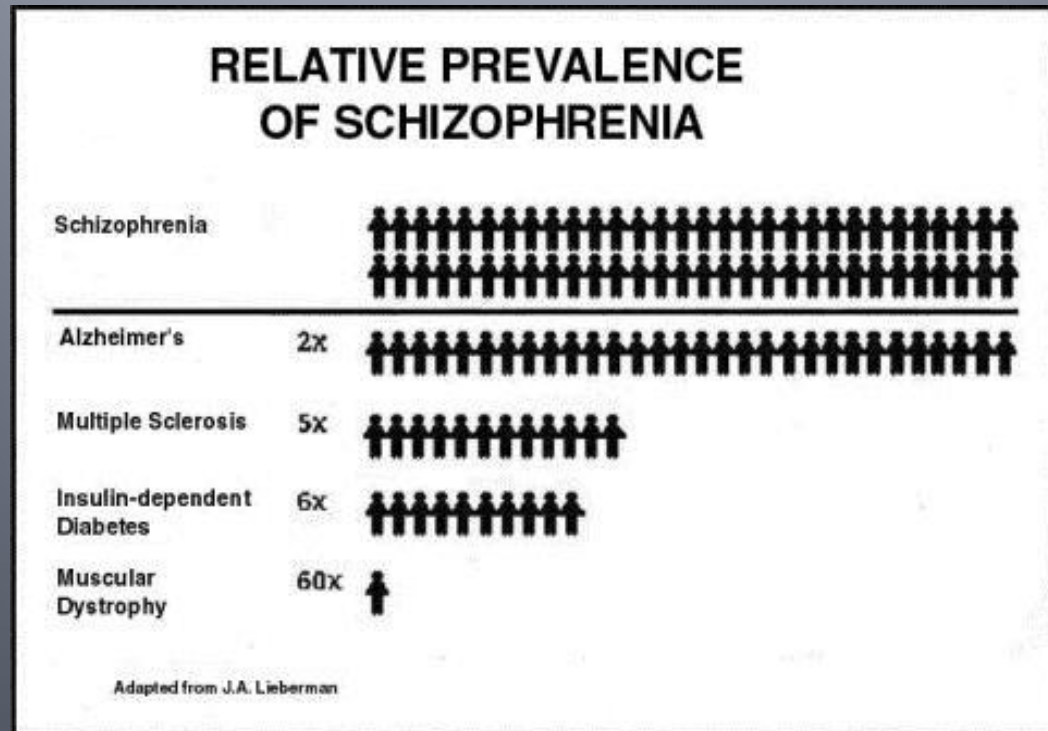


Rheumatoid Arthritis

- Methotrexate (MTX):
used in Rx of
rheumatoid arthritis
(RA).
- MTHFR A1298C
polymorphism
protects against
overall MTX toxicity
- *So what?* Genetic
polymorphisms in the
folate metabolic
pathway and MTX
transporters modify
toxicity but not efficacy
of MTX
 - Bohanec Grabar et al, 2008

SCHIZOPHRENIA (SCZ)

MTHFR, Reelin, Homocysteine, SAM



MTHFR C677T

- Meta-analysis: association between polymorphisms, including MTHFR C>T and A>C, and unipolar depression, anxiety disorders, bipolar disorder, and schizophrenia.
- *So what?* MTHFR C>T: more related to depression, schizophrenia, and bipolar disorder. Consider use of folate in treatment and prevention.

- Gilbody et al, 2007



Folate, Cobalamin, Homocysteine and MTHFR

- PubMed: association between folate, cobalamin, homocysteine, and MTHFR polymorphisms and schizophrenia and depression.
 - Folate supplementation - indicated in pregnancy but may exacerbate the effects of cobalamin deficiency.
 - Correct folate and cobalamin deficiencies
 - Cobalamin supplementation is probably not helpful.



So what? Check homocysteine and methylmalonic levels.

- Screen for MTHFR polymorphisms
- SAME may prove to be a useful antidepressant.
 - Frankenburg, 2007

Folate in SCZ



- 200 outpatients with SCZ: Positive and Negative Syndrome Scale (PANSS) - tested for MTHFR genotype, serum folate, homocysteine
 - A1298C: contributed only weakly to positive symptoms
 - C677T allele: associated with negative symptom severity of (depression, dysthymia.) T allele protected against positive symptoms (hallucinations, hearing voices.)
- ***So what?*** Interaction of low serum folate with C677T-variant MTHFR may induce negative symptoms.
Roffman et al, 2007

C677T and A1298C in Schizophrenia, Bipolar disorder and Depression

- Meta-analysis: schizophrenia, bipolar disorder and depression and C677T & A1298C polymorphisms
 - Marginally significant for A1298C polymorphism
 - No significant association between C677T polymorphisms and the risk of developing bipolar disorder *except in the east Asian population.*



So what? East Asians have a greater genetic risk from the MTHFR gene in developing schizophrenia and depression. The genetic effects in bipolar disorder and depression are different.

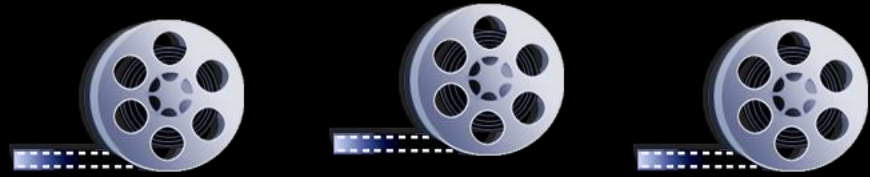
Zintzaras, 2006b

Metabolic Syndrome

-  MTHFR activity and  homocysteinemia increase risk of cardiovascular disease
- **Metabolic syndrome and insulin resistance** incidence in SCZ: 2-4x higher than the general population.
 - *So what?* C677T allele carriers are at greater risk for insulin resistance with increasing central adiposity, independent of age, gender, BMI, or metabolic syndrome diagnosis.
 - Ellingrod et al, 2008



Reelin



- Reelin:
 - secretory protease that plays major roles in neurodevelopment and synaptic plasticity
 - role in the pathogenesis of schizophrenia
 - Reelin-VLDLR/ApoER2 signaling pathway
- *So what?* Peripheral VLDLR mRNA levels may serve as a reliable peripheral biological marker of schizophrenia.
 - Suzuki et al, 2008

Reelin and Infections



REELIN

- Reelin is *hyper methylated in SCZ*. Methyl donors worsen symptoms in individuals with schizophrenia or bipolar disorder
- Some forms of autism may be related to SCZ or bipolar disorder
 - Schneider, 2007

INFECTIONS

- Viral infections reduce Reelin levels.
- *SO WHAT?*
 - 2nd trimester influenza may trigger schizophrenia.
 - Rubella, measles, herpes, and other viral infections can trigger autism.

Renal - Hemodialysis

Reducing Inflammation



5-MTHF in lowering CRP

- Randomized, prospective study with 341 hemodialysis patients:
 - Two groups: 1) received 50 mg of 5-MTHF intravenously; 2) received 5 mg/day folic acid. Both received vitamins B6 and B12 intravenously.
 - High-dose IV supplementation with 5-MTHF reduced inflammation and improved survival.
- *SO WHAT?* Intravenous 5-MTHF seems to improve survival in HD patients independent from homocysteine lowering, especially by lowering CRP.
 - Cianciolo et al, 2008

DRUGS THAT INTERFERE WITH FOLATE METABOLISM



Drugs that Interfere with Folate Metabolism

- Dihydrofolate reductase inhibitors

- pyrimethamine
- trimethoprim

- Oral contraceptives
- Anticonvulsants
- Alcohol and tobacco
- Antacids
- Aspirin

- Sulfonamides

(competitive inhibitors of para-aminobenzoic acid in the reactions of dihydropteroate synthetase.)

- Anticancer drug methotrexate (inhibits both folate reductase and dihydrofolate reductase).

Methotrexate for other conditions

- Rheumatoid arthritis, lupus, psoriasis, asthma, sarcoidosis, primary biliary cirrhosis, inflammatory bowel disease
- Low doses of methotrexate can deplete folate stores and cause side effects that are similar to folate deficiency.
- Both high folate diets and supplemental folic acid may help reduce the toxic side effects of low dose methotrexate without decreasing its effectiveness.

So what? Consider the need for an L-methylfolate supplement in individuals with MTHFR alleles.

Folinic Acid "Rescue"

- Folinic acid: a form of folate "rescues" or reverse toxic effects of methotrexate.
- Folic acid supplements are NOT the same as Folinic acid supplements.
- *So what?* Follow medical advice on the use of folic or folinic acid supplements when methotrexate is prescribed.



Available Forms of L-Methylfolate



Metagenics

Fola-Pro® (800 mcg L-5-methylfolate)

PamLabs – prescription only

- Cerefolin ® (5.6 mg L-methylfolate, 2 mg methylcobalamin, 600 mg N-acetylcysteine)
- Deplin ® (7.5 mg L-methylfolate)
- Metanx ® (2.8 mg L-methylfolate; 2 mg methylcobalamin; 25 mg pyridoxal 5-phosphate)



Folic Acid Fortification

- *MTHFR C-->T polymorphism:*
 - significant differences in serum folate and homocysteine concentrations in the US population before folic acid fortification.
- NHANES data analysis:
 - Effects of MTHFR C>T on homocysteine concentrations -- reduced by moderate daily folic acid intake.
 - Yang et al, 2008

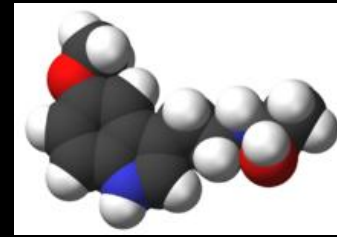


SLEEP DISORDERS

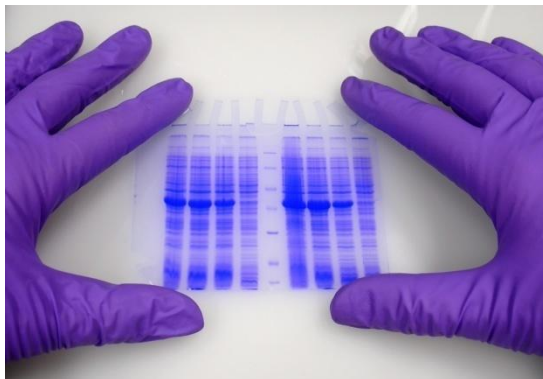
Serotonin-Melatonin-Tryptophan



Melatonin



- Pineal gland, retina, lens , and GI tract
 - Lower amounts in bone marrow cells and skin
- *Dietary **tryptophan** is a precursor*

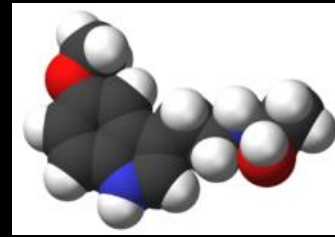


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RESEARCH AREAS:

- Cancer
 - T-cell lymphocytes
- Immune disorders
 - Immunostimulator when taken with calcium
 - May aggravate rheumatoid arthritis
- Sexual dysfunction
 - Inhibits LH and FSH secretion

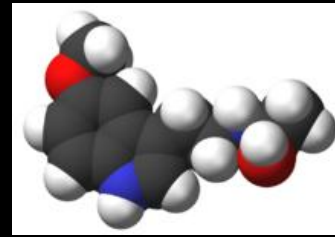
Melatonin



HIGHLIGHTS

- Important for circadian rhythms, including sleep
- Powerful antioxidant
- Regulates leptin
- Production inhibited by light and permitted by darkness
- Treating insomnia
- Protecting nuclear and mitochondrial DNA
 - Easily crosses blood-brain barrier
 - May protect against Parkinson's and Alzheimer's?
 - Levels often lower in Autism
- Lowers leptin levels at night
- Impacted by artificial lighting, especially blue light

Melatonin



OTHER RESEARCH TOPICS

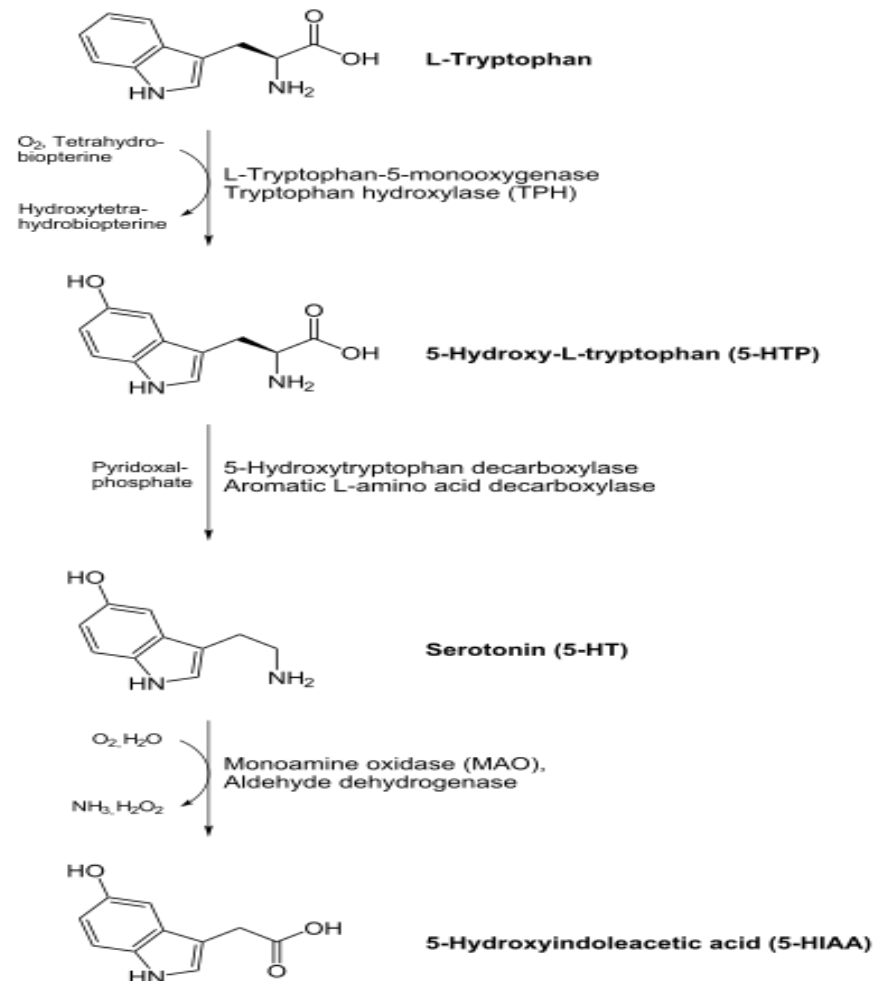
- Migraines
- ADHD
- Seasonal affective disorder
- Depression and bipolar disorders

USE SUPPLEMENTS WITH CAUTION



Serotonin and Sleep

- 5-HT(2A) receptor of serotonin: active role in the regulation of sleep.
- Slow wave sleep (SWS): crucial for restorative, restful sleep.



Melatonin agonist/Selective Serotonin Antagonists

- **Agomelatine**
 - melatonin MT(1) and MT(2) receptor agonist and 5-HT(2c) antagonist properties
 - treating patients with major depression (MDD)
- Rapid onset of action
- Improves the mood of depressed patients because it improves sleep quality.
- *So what?* **Melatonin analogues** are a promising alternative for the treatment of depression.
- Pandi-Perumal et al, 2008.

Implications



Implications

- Some genetic variations arise as a consequence of diet.

SO WHAT?

- Understand the molecular mechanisms underlying gene-nutrient interactions
- Understand their modification by genetic variation
- Provide dietary recommendations and nutritional interventions that optimize individual health.
 - Stover, 2006

Principles of Nutri-genomics

1. Common dietary chemicals alter gene expression and/or genome structure
2. The influence of diet on health depends upon an individual's genetic makeup
3. Genes or normal common variants are regulated by diet
4. Improper diets in some individuals and under some conditions promote some chronic diseases

Kaput, 2005

Most important...



- Dietary interventions based upon knowledge of nutritional requirements, nutritional status, and genotype can be used to **develop individualized nutrition plans that optimize health and prevent or mitigate chronic diseases.**
- *See Castle and DeBusk article in JADA – August 2008.*

Nutrition Diagnosis Example #1

PES Statement:

Problem: **Altered nutrient utilization**

Etiology: related to inability to metabolize dietary and supplemental folic acid

Signs/Symptoms: as evidenced by C>T polymorphism of MTHFR and elevated tHcy levels

Intervention

- Nutrient delivery: L-methylfolate



Nutrition Diagnosis Example #2

- Problem: Excessive intake of folate
- Etiology: Related to excessive use of supplemental folic acid
- Signs and Symptoms: As evidenced by medical Dx of pernicious anemia and use of multi vitamin-mineral supplement 3x daily.
 - *Check out Cena et al, August 2008 article in JADA*

Masking of B-12 Deficiency

- Folic acid will not correct changes in the nervous system that result from vitamin B₁₂ deficiency.
- Permanent nerve damage could theoretically occur if vitamin B₁₂ deficiency is not treated.
- Supplemental folic acid should not exceed the **UL of 1000 mcg (1 mg) per day** to prevent masking symptoms of vitamin B₁₂ deficiency.
- **Older persons should test first for serum B-12 levels before folic acid supplements are given.**

Think about it. It isn't simple!!



What IS YOUR Gut Reaction???

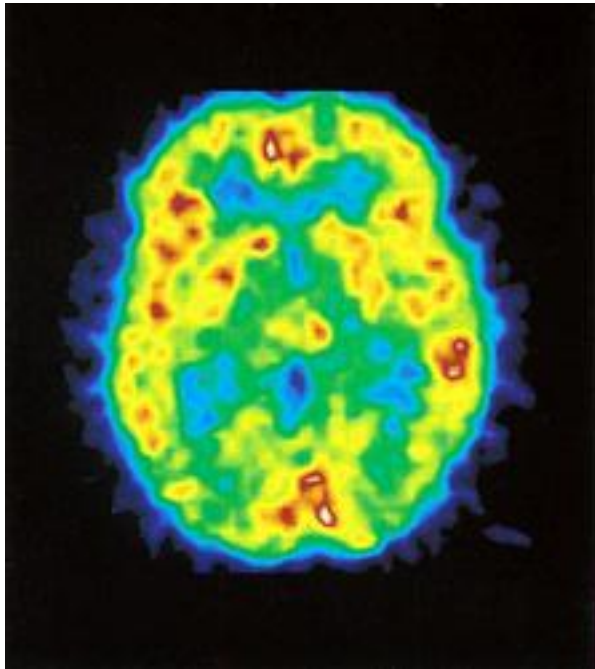


Ask the Right Questions

- To find what you seek in the road of life... “leave no stone unturned.”

Edward Bulwer Lytton





- “If you can't explain it simply, you don't understand it well enough.”– Albert Einstein

Thank you for this privilege

Thank You

Ευχαριστώ

Gracias

Grazie

Díky

Merci

Bedankt

Teşekkürler

Hvala

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