Ageless Neurological System

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- **Academic**
  - Founding president (1978) of Bastyr University, first accredited, natural medicine university
  - Editor-in-Chief: *Integrative Medicine: A Clinician's Journal*
  - *Textbook of Natural Medicine*, 4th ed 2012; *Clinical Pathophysiology*, 2012
- **Policy**
  - Member Medicare Coverage Advisory Committee, 2003-2005
  - Member White House Commission on CAM Policy, 2000-2002
- **Public**
  - *Encyclopedia of Natural Medicine*, 3rd ed 2012 (>1,000,000 copies in 6 languages)
  - *Encyclopedia of Healing Foods*, 2005
- **Example Awards and Recognitions**
  - Natural Products Association: Clinician of the Year, 2012
  - Juror for Roger's Prize: 2009, 2011
  - Institute for Functional Medicine: Linus Pauling Award, 2004
  - American Holistic Medical Association: *Pioneer in Holistic Medicine*, 2003
  - *Natural Health Magazine*: *Leading health educator in the past 30 years*. 2001
  - Alternative Healthcare Management: *1 of the 4 most influential CAM leaders*, 2000
  - *Seattle Magazine*: *1 of the top 20 national intellectual leaders from Seattle*, 1996

Foundations of Health

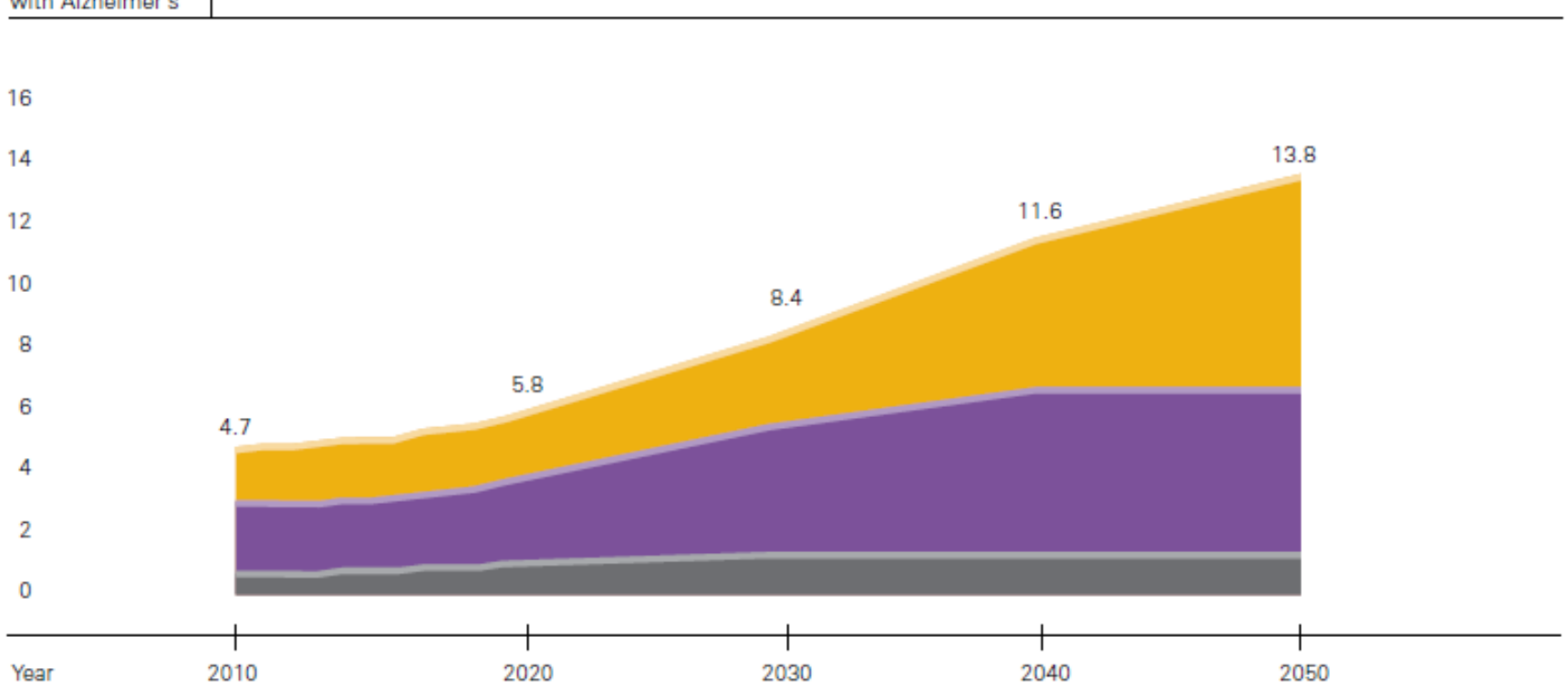
1. Abundant energy production
2. Optimal nutrition and digestion
3. Toxin avoidance and effective detoxification
4. Strong, accurate immune system
5. Balanced inflammatory function
6. Well-regulated endocrine control
7. Sensitive and stable insulin and sugar
8. Strong musculoskeletal system
9. Ageless neurological system
10. Flowing cardiovascular system
11. Rapid regeneration/Longevity
12. Living in harmony with the spirit/life-force

Neurological Health

- Neurodegeneration epidemic
- Clear genetic susceptibility
- Prevalent environmental and lifestyle causes
- Key underlying pathophysiology:
  - Neurotoxin exposure
  - Mitochondrial dysfunction
  - Microglia over-activation
- Research supporting natural medicine:
  - Glutathione!
  - Vitamin D
  - Resveratrol
  - CoQ10
  - PQQ

Neurodegeneration Epidemic

FIGURE 4 PROJECTED NUMBER OF PEOPLE AGE 65 AND OLDER (TOTAL AND BY AGE GROUP) IN THE U.S. POPULATION WITH ALZHEIMER'S DISEASE, 2010 TO 2050



- Expensive, annual cost (2010 dollars):
  - Dementia care: $109 billion
  - Heart disease: $102 billion
  - Cancer: $77 billion

http://www.alz.org/downloads/facts_figures_2013.pdf

Hurd MD, et al. Monetary costs of dementia in the United States. N Engl J Med. 2013 Apr 4;368(14):1326-34

Overview

- The primary types of neurological dysfunction
  1. Neurodegeneration
     - Cognitive dysfunction, Alzheimer's disease, Parkinson's disease
  2. Hyper-excitability
     - Migraine (with aura), Epilepsy
  3. Hypo-excitability
     - Depression, Lethargy
- Fundamentals of a healthy neurological system
  - Optimal mitochondrial function
  - Protection from oxidative stress
  - Avoidance of neurotoxins

Related Diseases

ADHD
ALS
Alzheimer's disease
Cancer
Cognitive impairment
Dementia
Depression
Dizziness
Emotional lability
Epilepsy
Fatigue
Huntington's disease
Lethargy
Loss of sense of taste & smell
Memory loss
Migraine headache
Multiple sclerosis
Parkinson's disease
SAD (seasonal affective disorder)

1. Neurological Degeneration

- Degeneration
  - Loss in number of neurons
  - Decreased function of neurons
  - Damaged interconnections
- Signs and symptoms
  - Memory loss
  - Cognitive impairment
  - Loss of taste and smell
- Diseases
  - Alzheimer's
  - Parkinson's
  - Huntington's
  - ALS
  - Dementia
  - Multiple sclerosis

Neurological Degeneration: Causes

Basic Mechanisms

- Mitochondrial damage
- Mis-folded proteins
- Inflammation
- Oxidative stress

Common Etiologies

- Psychological stress
- Glucocorticoids
- Hypoxia
- APOE e4 allele
- Lack of sleep
- Sugar dysregulation
- Animal product consumption?
- Hyperhomocysteinemia
- Pesticides
- Mercury

Microglia Activation Central to Damage

- Resident macrophages of the brain and spinal cord
- Main form of active immune defense in the central nervous system
- Scavenging the CNS for plaques, damaged neurons, and infectious agents
- Extremely sensitive to even small pathological changes in the CNS
- In response to environmental toxins and endogenous proteins, microglia become over-activated and release reactive oxygen species (ROS) that cause neurotoxicity
  - NOX_2
  - Cytokines

Microglia Activated by Many Toxins

Microglia activator (toxin)	NADPH oxidase induced ROS	Pro-inflammatory cytokine release	References
Rotenone	Yes	No	147
Paraquat	Yes	No	146,228
Substance P	Yes	IL-6	121,229
Lipopolysaccharide	Yes	Yes	100,203,210,230
Neuromelanin	Yes	Yes	60
α-Synuclein	Yes	No	56,231
Diesel exhaust particles	Yes	No	150
Gangliosides	Yes	Yes	208
Thrombin	Yes	Yes/No	232–234
Amyloid-β	Yes	Yes	16,41,195
Matrix metalloproteinase 3	Yes	Yes	57,58

ROS, reactive oxygen species

Block *et al. Nature Reviews Neuroscience* **8**, 57–69 (January 2007) | doi:10.1038/nrn2038

Hyperglycemia is a Risk Factor For Neurodegeneration

- Prospective study of over 6000 participants
- Diabetes was found to almost double the risk of dementia
- Those being treated with insulin had more than quadruple the risk
- Diabetes may account for nearly 10% of the population with dementia
- Having diabetes & APOE 4 (e4) allele nearly 5-fold risk for AD compared to having neither
  - apoE4 recently shown to bind to mitochondrial complex III and complex IV, inhibiting their activity

Ott A, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999 Dec 10;53(9):1937-42.
Irie F, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. Arch Neurol. 2008 Jan;65(1):89-93
Nakamura et al. Apolipoprotein E4 (1-272) fragment is associated with mitochondrial proteins and affects mitochondrial function in neuronal cells. Mol Neurodegener. 2009 Aug 20;4:35.

POPs and Neurodegenerative disease

- Persistent organic pollutants (POPs) associated with premature aging, as well as neurodegenerative disease
- Many POPs directly neurotoxic
  - OC pesticide exposure correlated with Parkinson's disease
  - Dieldrin associated with >2.4 fold risk PD among never-smokers
- Clear evidence that neurogenesis can occur later in life
  - May in large part be hormonal/neuroendocrine controlled
  - POPs interfere with this process
    - E.g. BPA: Inhibits hippocampal synaptogenesis induced by estradiol, prevents synaptogenesis induced by testosterone

Weiss B. Endocrine disruptors as a threat to neurological function. J Neurol Sci. 2011 Jun 15;305(1-2):11-21.
Weisskopf MG, et al. Persistent organochlorine pesticides in serum and risk of Parkinson disease. Neurology. 2010 Mar 30;74(13):1055-61.

Mercury Causes Neurological Damage

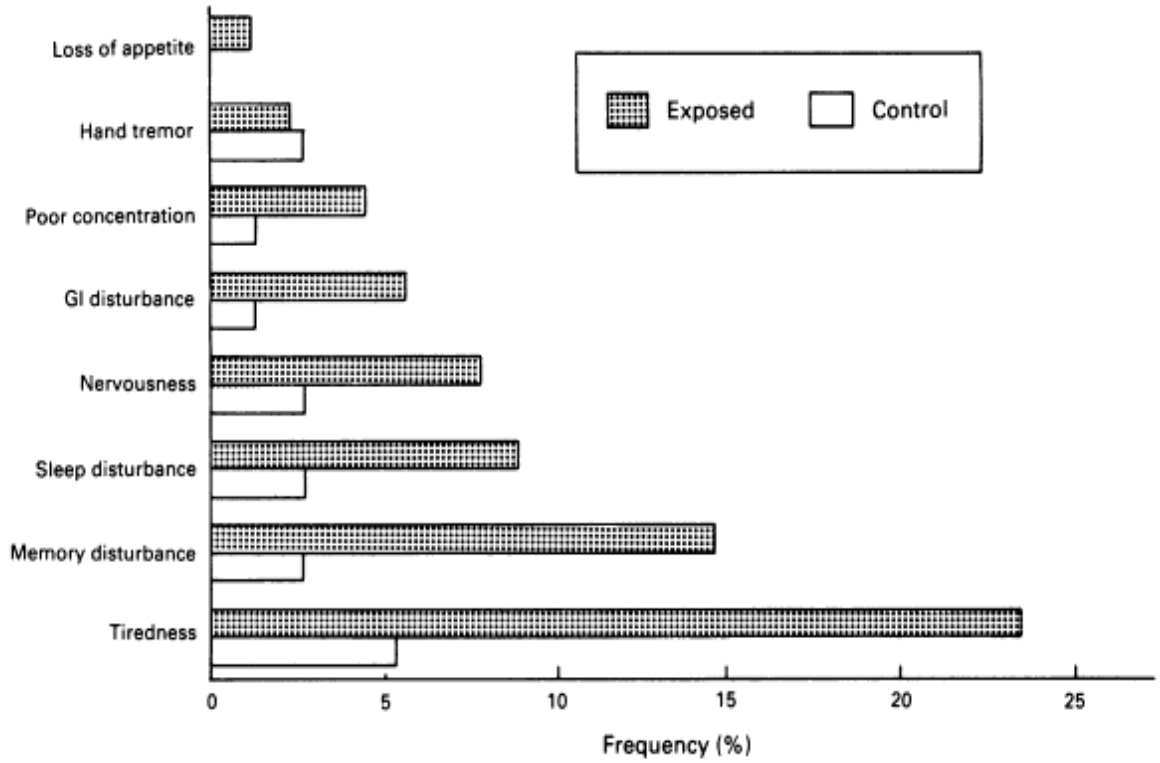
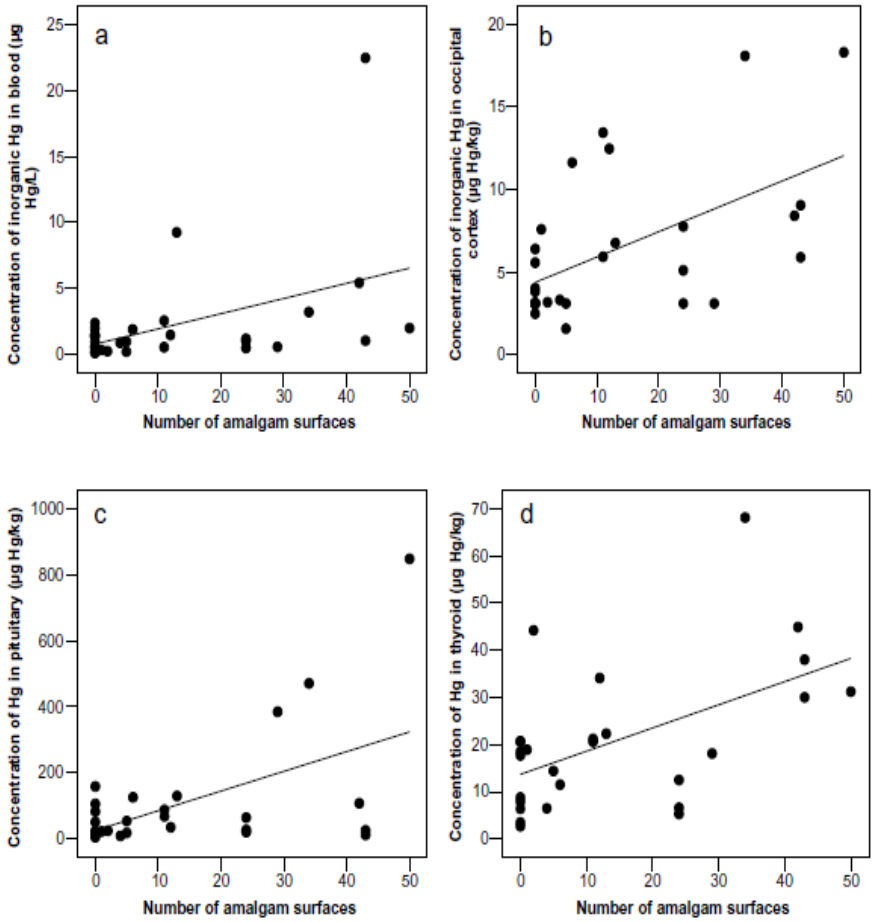


Figure 1 Symptom frequency in exposed and control groups.

S Langworth, O Almkvist, E Söderman, and B O Wikström. Effects of occupational exposure to mercury vapour on the central nervous system. Br J Ind Med. 1992 August; 49(8): 545–555

Hg Accumulates in Brain

- Mercury accumulates in the brain in proportion to surface area of amalgams
- Study of 18 cadavers
  - Hg in brain, thyroid and kidneys proportional to the number of amalgam surfaces
  - For those with more than 12, Hg in brain disproportionately higher
  - Suggests that at higher levels of exposure the brain's mercury excretion pathways become overloaded.

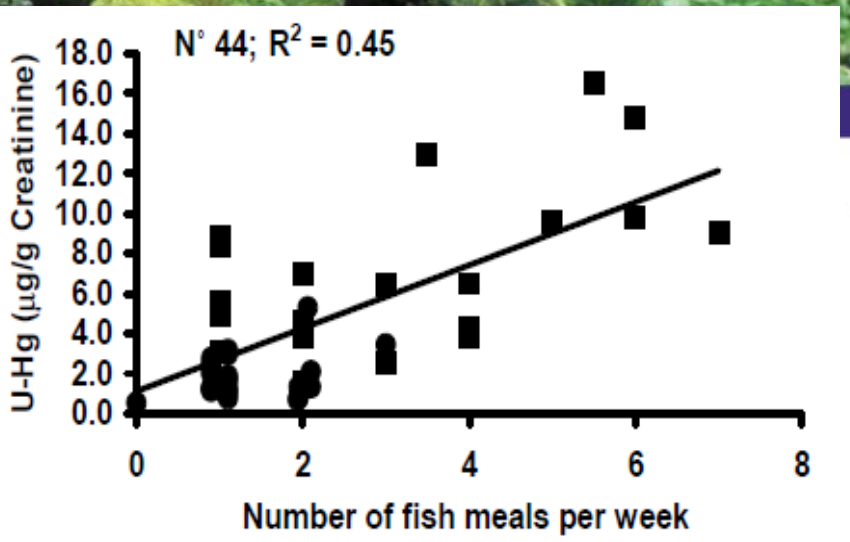


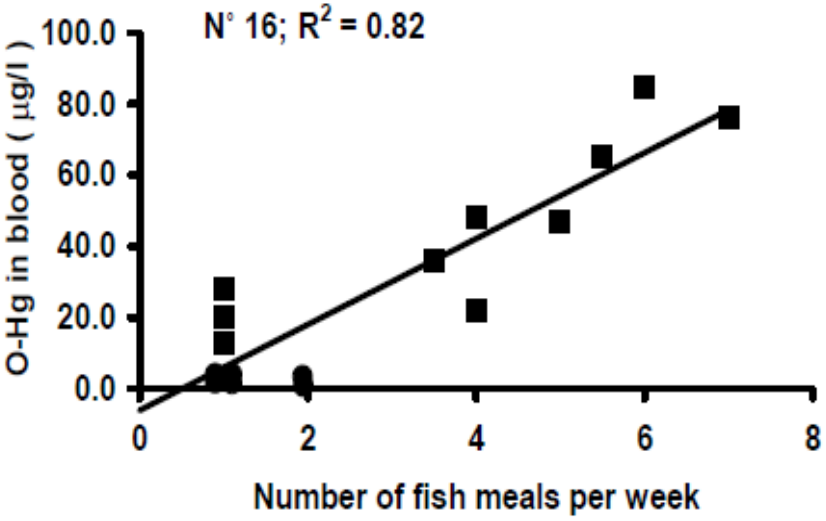
J.W. Reinhardt. Side-Effects: Mercury Contribution to Body Burden From Dental Amalgam. Adv. Dent. Res. 1992; 6; 110

Guzzi G, et al. Dental amalgam and mercury levels in autopsy tissues. Am J Forensic Med Pathol. 2006 Mar;27(1):42-5

Hg From Fish and Psychomotor Dysfunction

- Total Hg urinary excretion proportional to amount of fish eaten
- Impaired psychomotor performance
  - R = 0.38 blood
  - R = 0.77 urine



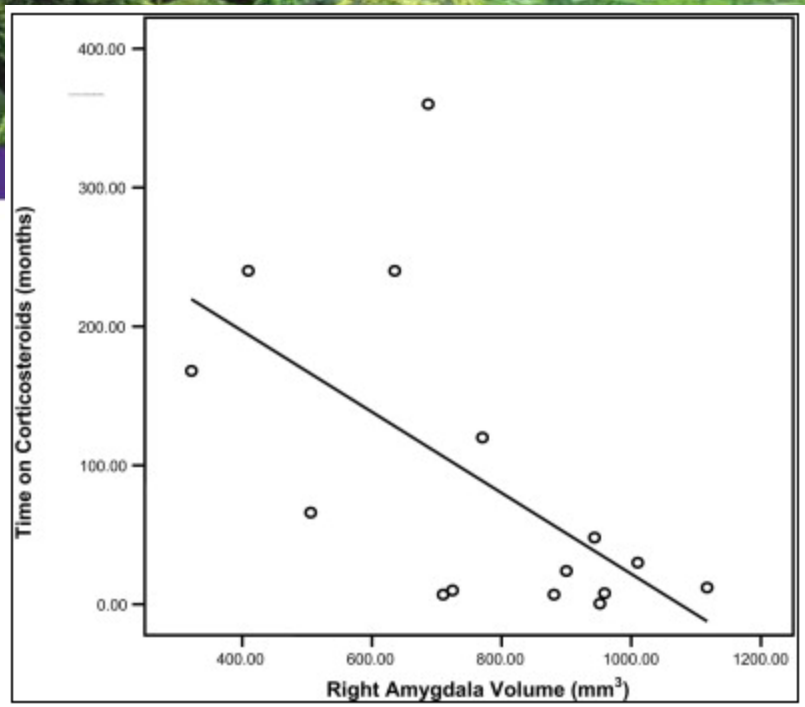


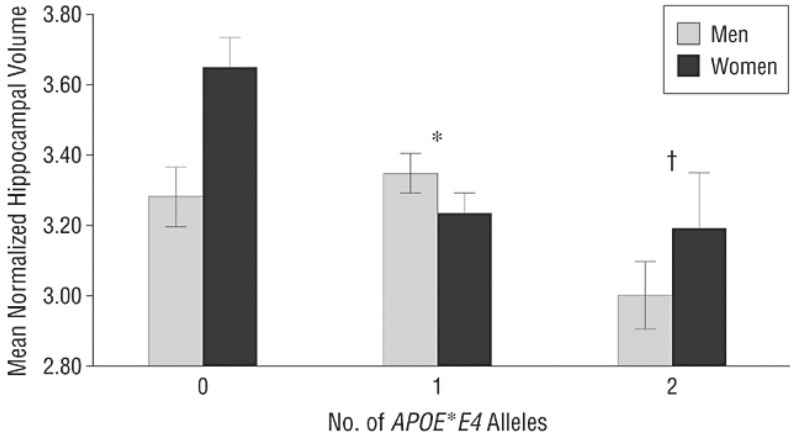
Apostoli P, ICortesi I, Mangili A, et al. Assessment of reference values for mercury in urine: the results of an Italian polycentric study. The Science of the Total Environment 289 (2002)13-24

Carta P, et al. Sub-clinical neurobehavioral abnormalities associated with low level of mercury exposure through fish consumption. NeuroToxicology 24 (2003) 617–623

Glucocorticoids/Stress Damage Neurons

- Hippocampus role in cognition and memory
- Damaged by stress/glucocorticoids
- Worse with APOE*E4
- Decrease in brain volume!





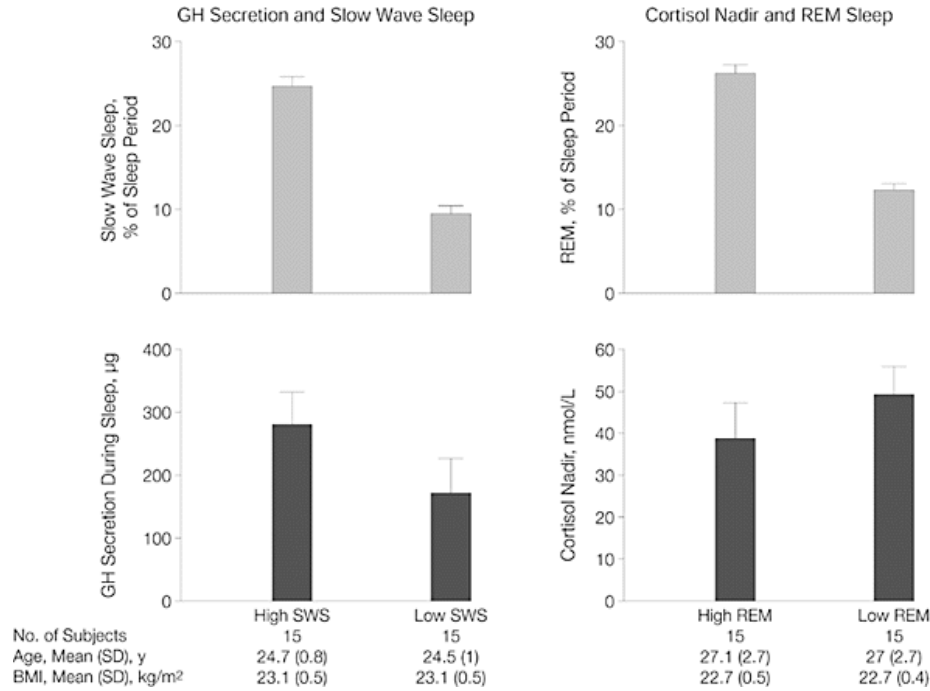
Brown ES, et al. Amygdala volume in patients receiving chronic corticosteroid therapy. Biol Psychiatry. 2008;63:705-9

Fleisher A, et al. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. Arch Neurol 2005;62:953-7

Sleep Deprivation Increases Cortisol and Damages Neurons

- Age related increases in cortisol are directly related to sleep fragmentation and reduction of REM sleep
- "Elevated evening cortisol levels in late life probably reflect an impairment of the negative feedback control of the HPA axis in aging.

  Our analysis suggests that there is a relationship between this alteration of HPA function and decreased amounts of REM sleep that is independent of age."



Van Couter, E., et al. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000;284: 861-8

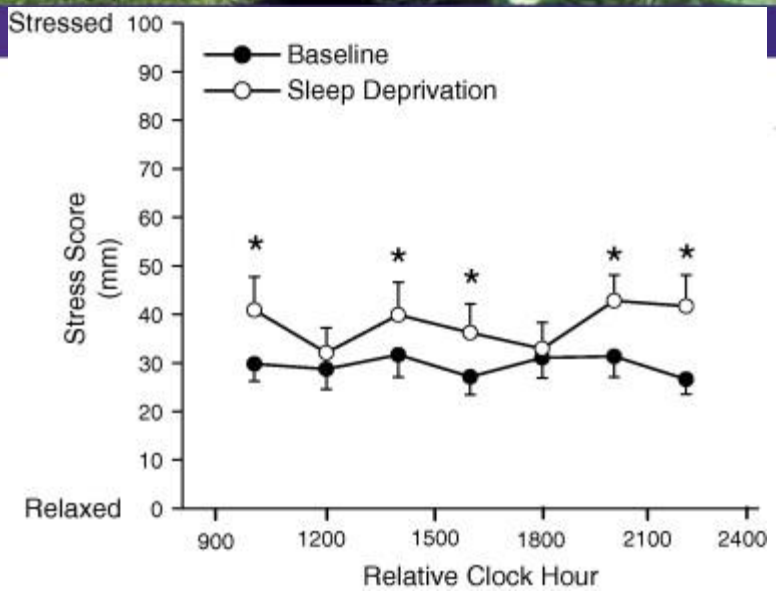
Sleep and Neurological Degeneration

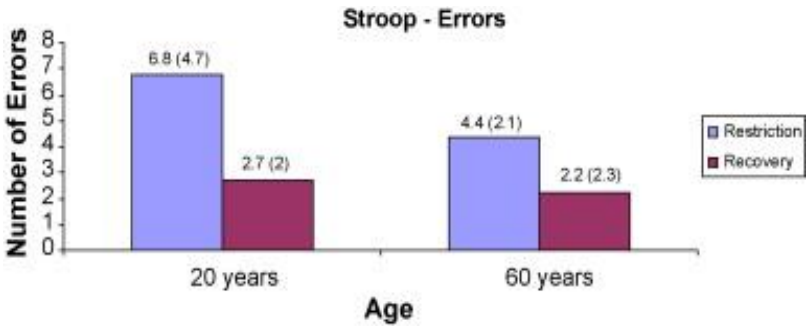
- With age, the percentage of deep, slow wave sleep has been shown to decrease, and sleep fragmentation increases
- Associated with higher evening cortisol concentrations independent of age
- Sleep disturbances are also found early in many neurodegenerative disease processes, even in the presence of mild cognitive impairment

Van Couter, E., et al. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000;284: 861-8
Chokroverty S. Sleep and neurodegenerative diseases. Semin Neurol. 2009 Sep;29(4):446-67.

Sleep Disorders

- Inadequate sleep: Common
  - Elderly: 40-70%
  - Delayed sleep: 25% teenagers
  - Wake early: 25% seniors
- Inadequate sleep increases inflammation
  - As little as 1 night of sleep loss triggers a stress response increasing both pro- and anti-inflammatory proteins
- Impairs cognitive function
  - 3 nights limited to 4 hours



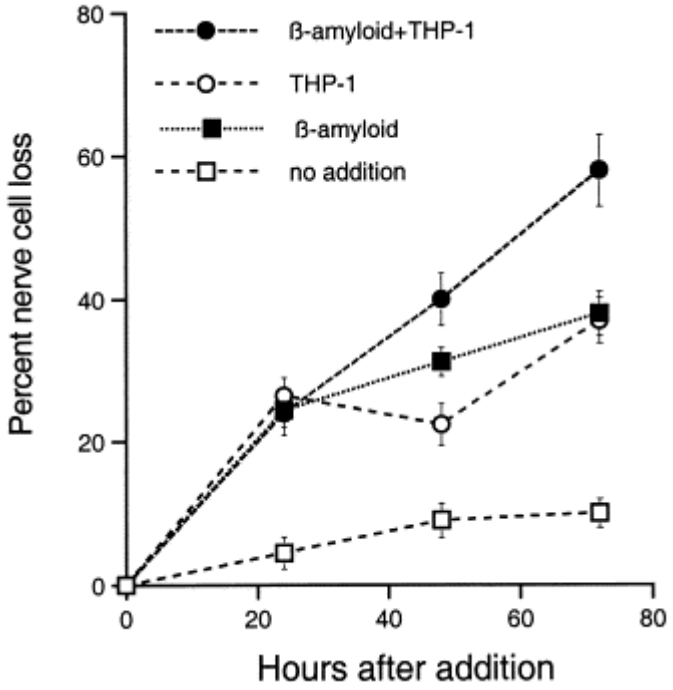


Frey DJ, et al. The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. Brain Behav Immun 2007;21:1050-7

Stenuit P, Kerkhofs M. Effects of sleep restriction on cognition in women. Biol Psychol 2008;77:81-8

ß-Amyloid

- Generates ROS
- Activates NFKB
- Activates microglia
- Increases production of superoxide radical and nitric oxide
- Strongly correlates with dementia and rate of decline
- Kills neurons



Näslund J, et al. Correlation between elevated levels of amyloid b-peptide in the brain and cognitive decline. JAMA 2000;283:1571-77

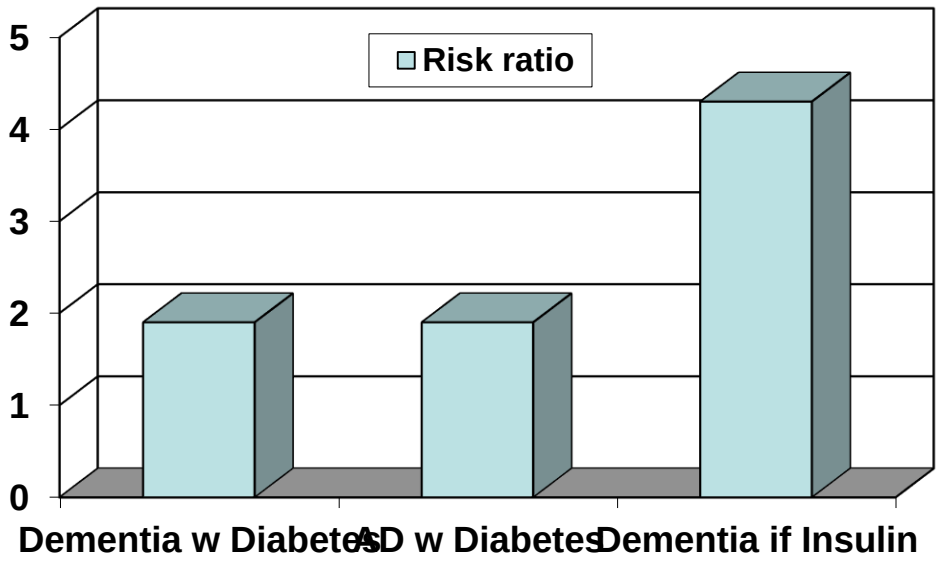
Wu Q,et al. Beta-amyloid activated microglia induce cell cycling and cell death in culturedcortical neurons. Neurobiol Aging. 2000;21:797-806

APOE E4 and Neurodegeneration

- APOE E4 genotype substantially increases the risk of cognitive decline in combination with atherosclerosis, peripheral vascular disease, or diabetes mellitus
- Associated with a reduced volume of the amygdala
- Accounts for 13-20% cases of dementia
- Heterozygotes, onset 5-10 years earlier
- Homozygotes, onset of Alzheimer's 10-20 years earlier
- Modulates effects of other risk factors
- APO E4 also binds to mitochondrial complex III and complex IV, inhibiting their activity

Sugar Dysregulation Damages Neurons

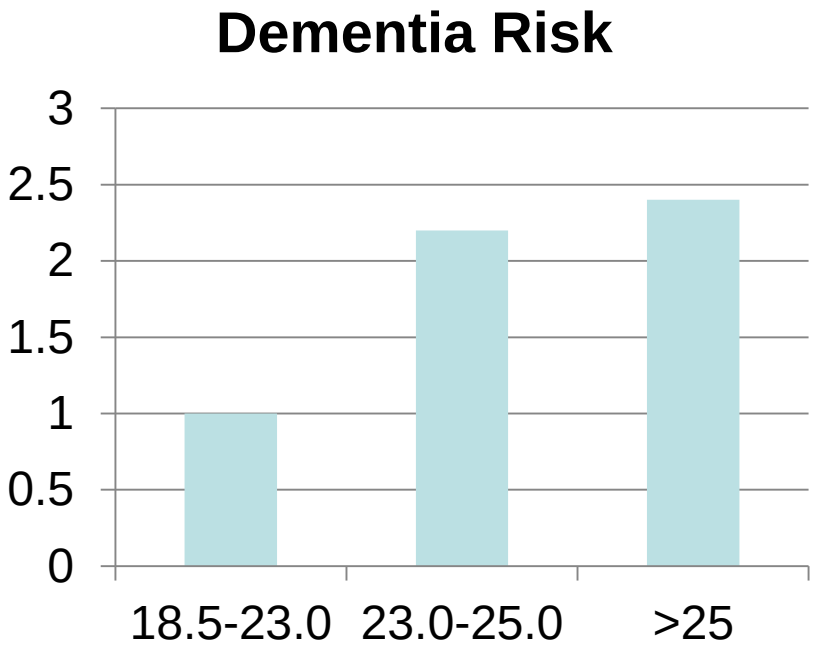
- 6,370 patients
- Type II diabetes
- Followed for 2 years



Ott, A., et al. Diabetes mellitus and the risk of dementia - The Rotterdam Study Neurology. 1999;53:1937-42
Näslund, J., et al. Insulin use - 4.3X risk more severe diabetes longer history direct effects. JAMA 2000;283:1571-7

Obesity Associated w Dementia

- Direct association between excessive weight and dementia
- Weight loss in obese older adults improves cognitive function



Chang WS, Won KH, Lee JY, et al. The Relationship between Obesity and the High Probability of Dementia Based on the Body Mass Index and Waist Circumference. Korean J Fam Med. 2012 Jan;33(1):17-24
Siervo M, Nasti G, Stephan BC, et al. Effects of intentional weight loss on physical and cognitive function in middle-aged and older obese participants: a pilot study. J Am Coll Nutr. 2012 Apr;31(2):79-86

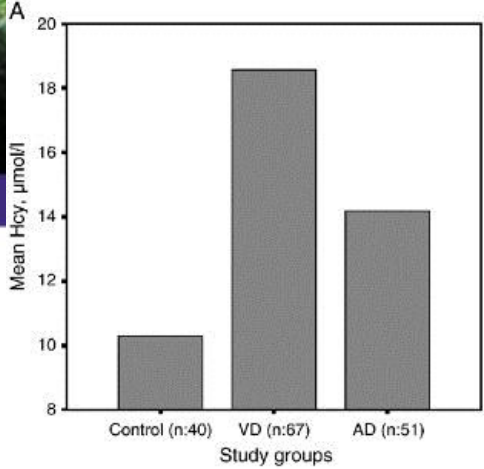
Cognitive Function, Obesity & Metabolic Abnormalities

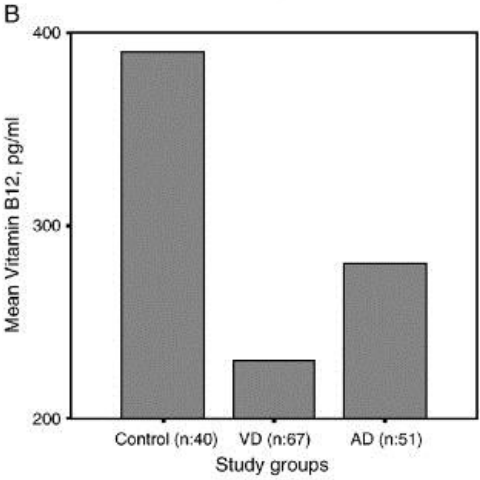
- 6,401 adults (71.2% men), aged 39–63 years
- Fastest decline observed in those both obese & with metabolic abnormality defined as at least 2 of following:
  - Abnormal glucose
  - Elevated triglycerides
  - Decreased HDL
  - Elevated blood pressure)

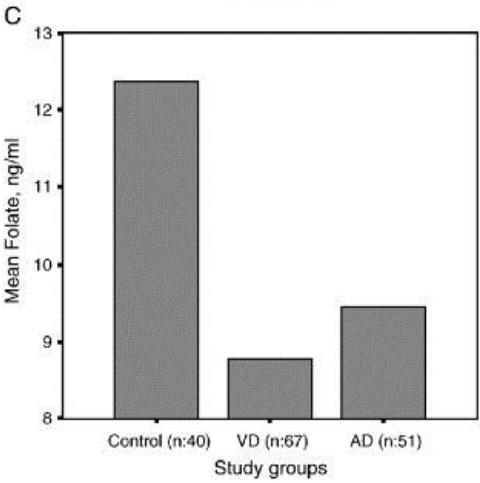
Singh-Manoux A, et al. Obesity phenotypes in midlife and cognition in early old age: The Whitehall II cohort study. Neurology. 2012 Aug 21;79(8):755-62.

Homocysteine Damages Neurons

- Homocysteine is a neurotoxin
- Homocysteine levels increased 60% in PD
- L-dopa increases homocysteine level
- L-dopa enhances conversion of S-adenosylmethionine to homocysteine
- PD treated with L-dopa experience increased levels of heart disease
- Direct correlation between homocysteine levels and Alzheimer's
- >14 mmol/L doubles risk of Alzheimer's







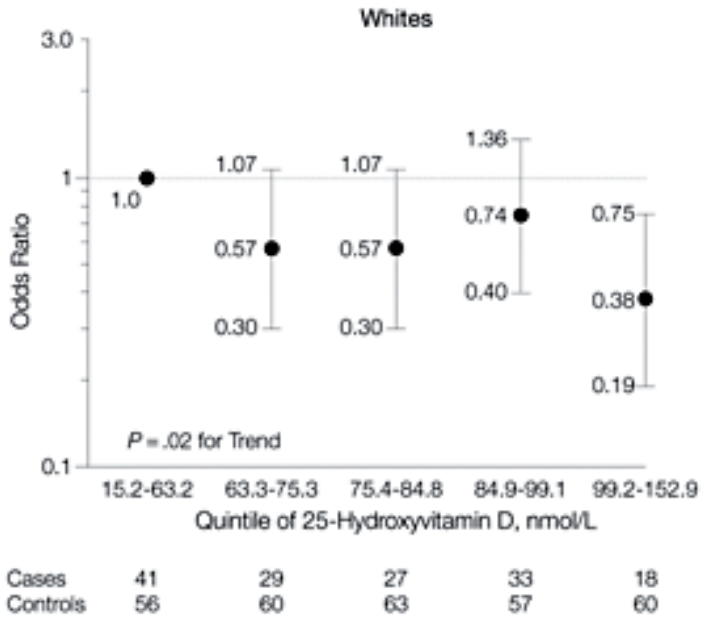
Müller T, et al. Nigral endothelial dysfunction, homocysteine, and Parkinson's disease. Lancet 1999;354:126
Seshadri S, et al. Alzheimer's disease. NEJM 2002; 346:476-83
Köseoglu E, Karaman Y.Relations between homocysteine, folate and vitamin B12 in vascular dementia and in Alzheimer disease. Clin Biochem 2007;40:859-63

Vitamin D and the Brain

- Decreases inflammatory cytokines
- Antimicrobial
- Facilitates neurotrophins
- Membrane antioxidant

Vitamin D Deficiency Damages Neurons

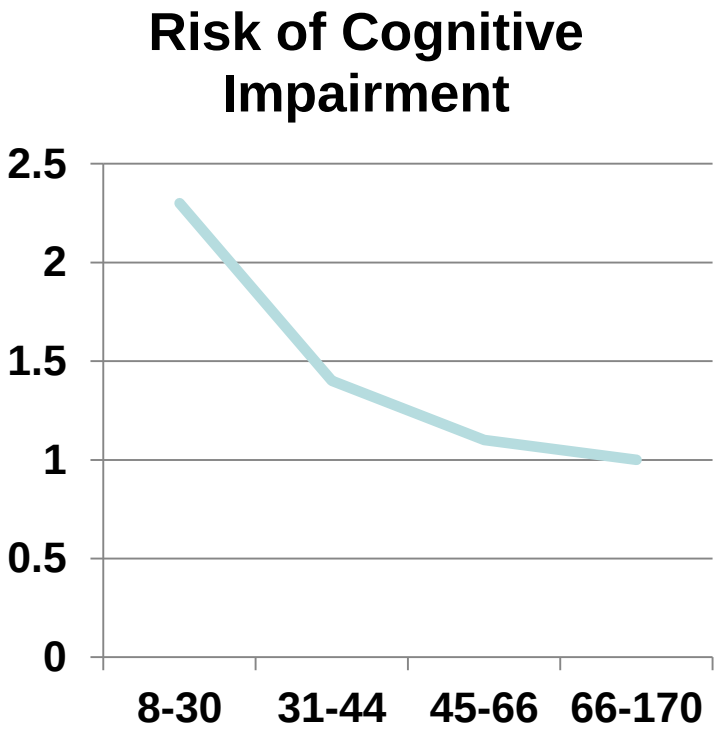
- Up regulates cytokines
- Macrophages overactive
- Increases risk of MS in whites but not blacks
- VDR receptor defect gene:
  - 2.3 risk of Alzheimer's disease



Munger KL, et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296:2832-8
Gezen-Ak D, et al. Association between vitamin D receptor gene polymorphism and Alzheimer's disease. Tohoku J Exp Med. 2007;212:275-82

Vitamin D & Cognitive Decline

- 1,766 adults >65 yo in England
- Worse in black Americans:
  - 45.0 nmol/L vs. 63.0 nmol/L
  - 40% worse cognitive impairment
- In those >65, <50 nmol/l = 11.7 odds ratio of active mood disorder



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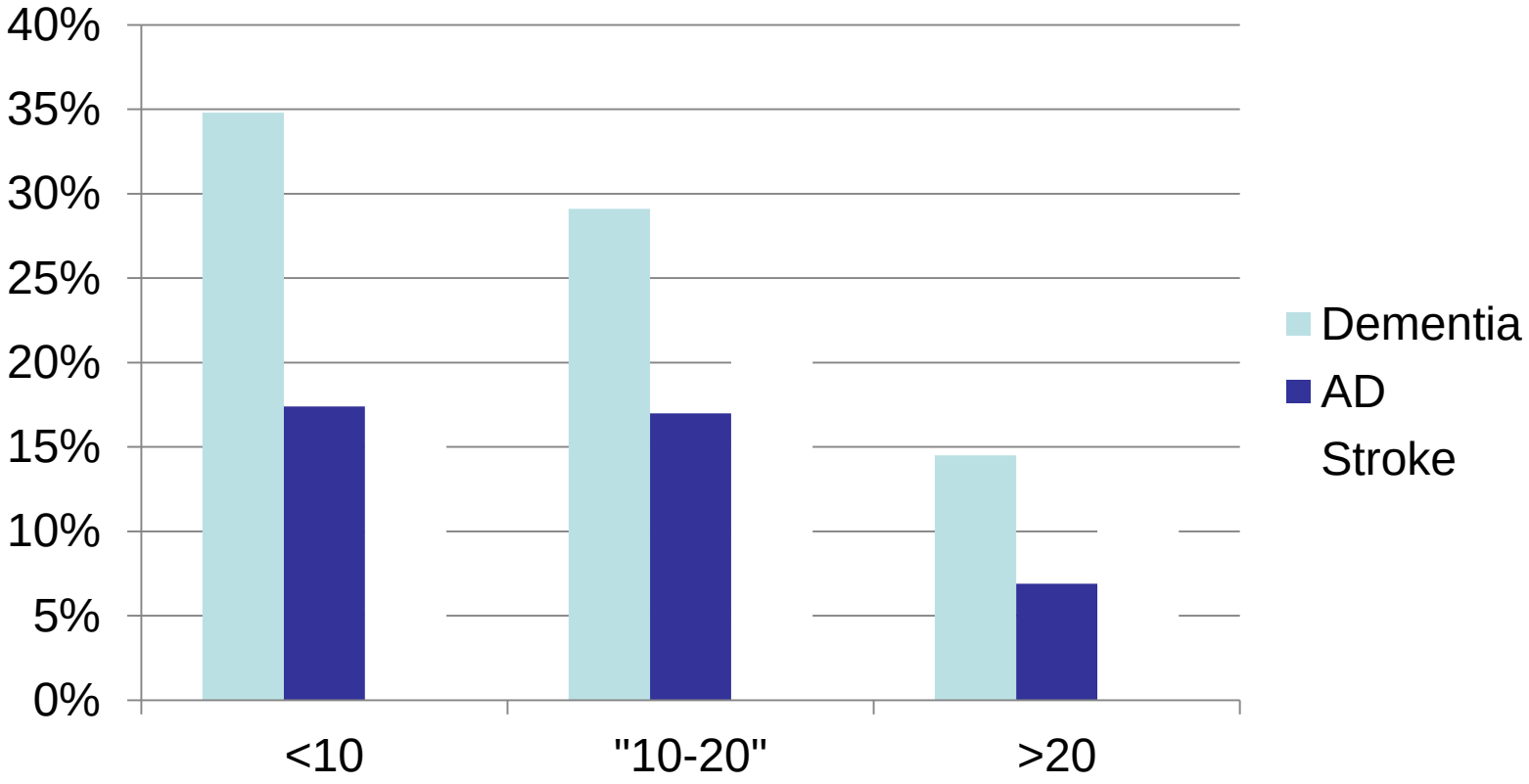
Wilkins CH, Birge SJ, Sheline YI, Morris JC. Vitamin D deficiency is associated with worse cognitive performance and lower bone density in older African Americans. J Natl Med Assoc. 2009 Apr;101(4):349-54
Wilkins CH, Sheline YI, Roe CM, et al. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. Am J Geriatr Psychiatry. 2006 Dec;14(12):1032-40

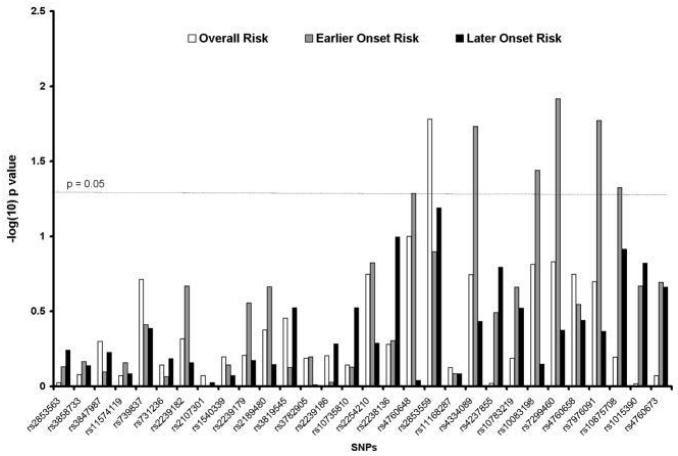
Vitamin D Critical for Brain Health

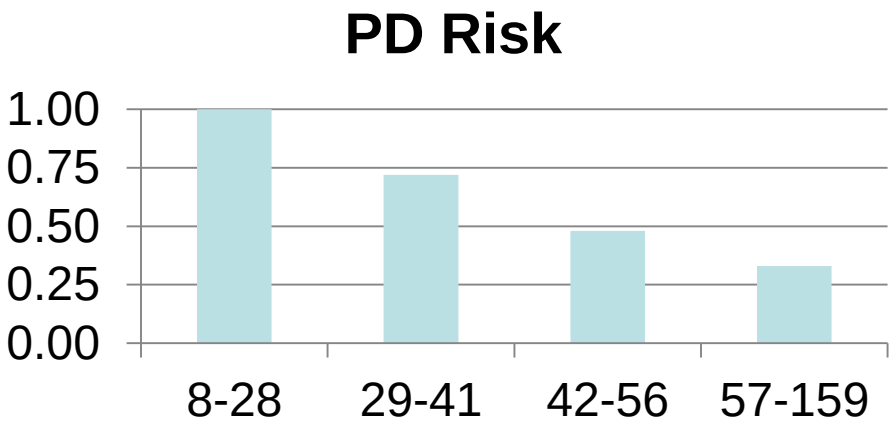


Buell JS, Dawson-Hughes B, Scott TM. 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. Neurology. 2010 January 5; 74(1): 18–26

Vitamin D and Parkinson's

- Direct inverse correlation
- VDR polymorphisms increases risk
- Strong correlation between PD and osteoporosis
  - 91% in women; 61% in men
  - Cause or effect?





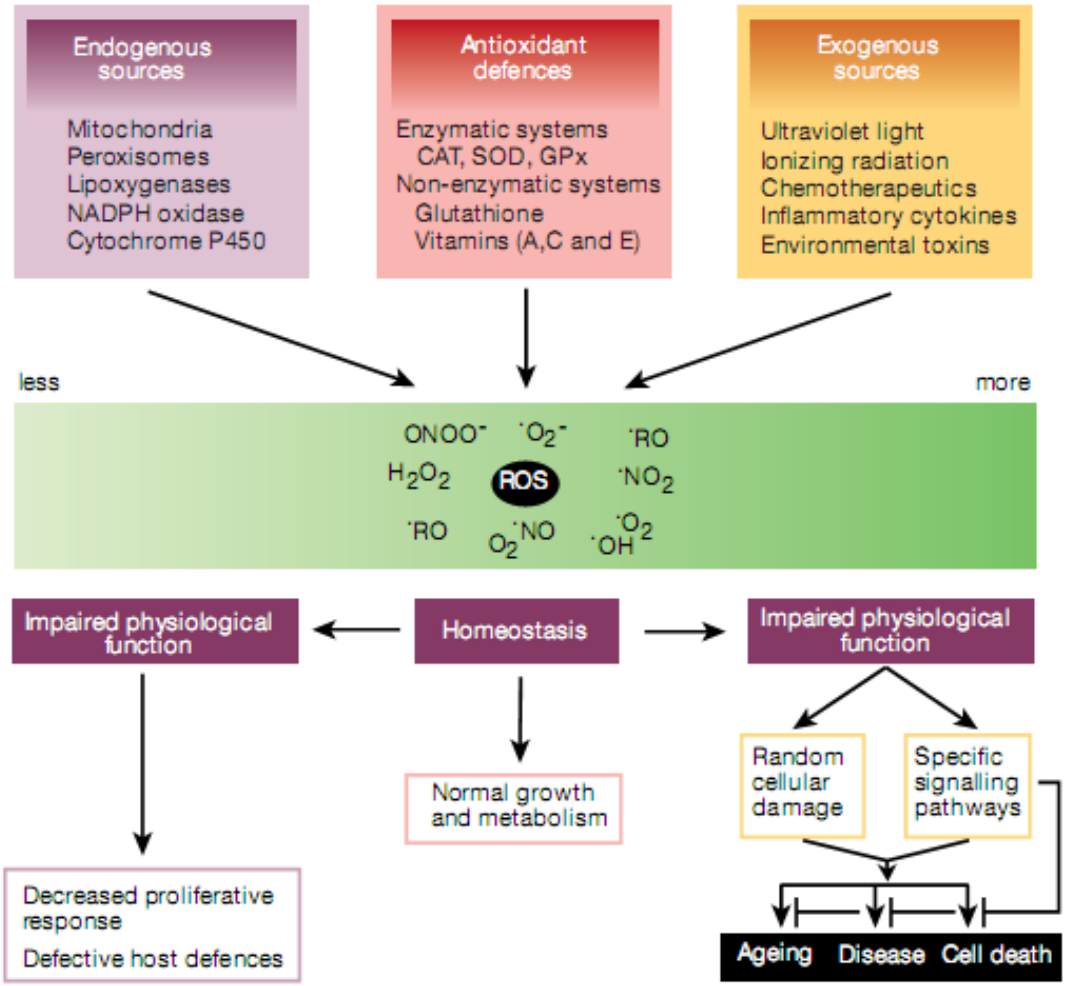
Knekt P, Kilkkinen A, Rissanen H, et al. Serum vitamin D and the risk of Parkinson disease. Arch Neurol. 2010 Jul;67(7):808-11

Butler MW, Burt A, Edwards TL, et al. Vitamin D receptor gene as a candidate gene for Parkinson disease. Ann Hum Genet. 2011 Mar;75(2):201-10

Invernizzi M, Carda S, Viscontini GS, Cisari C. Osteoporosis in Parkinson's disease. Parkinsonism Relat Disord. 2009 Jun;15(5):339-46

Oxidative Stress

- Major cause of degeneration
- Many causes:
  - Environmental toxins
  - Mitochondrial leakage most significant source of ROS



From: Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000 Nov 9;408(6809):239-47.

Mitochondrial Function Key to Neural Health

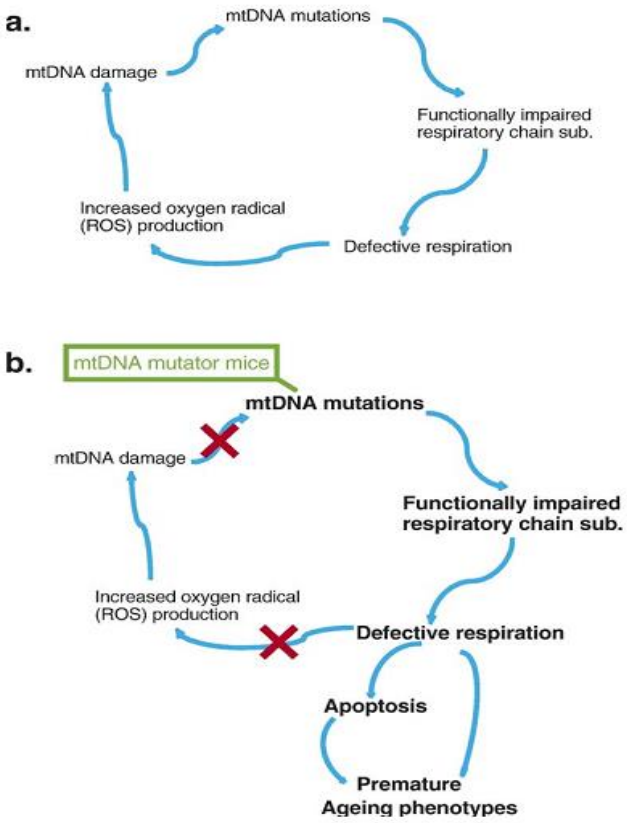
"Mitochondrial dysfunction from oxidative stress, mitochondrial DNA deletions, pathological mutations, altered mitochondrial morphology, and interaction of pathogenic proteins with mitochondria leads to neuronal demise."

- Strong research: Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease

Chaturvedi RK, Beal MF. Mitochondrial approaches for neuroprotection. Ann N Y Acad Sci. 2008 Dec;1147:395-41

Mitochondrial ROS Production

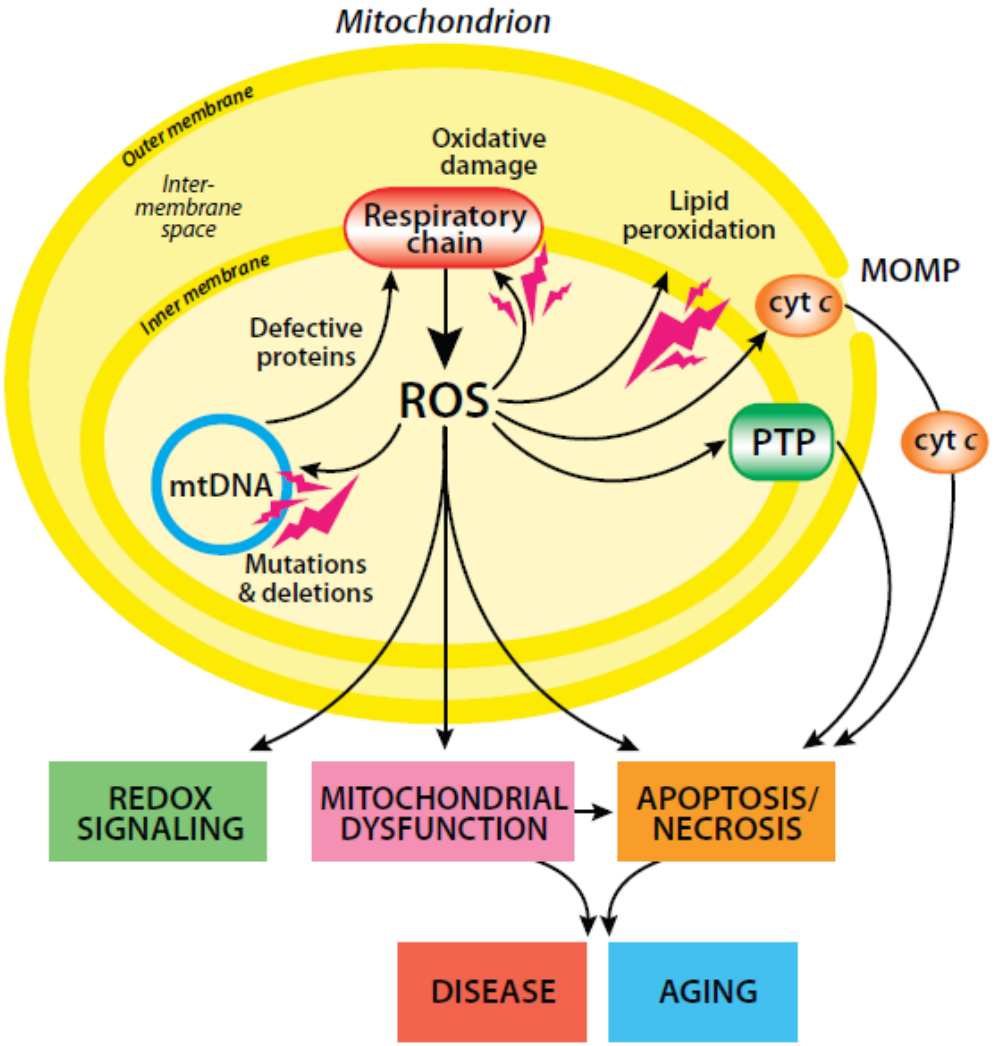
- Mitochondrial ROS production strong species predictor for longevity
- Mitochondrial ROS production and leakage increase with age



Trifunovic A. Mitochondrial DNA and ageing. Biochim Biophys Acta. 2006 May-Jun;1757(5-6):611-7.

Role of Mitochondria

- Complexes I, IV, and mtNOS are selectively affected in aging
- Aging more than just ROS damage – altered signaling pathways & crosstalk with cell nucleus affects multiple cellular functions & gene expression
- Thus therapy targeting mitochondrial function may be more effective than ROS scavenging, i.e. antioxidants



Dai 2012

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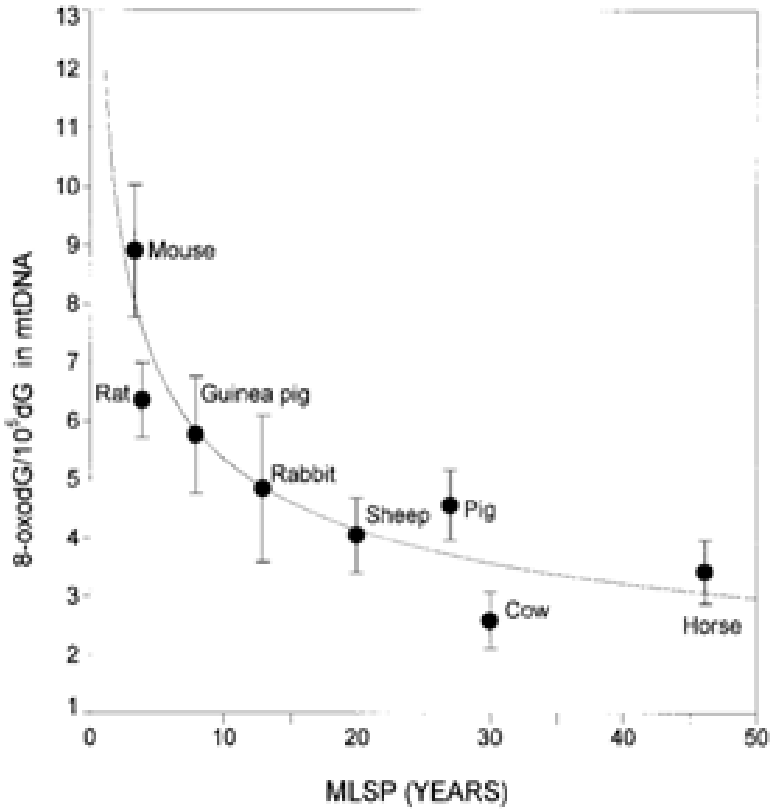
Navarro A, et al. The mitochondrial energy transduction system and the aging process. Am J Physiol Cell Physiol. 2007 Feb;292(2):C670-86.

Mitochondrial Damage & Lifespan

- 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), marker of oxidative stress, measured in 8 species of varying lifespan
- Inverse relationship between maximum lifespan and 8-oxodG mtDNA – not observed with nuclear DNA

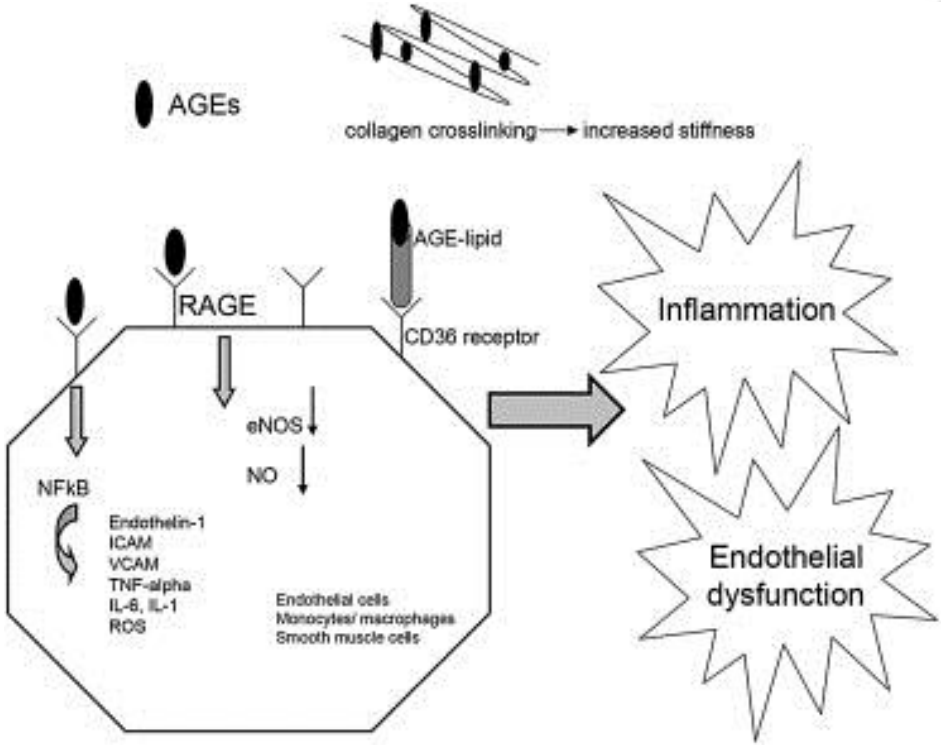


Barja 2000

Barja G, Herrero A. Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals. FASEB J. 2000 Feb;14(2):312-8.

The Damage of AGEs

- AGEs
  - Advanced glycated end-products
  - Non-enzymatic glucose adducts with proteins, lipids, nucleic acids
  - Induce cross-linking of collagen, elastin, proteins
  - Bind to AGE-specific receptors (RAGEs) increasing release of inflammatory mediators



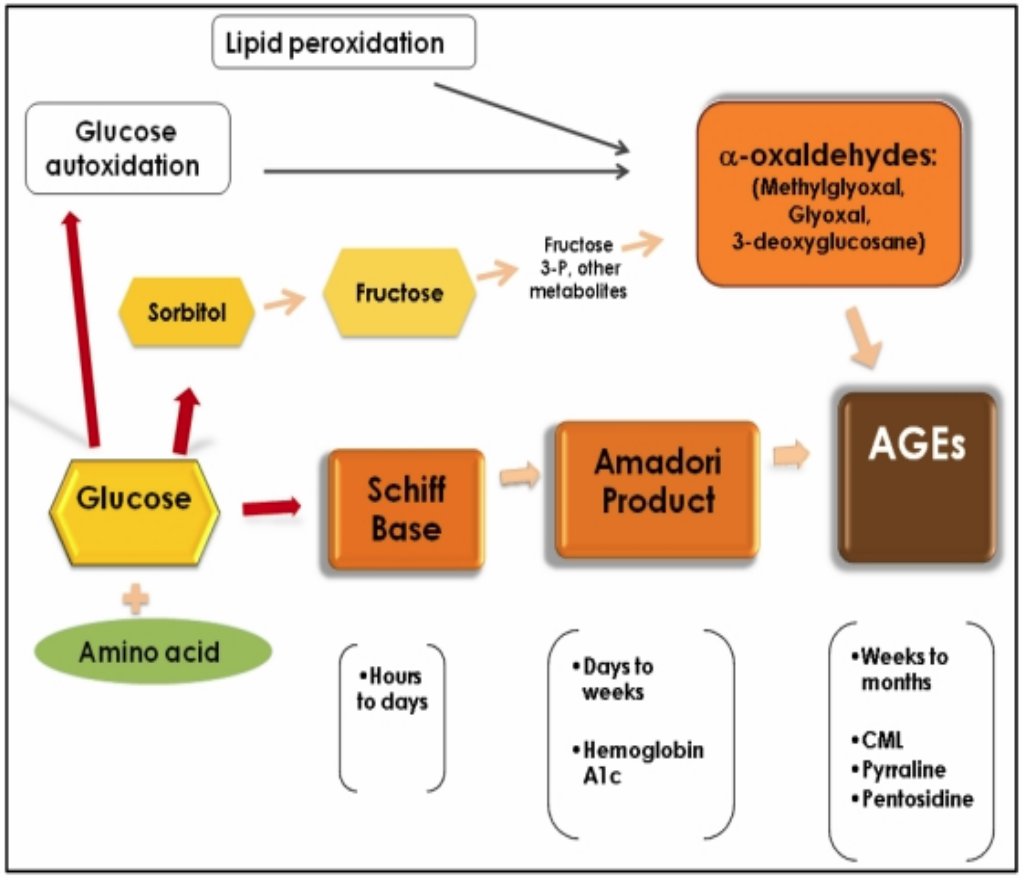
Meerwaldt 2008

⇒ Tissue thickening, scarring and dysfunction in skin, heart, vessels, kidneys, eyes, brain, etc.

Meerwaldt R, et al. Clinical relevance of advanced glycation end products for vascular surgery. Eur J Vasc Endovasc Surg. 2008;36(2):125-31

AGE Formation

- Formation of AGEs through the Maillard reaction occurs in three phases
- Also form by oxidation of glucose; and peroxidation of lipids and through the polyol pathway
- Very stable, and accumulate inside and outside the cell, and interfere with protein function

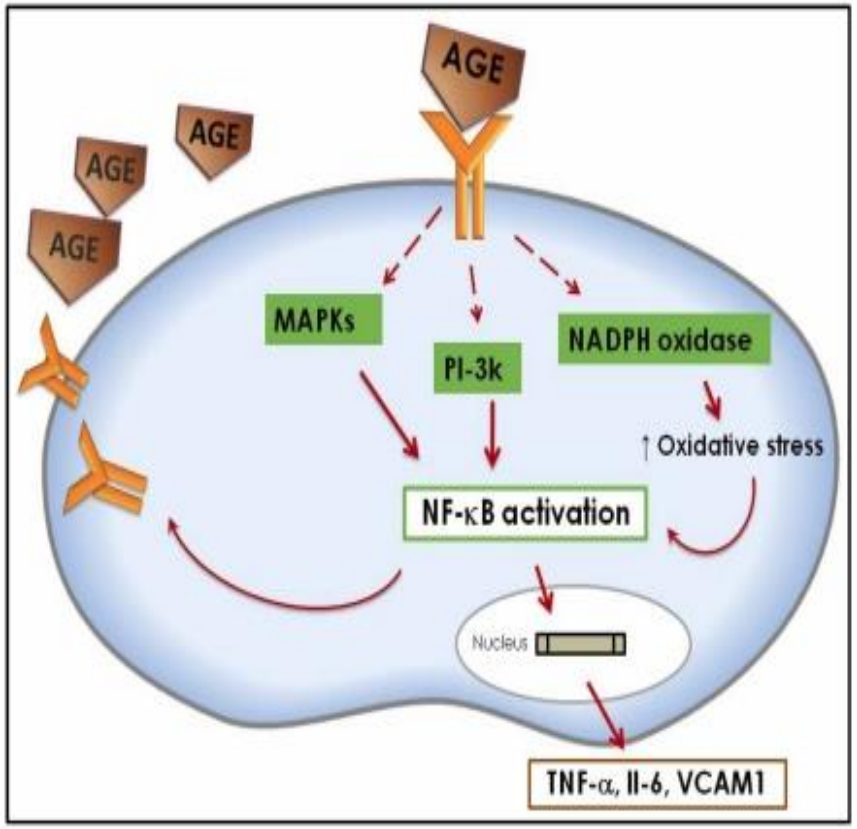


Luevano-Contreras 2010

Luevano-Contreras C et al. Dietary advanced glycation end products and aging. Nutrients. 2010 Dec;2(12):1247-65.

How AGEs Cause Damage

- Independent of receptor (pro-oxidant, pro-inflammatory, direct damage to protein structure, etc.)
- Receptor for advanced glycation end-products (RAGE)
  - AGE binding to RAGE triggers NF-κB activation
  - Leads to nuclear activation of multiple genes, including tumor necrosis factor α (TNFα), interleukin 6 (Il-6)
  - Positive inflammatory feedback cycle

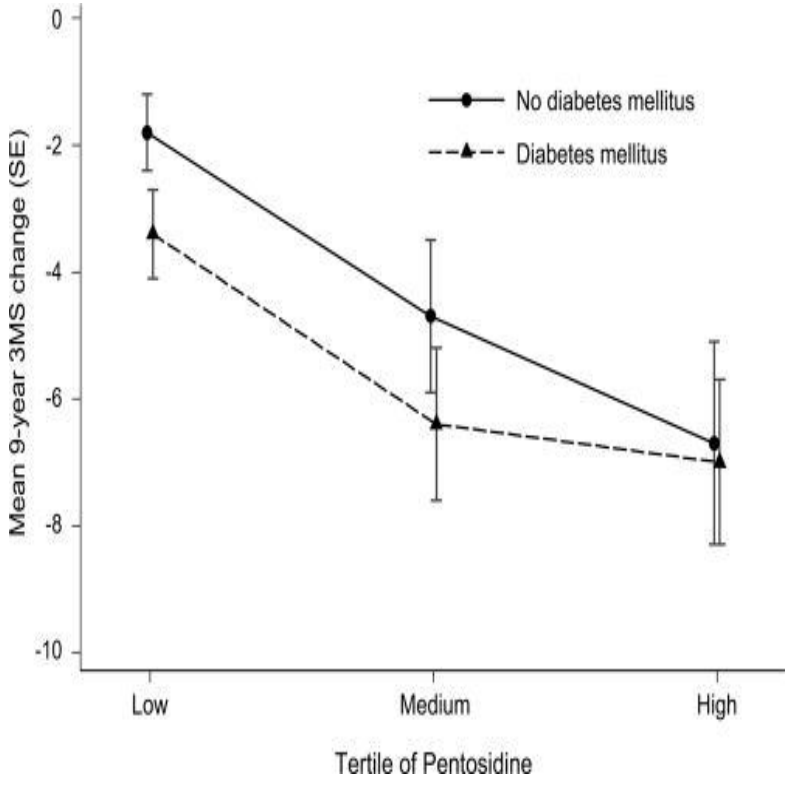


Luevano-Contreras 2010

Luevano-Contreras C et al. Dietary advanced glycation end products and aging. Nutrients. 2010 Dec;2(12):1247-65.

AGEs & Cognitive Aging

- Prospective cohort study of 3,075, aged 70–79 years
- Urine levels of the AGE pentosidine measured
- Higher urine levels associated with greater decline in cognitive function over 9 years
- Independent of demographic factors and comorbidities, including diabetes

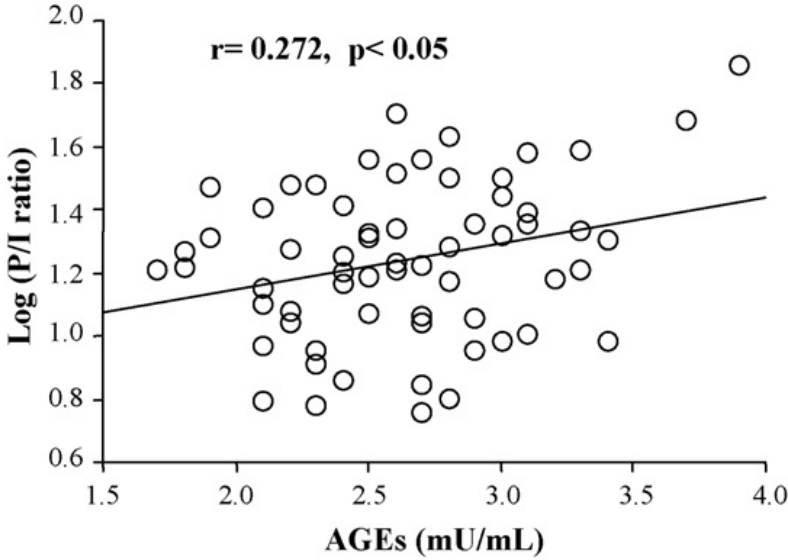


Rosano 2011

Rosano C et al. Advanced glycation end product level, diabetes, and accelerated cognitive aging. Neurology. 2011 Oct 4;77(14):1351-6.

Sources of AGEs

- Hyperglycemia
  - HBA1c = glycosylated hemoglobin
  - AGEs block conversion of proinsulin
  - Also block the production of insulin
- Oxidative stress, smoking
- Browned foods
  - Foods high in fat and protein cooked at high temperatures
  - 10% of dietary AGEs absorbed
  - Direct correlation with blood levels



Saisho y, et al. Relationship between proinsulin-to-insulin ratio and advanced glycation endproducts in Japanese type 2 diabetic subjects. Diabetes Research and Clinical Practice 2007;78:182–8

Goldberg T, et al. Advanced glycoxidation end products in commonly consumed foods. J Am Diet Assoc. 2004;104:1287-91

Zhao Z, Zhao C, Zhang XH et al. Advanced glycation end products inhibit glucose-stimulated insulin secretion through nitric oxide-dependent inhibition of cytochrome c oxidase and adenosine triphosphate synthesis. Endocrinology. 2009 Jun;150(6):2569-76.

Dietary AGEs

- Exogenous AGEs significant contributor to total AGE pool
- Low AGE diet has multiple benefits – just mildly steaming food has significant reduction vs. high temp cooking
- Without diabetes
  - Ex: Randomized cross-over trial
    - Similar foods, one group had food cooked at high temp, other at low (mild steam cooking)
    - After 1 month, high temp group had lower insulin sensitivity, n-3 fatty acids, vitamin C & E, yet higher cholesterol and TGs.
- With Diabetes
  - Ex: 4 months on high or low AGE diet
  - High AGE diet contributed to insulin resistance & inflammation via several mechanisms, including decrease in SIRT1 mRNA, and increase in tumor necrosis factor-α and nuclear factor-κB p65 acetylation

Birlouez-Aragon I, et al. A diet based on high-heat-treated foods promotes risk factors for diabetes mellitus and cardiovascular disease. Am J Clin Nutr 2010; 91:1220-6
Uribarri J, et al. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care. 2011 Jul;34(7):1610-6.

AGEs in Common Foods

Food	Serving	KU/serving
Onion, raw	3.5 oz	36
Tomato, raw	3.5 oz	23
Grilled vegetables (broccoli, carrots, etc)	3.5 oz	226
Almonds, roasted	1.0 oz	1,995
Butter	1.0 tsp	1,324
Hamburger, fast food	3.0 oz	4,876
Chicken breast w/skin, roasted 45 min	3.0 oz	7,469
Frankfurter, broiled 5 min	3.0 oz	10,143
Tuna, roasted 25 min	3.0 oz	827
Mozzarella, part skim	1.0 oz	503
Feta	1.0 oz	2,527
Egg, boiled 10 min	1 egg	195
Egg, fried with margarine	1 egg	1,237
Tofu, raw	3.0 oz	709
Tofu, sauteed	3.0 oz	3,447
Beans, kidney canned	3.5 oz	191
White potato, boiled 25 min	3.5 oz	17
White potato, roasted, 45 min, in 5 mL oil	3.5 oz	218
French fries, fast food	3.5 oz	1,522
Human milk	1 cup	2
Infant formula	1 cup	146

From: **Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial**

JAMA. 2003;289(20):2651-2662. doi:10.1001/jama.289.20.2651

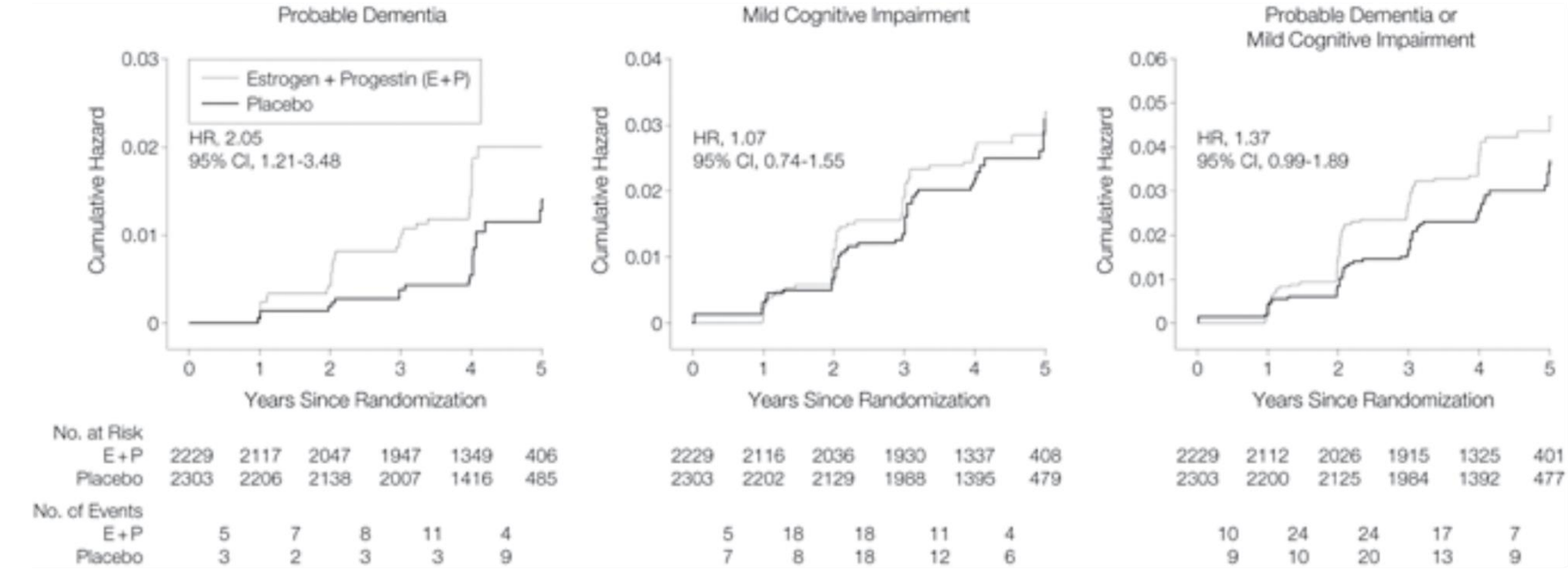
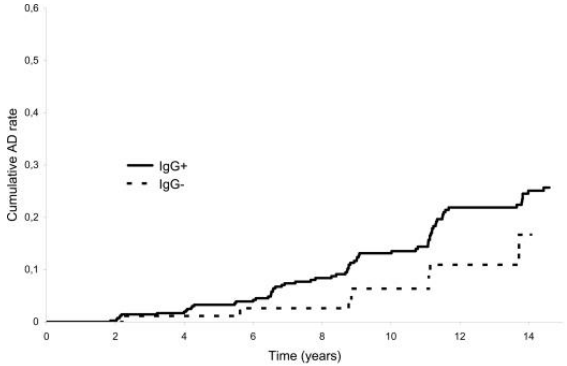


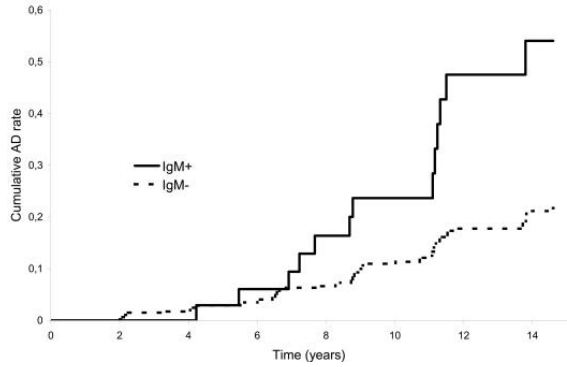
Figure Legend:

CI indicates confidence interval; HR, hazard ratio. Data shown onlythrough 5 years of follow-up because numbers at risk are too small after thispoint for precise estimates.

Infectious Cause?

- Theory that unrecognized neurological infection chronically activates microglia
- The Alzheimer's disease-associated amyloid β-protein is an antimicrobial peptide against
  - *Candida albicans, Escherichia coli, Staphlyococcus epidermidis, Streptococcus pneumonia*
- AD brain isolates have antimicrobial activity against *C. albicans*
- “Reactivation of HSV seropositivity is highly correlated with incident AD. HSV chronic infection may therefore be contributive to the progressive brain damage characteristic of AD.”



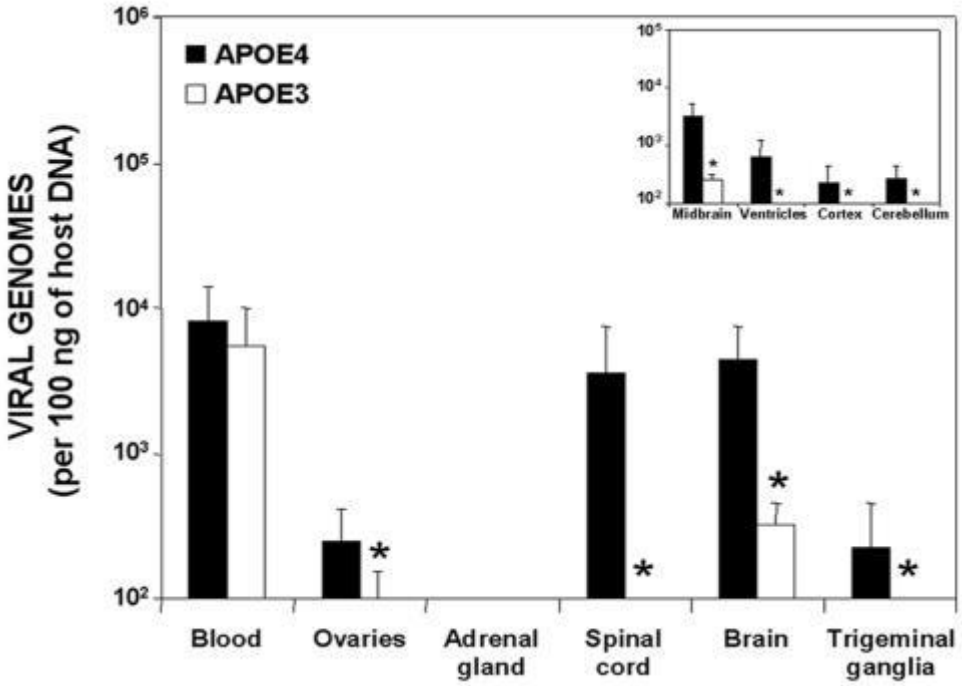


Soscia SJ, Kirby, JE, Washicosky KJ, et al. The Alzheimer's Disease-Associated Amyloid β-Protein Is an Antimicrobial Peptide. PLoS One. 2010; 5(3): e9505

Letenneur L, Pérès K, Fleury H, et al. Seropositivity to Herpes simplex virus antibodies and risk of Alzheimer's disease: A population-based cohort study. PLoS ONE. 2008; 3(11): e3637

APOE4 Increases Neuron Susceptibility to Viral Infection

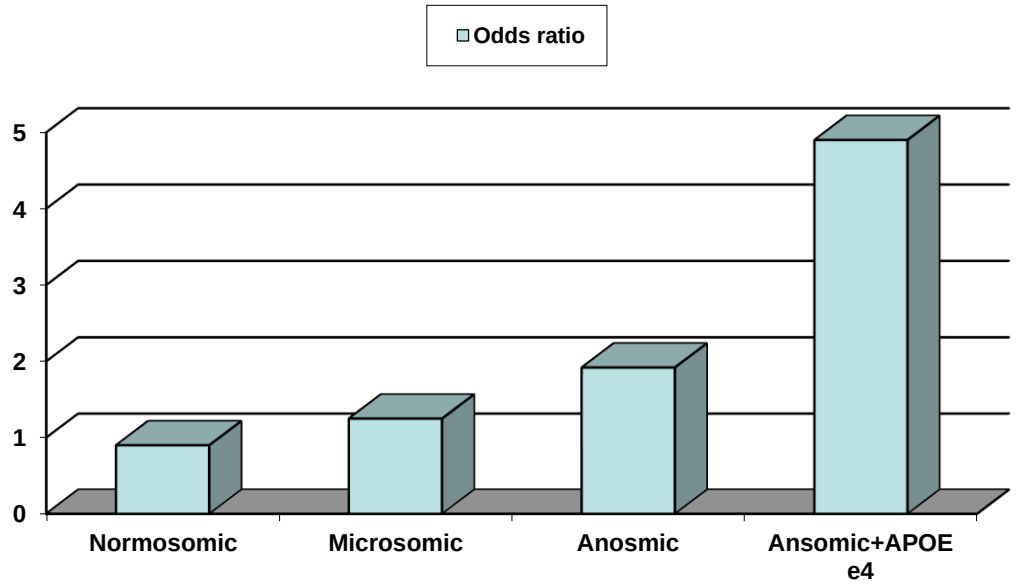
- May explain strong correlation between APOE type and AD
- May also explain protective effects of vitamin D



Burgos JS, Ramirez C, Sastre I, Valdivieso F. Effect of apolipoprotein e on the cerebral load of latent Herpes simplex virus type 1 DNA virol. 2006 June; 80(11): 5383–5387z

Impaired Olfaction Is a Marker for Cognitive Decline

- 1,604 non-demented participants
  - Cognitive Abilities Screening Instrument
  - 12 - item Cross-Cultural Smell Identification Test
  - APOE status
- Followed for 2 years
- Adjusted for age, education, smoking, gender



Borenstein Graves, A., et al. Impaired olfaction as a marker for cognitive decline - Interaction with APOE e 4 status. Neurology 1999;53:1480-7

Neurological Degeneration: Treatment

Control Causes

- Improve sugar regulation
- Stress reduction
  - Spouse/significant other
  - Sleep
- Inflammation control
- Avoid neurotoxins
- Avoid allergens
- Caloric restriction
- Eliminate POPs
- Eliminate Hg

Intervention

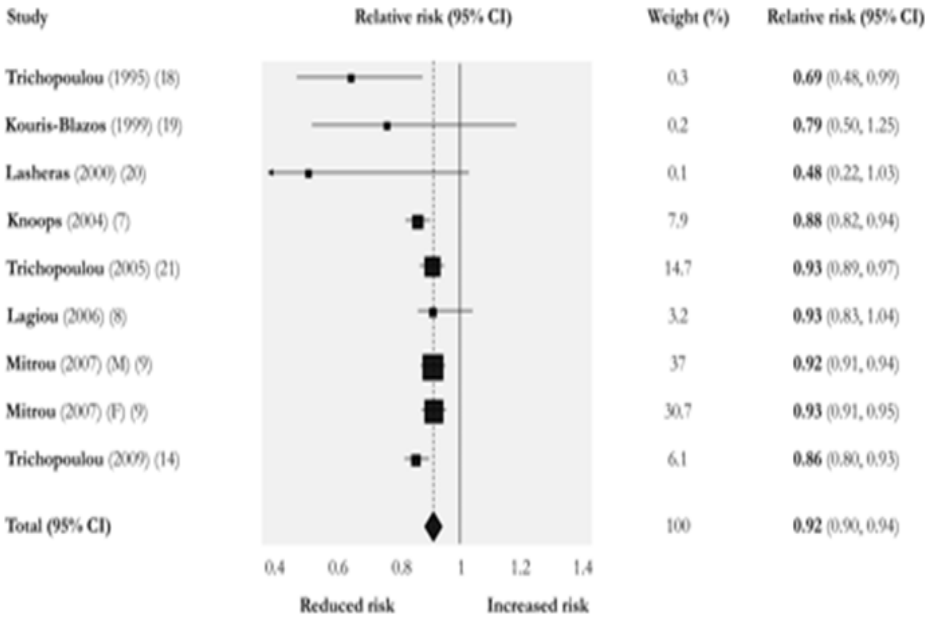
- Anti-inflammatories
- Ginkgo biloba
- Hyperhomocysteinemia
  - B6 (P5P)
  - Folic acid (BH4)
  - B12 (methyl-B12)
- Cerebral glutathione
  - NAC
- Mitochondrial function
  - CoQ10
  - PQQ

Mediterranean Diet Slows Aging and Prevents Neurological disease

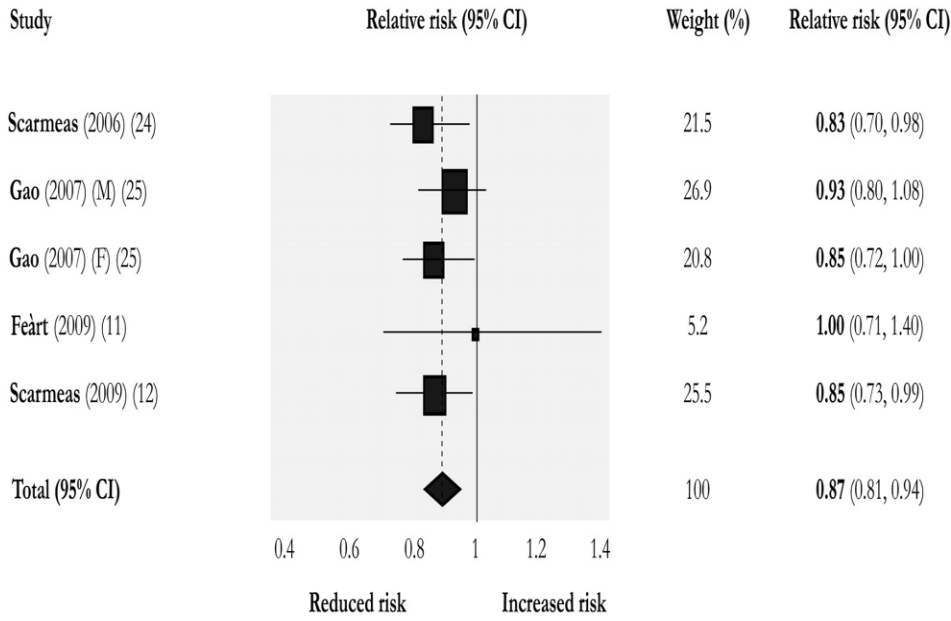
- Those following most closely this dietary pattern have a longer lifespan and a reduced risk of neurodegenerative disease, including Alzheimer's
- Review of all prospective cohort studies (nearly 600,000 subjects)
- Greater adherence to a Mediterranean diet is associated with a significant reduction in:
  - Overall mortality (8%),
  - Mortality/incidence of cardiovascular diseases (10%),
  - Incidence of or mortality from cancer (6%),
  - Incidence of Parkinson's disease and Alzheimer's disease (13%)

Pérez-López FR, Chedraui P, Haya J, Cuadros JL. Effects of the Mediterranean diet on longevity and age-related morbid conditions. Maturitas. 2009 Oct 20;64(2):67-79. Epub 2009 Aug 31.
Sofi F, et al. Adherence to Mediterranean diet and health status: meta-analysis. Am J Clin Nutr. 2010 Nov;92(5):1189-96.

Mediterranean Diet



All-cause mortality



Neurodegenerative disease

Sofi F, et al. Adherence to Mediterranean diet and health status: meta-analysis. Am J Clin Nutr. 2010 Nov;92(5):1189-96.

Marital Status and AD

- 3,675 non-demented individuals - married, divorced, widowed, never married (at outset of study)
- Followed up at 1, 3, and 5 years
- RR = 2.31 never married vs married

Helmer C, et al. Marital status and the risk of Alzheimer's disease. Neurology 1999;53:1953-8

Curcumin, Inflammation & AGEs

- Curcumin prevented effect of AGEs on hepatic stellate cells, via activating PPARγ and attenuating oxidative stress
- Curcumin also mitigates hyperglycemia-induced cytokine production in monocytes via epigenetic changes involving NF-κB – may reduce vascular inflammation & diabetic complications

Lin J, et al. Curcumin inhibits advanced glycation end-products (AGEs)-induced gene expression of receptor for AGEs (RAGE) in hepatic stellate cells in vitro by elevating PPARγ activity and attenuating oxidative stress. Br J Pharmacol. 2012 Feb 21. doi: 10.1111/j.1476-5381.2012.01910.x.
Yun et al. Epigenetic regulation of high glucose-induced proinflammatory cytokine production in monocytes by curcumin. J Nutr Biochem. 2011 May ; 22(5): 450–458. doi:10.1016/j.jnutbio.2010.03.014

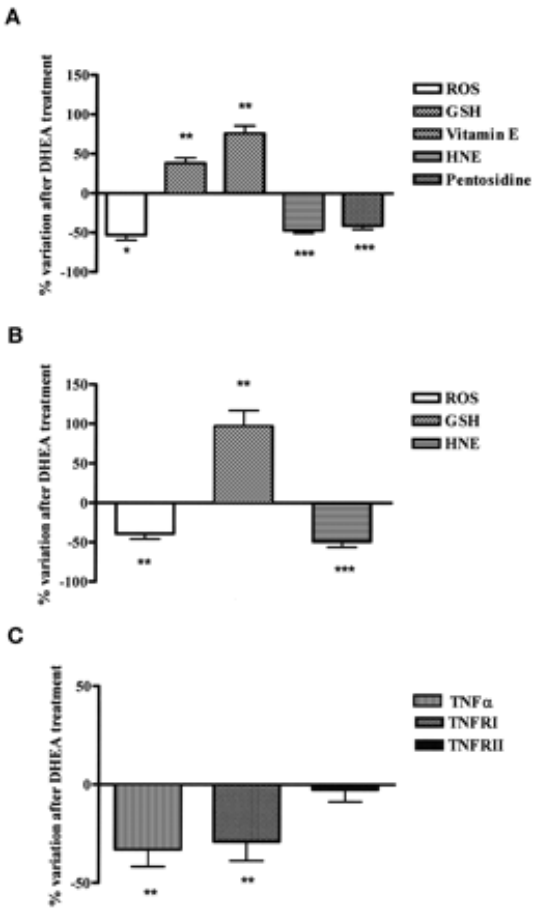
Foods with Anti-AGE Properties

- Ginger, cinnamon, allspice, and cloves among most potent inhibitors of albumin glycation
- Sage, marjoram, tarragon, and rosemary also effective
- Silymarin, blueberry extract, ellagic acid, rutin, and quercetin have all shown benefit

Farris PK. Innovative cosmeceuticals: sirtuin activators and anti-glycation compounds. Semin Cutan Med Surg. 2011 Sep;30(3):163-6.
Muthenna P, et al. Inhibition of advanced glycation end-product formation on eye lens protein by rutin. Br J Nutr. 2012 Apr;107(7):941-9.
Muthenna P, et al. Ellagic acid, a new antiglycating agent: its inhibition of Nϵ-(carboxymethyl)lysine. Biochem J. 2012 Feb 15;442(1):221-30.

DHEA Reverses AGEs Damage

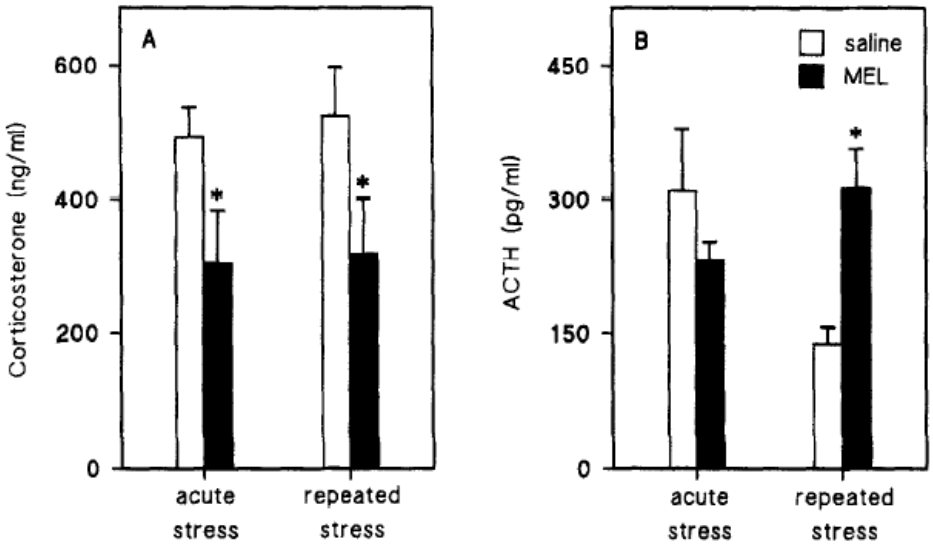
- Diabetics with good blood sugar control
  - Increased production of highly reactive oxygen species
  - Lower-than-normal antioxidant levels
  - Elevated AGEs
- DHEA
  - Decreases ROSs
  - Decreases AGEs markers
  - Increases glutathione
  - PPARα activator, similar effects to fibrates



Brignardello E, et al. DHEA administration counteracts oxidative imbalance and advanced glycation end product formation in type 2 diabetic patients. Diabetes Care 2007;30:2922-7

Melatonin Counteracts Glucocorticoid Damage

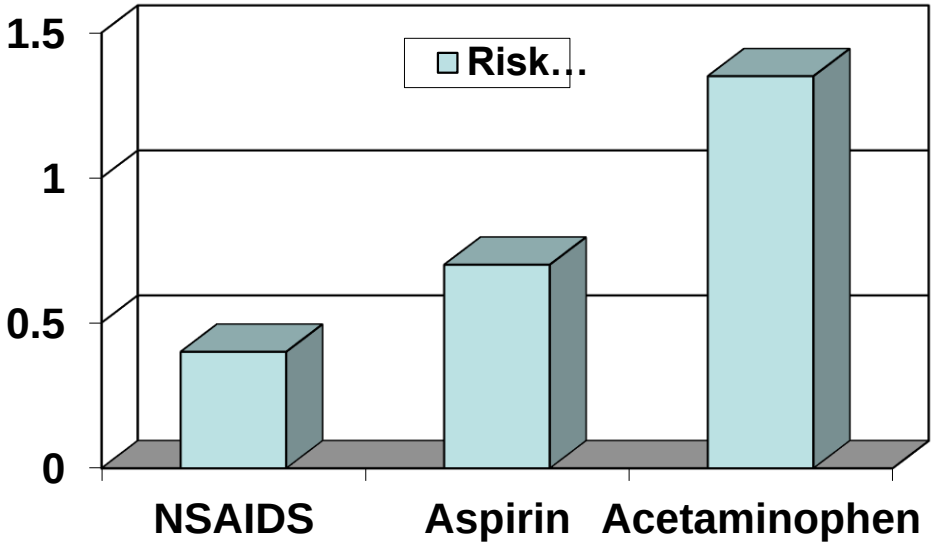
- Dexamethasone treated rats (5 days) show HPA axis dysregulation
- Melatonin decreases adrenalcortical secretory response to both acute and chronic stress



Konakchieva, R., et al. Chronic melatonin treatment and the hypothalamo-pituitaryadrenal axis in the rat: Attenuation of the secretory response to stress and effects on hypothalamic neuropeptide content and release. Biol Cell 1997;89:587-96

Anti-Inflammatory Drugs Prevent AD

- Brain “on fire”
  - Elevated pro-inflammatory cytokines
  - Over-reactive microglia
  - Alternative complement pathway activated
- 1,686 participants taking NSAIDS followed for 2 years
  - NSAIDS
  - Aspirin
  - Acetaminophen increases!
    - Pain reliever,
    - NOT anti-inflammatory



Stewart WF, et al. Risk of Alzheimer’s disease and duration of NSAID use. Neurology 1997;48:626-32

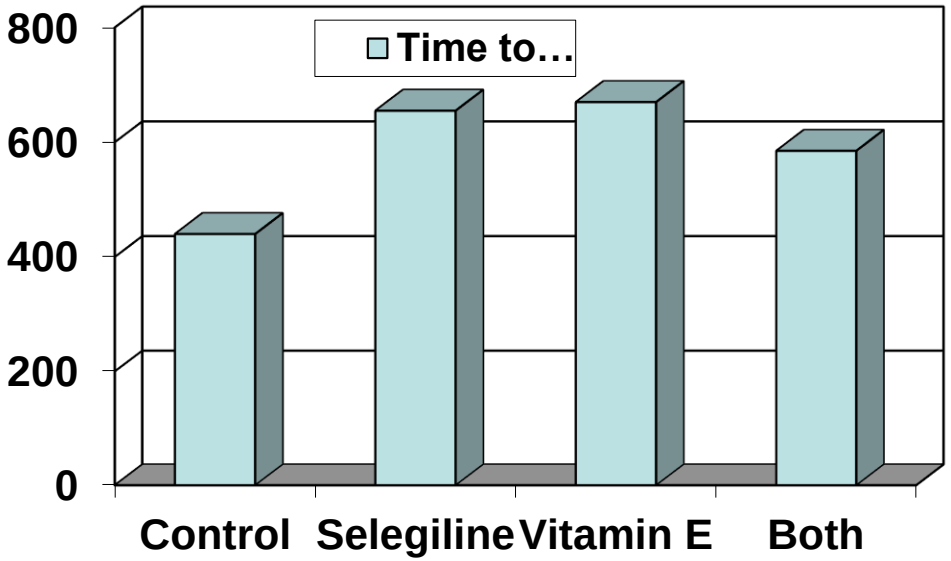
Indomethacin in Alzheimer's Disease

- 6 - month, double-blind, placebo-controlled
- 100 - 150 mg indomethacin per day
- Mild to moderate impairment
- On cognitive tests:
  - Indomethacin group improved 1.3%
  - Non treated group declined 8.4%

Rogers, J., et al. Clinical trial of indomethacin in Alzheimer's disease. Neurology 1993

Vitamin E vs Selegiline in Alzheimer's Disease

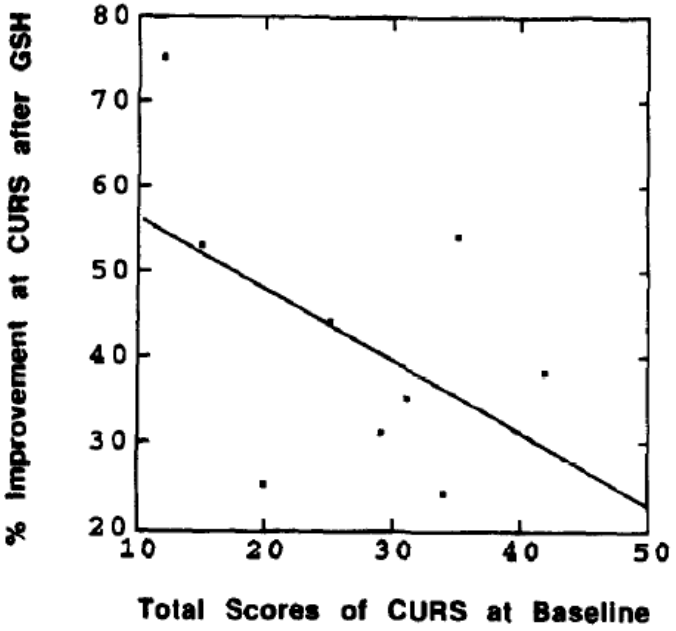
- Selegeline (selective monoamine oxidase inhibitor) 10mg/d vs. dl-alpha tocopherol 2,000 IU/d
- 341 patients
- Time to end point:
  - Death, severe dementia
  - Institutionalization
- Cost per month:
  - $ 137 selegeline
  - $ 8 vitamin E



Sano M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. NEJM 1997;336:1216-22

Glutathione Protects Neurons

- 50% less glutathione (GSH) in the substantia nigra of Parkinson's patients
- But not in other parts of brain => used up in neutralization of local toxins
- GSH 600 mg IV bid x 30 days
  - 42 % decline in disability
  - Lasted 2-4 months after stopped
- Protects both telomeres and mtDNA



Perry TL, et al. Idiopathic Parkinson's disease: A disorder due to nigral glutathione deficiency. Neuroscience Letter 1986;67:269-74

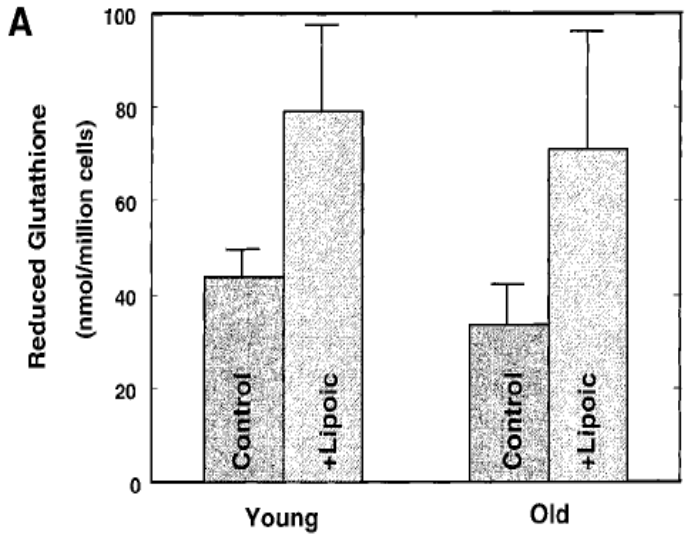
Sechi G, et al. Reduced intravenous glutathione in the treatment of early Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:1159-70

Glutathione Strategies

- Decrease depletion
- Directly administer
- Promote production
- Lifestyle

Glutathione: Decrease Depletion

- Decrease utilization
  - Decrease toxic exposure, esp alcohol
- Decrease oxidative stress
  - Decrease oxidative markers, increase GSH
  - Alpha-lipoic acid for mitochondria
  - Vitamin D for brain
  - Melatonin for brain



Addolorato G, et al. Effects of short-term moderate alcohol administration on oxidative stress and nutritional status in healthy males. Appetite. 2008 Jan;50(1):50-6

Liu J. The effects and mechanisms of mitochondrial nutrient alpha-lipoic acid on improving age-associated mitochondrial and cognitive dysfunction: overview. Neurochem Res 2008;33:194-203

Garcion E, et al. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab. 2002 Apr;13(3):100-5

Herrera J,. Melatonin prevents oxidative stress resulting from iron and erythropoietin administration. Am J Kidney Dis. 2001 Apr;37(4):750-7

Glutathione: Direct Administration

- Oral glutathione
  - Inconsistent research; 3 g did not work in humans
- Oral liposomal glutathione
  - Early promising research
- Topical glutathione
- IV glutathione
  - Very effective, but may increase Hg transport into brain
- Intranasal glutathione
  - Intriguing, does not transport Hg from blood
  - Lung absorption documented (very effective)
  - Children with chronic otitis media with effusion given glutathione as a nasal aerosol had improvement in 67% of patients, versus only 8% of controls

Witschi A, et al. The systemic availability of oral glutathione. Eur. J. Clin. Pharmacol 1992;43(6): 667–9
Cooke RW, Drury JA. Reduction of oxidative stress marker in lung fluid of preterm infants after administration of intra-tracheal liposomal glutathione. Biol Neonate. 2005;87(3):178-80
Buhl R, et al. Augmentation of glutathione in the fluid lining the epithelium of the lower respiratory tract by directly administering glutathione aerosol. Proc Natl Acad Sci USA 1990;87:4063–7
Testa B, et al. Management of chronic otitis media with effusion: the role of glutathione. Laryngoscope. 2001 Aug;111(8):1486-9.

Glutathione: Increase Production

- Silymarin
  - Standardized extract, 100 mg tid
- NAC (Also directly binds methyl-Hg)
  - 300-1000 mg bid
- Whey powder
  - 15 g bid
- Alpha-lipoic acid (decreases depletion)
  - R form preferred: 250 mg bid
- SAMe
  - Not methionine as it also increases homocysteine

Soltan-Sharifi MS, et al. Improvement by N-acetylcysteine of acute respiratory distress syndrome through increasing intracellular glutathione. Hum Exp Toxicol. 2007;26(9):697-703

Micke P, et al. Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients. Eur J Clin Invest. 2001;31(2):171-8

Jariwalla RJ, et al. Restoration of blood total glutathione status and lymphocyte function following alpha-lipoic acid supplementation in patients with HIV infection. J Alt Comp Med. 2008;14(2):139-46

Liber CS, Packer L (November 2002). "S-Adenosylmethionine: molecular, biological, and clinical aspects—an introduction". Am J Clin Nutr. 76 (5): 1148S–50S

Glutathione: Lifestyle Interventions

- Hours/week of moderate exercise positively associated with blood glutathione levels (not excessive exercise!)
- Aerobic and weight training combined more effective than either alone
- Cruciferous vegetables with intact glucosinolates likely to boost glutathione levels and detoxifying enzyme activity

Rundle AG, et al. Preliminary studies on the effect of moderate physical activity on blood levels of glutathione. Biomarkers. 2005 Sep-Oct;10(5):390-400.
Elokda et al. Effects of exercise training on the glutathione antioxidant system. Eur J Cardiovasc Prev Rehabil. 2007 Oct;14(5):630-7.
Abdull Razis AF, et al. Intact glucosinolates modulate hepatic cytochrome P450 and phase II conjugation activities and may contribute directly to the chemopreventive activity of cruciferous vegetables. Toxicology. 2010 Nov 9;277(1-3):74-85.

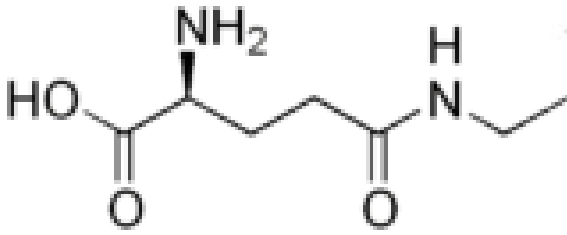
Coffee!

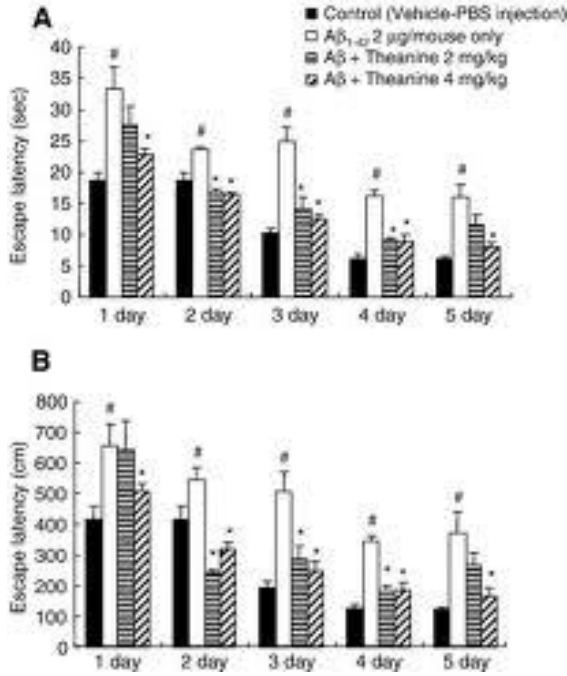
- Growing number of studies showing caffeine protects from dementia and Alzheimer’s disease
- 2,475 women aged 65+ in the Women's Antioxidant Cardiovascular Study (high vascular risk)
- Randomized trial of antioxidants and B vitamins
- Independent of all other factors, significantly slower rates of cognitive decline with increasing caffeine intake
- Top quintile intake cognitively 7 years younger than bottom quintile
- Coffee more effective than decaf, tea, cola, chocolate
- Strongest protection when also taking B-vitamins

Vercambre MN, et al. Caffeine and Cognitive Decline in Elderly Women at High Vascular Risk. J Alzheimers Dis. 2013 Feb 19. [Epub ahead of print]

L-Theanine

- Amino acid from green tea
- Crosses blood-brain barrier
- Reduce mental and physical stress, improves cognition and boosts mood
- Synergistic with caffeine
- Neuroprotective
- Reduces toxicity of beta-amyloid
- 100-200 mg/d 1-3x/d

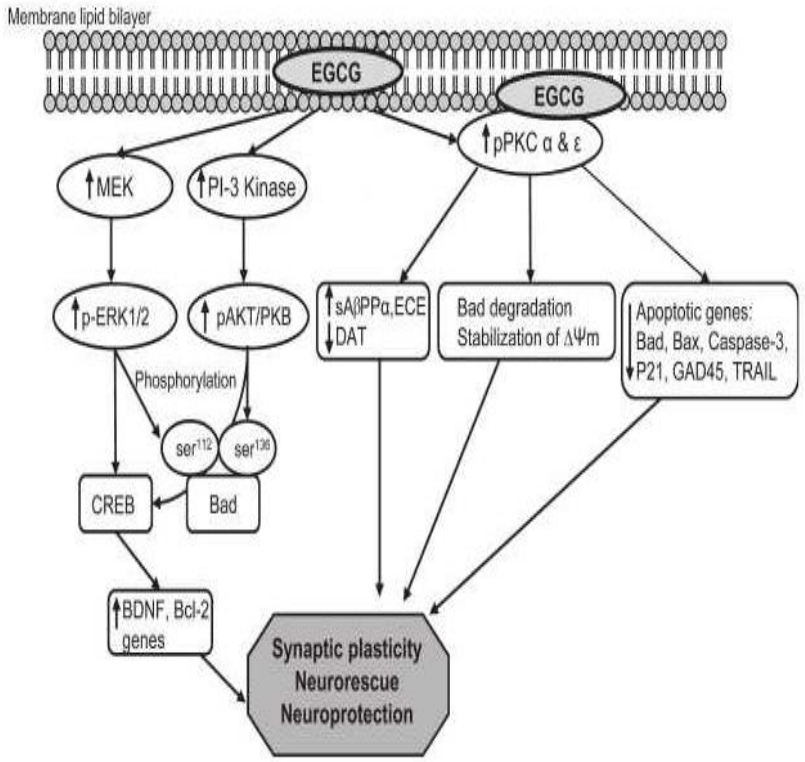




Kim TI, Lee YK, Park SG, et al. L-theanine, an amino acid in green tea, attenuates beta-amyloid-induced cognitive dysfunction and neurotoxicity: reduction in oxidative damage and inactivation of ERK/p38 kinase and NF-kappaB pathways. Free Radic Biol Med. 2009 Dec 1;47(11):1601-10

Green Tea (EGCG)

- Multiple mechanisms of action
- Antioxidant and iron chelator
  - Decreases the generation of amyloid-(A) peptide and synuclein fibrils
- Modulates signaling pathways, e.g. protein kinase C (PKC, involved in cell survival, apoptosis, and long-term potentiation
- Mitochondrial protection and augmentation

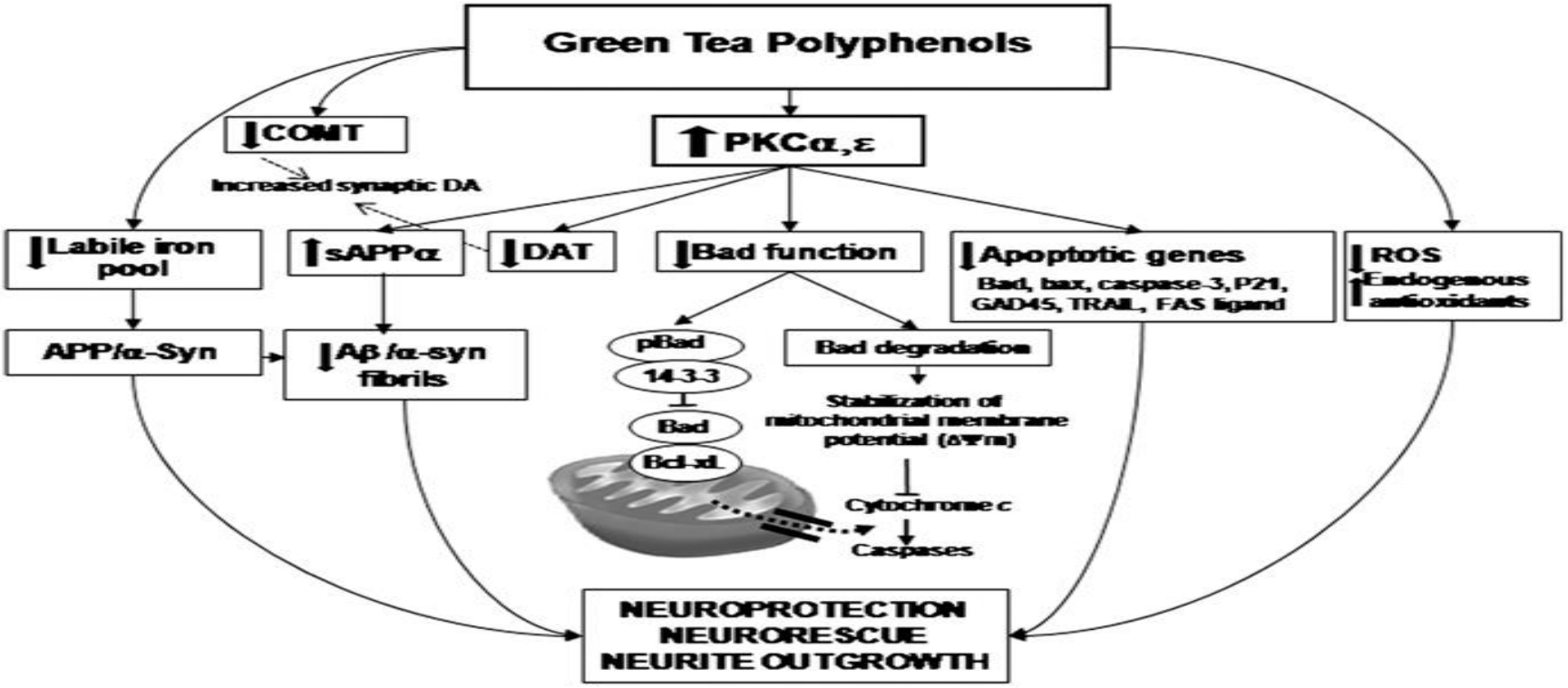


Mandel 2011

Mandel SA, et al. Understanding the broad-spectrum neuroprotective action profile of green tea polyphenols in aging and neurodegenerative diseases. J Alzheimers Dis. 2011;25(2):187-208.

Srividhya R, et al. Mitochondrial alterations in aging rat brain: effective role of (-)-epigallo catechin gallate. Int J Dev Neurosci. 2009 May;27(3):223-31.

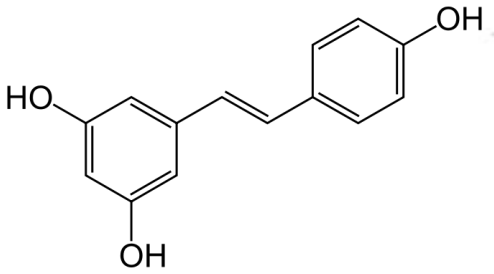
Green Tea Mechanisms of Neuroprotection



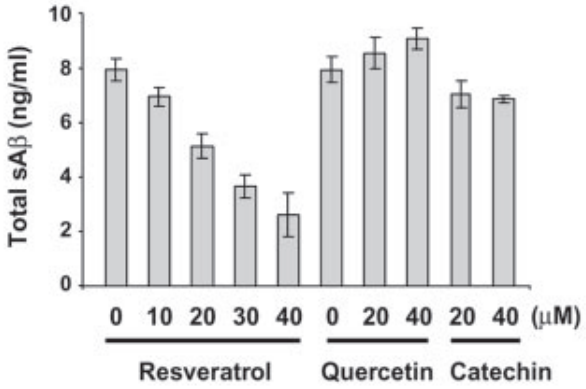
Mandel 2008

Mandel SA, et al. Targeting multiple neurodegenerative diseases etiologies with multimodal-acting green tea catechins. J Nutr. 2008 Aug;138(8):1578S-1583S.

Resveratrol



- Many of same benefits as caloric restriction
- Free radical scavenger
- Beta-amyloid
  - Inhibits formation
  - Clears from brain cells in cell cultures
- May explain protective effects of wine



Kim J, Lee HJ, Lee KW. Naturally occurring phytochemicals for the prevention of Alzheimer's disease. J Neurochem. 2010 Mar;112(6):1415-30

Marambaud P, Zhao H, Davies P. Resveratrol promotes clearance of Alzheimer's disease amyloid-beta peptides. J Biol Chem. 2005 Nov 11;280(45):37377-82

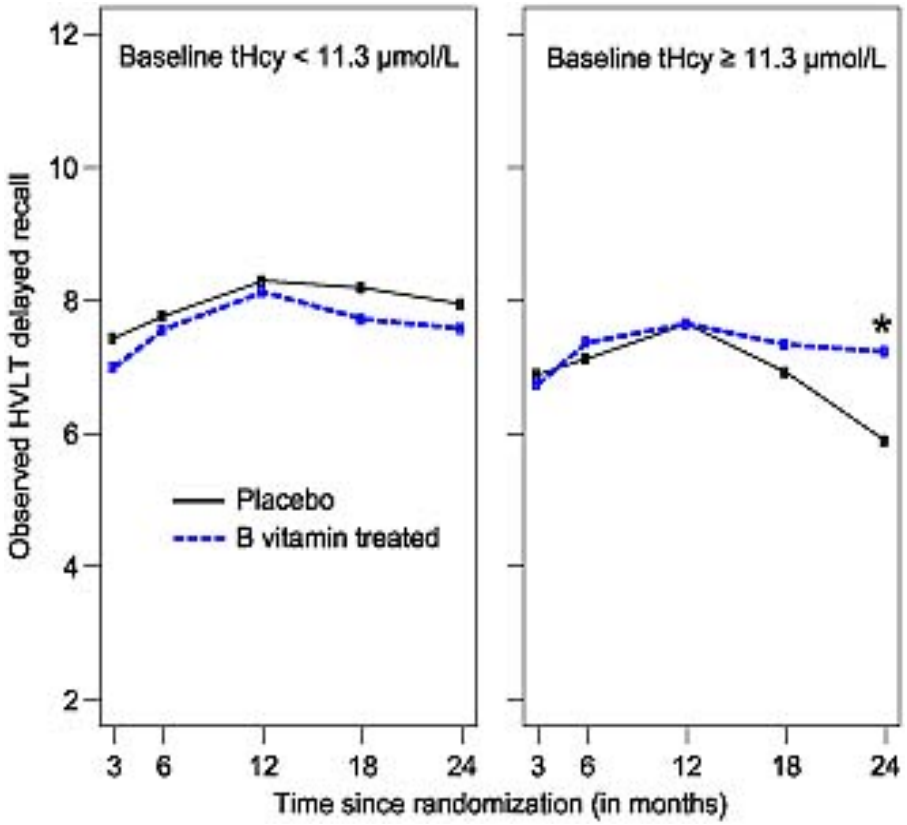
Resveratrol – Clinical Trial

- 11 healthy, obese men given placebo and 150 mg/day resveratrol (99% pure trans-resveratrol) in a randomized double-blind crossover study for 30 days
  - Resveratrol had favorable metabolic adaptations that mimicked the effects of calorie restriction and/or endurance training
  - It reduced hepatic lipid content, improved skeletal muscle intrinsic mitochondrial function and several plasma markers of general health
  - Subjects had a significantly lower sleeping metabolic rate compared to placebo
  - Resveratrol significantly lowered systolic blood pressure and mean arterial pressure

Timmers S, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab. 2011 Nov 2;14(5):612-22.

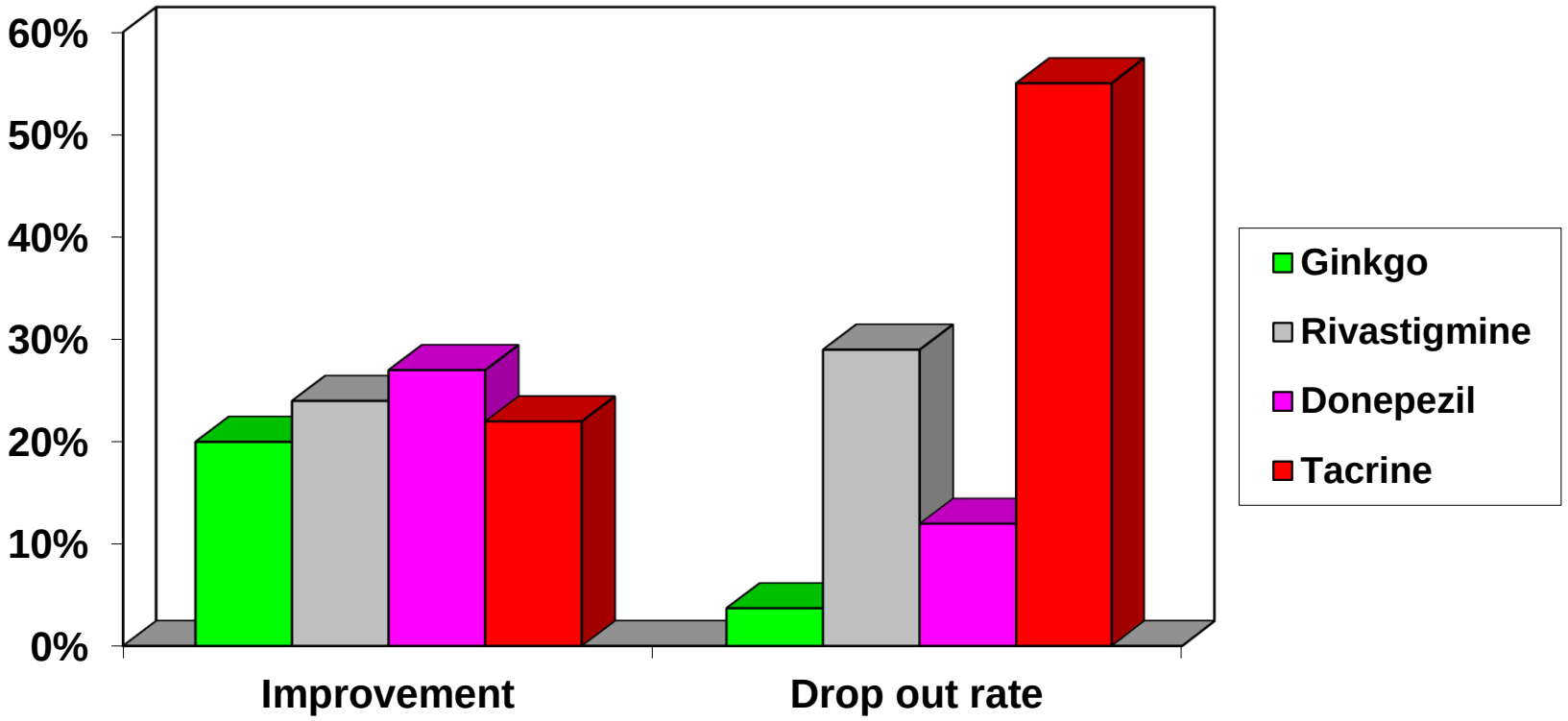
B Vitamins Also Slow Cognitive Decline

- Double-blind study
- Participants with mild cognitive impairment, aged ≥ 70 y
- Randomly assigned to receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B(12) and 20 mg vitamin B(6) (133 participants) or placebo (133 participants) for 2 y
- Found to slow cognitive and clinical decline, particularly in those who have high tHcy concentrations.



de Jager CA, et al. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry. 2012 Jun;27(6):592-600.

Ginkgo vs Acetylcholinesterase Inhibitors in Mild-Moderate AD



Key Mitochondrial Nutrients

- Magnesium
  - Cofactor in OXPHOS enzymes, ATP synthase
- B_1, B_2, B_3, B_6, NADH
  - Riboflavin is the major cofactor for the flavoproteins FAD and FMN, which shuttle energy from the citric acid cycle and β-oxidation to complex II of the electron transport chain
- Vitamin A
  - Cofactor for protein kinase C
  - Regulates the amount of pyruvate that is funneled through the Kreb's cycle

Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. Arch Biochem Biophys. 2007 Feb 1;458(1):40-7.
[Zorzano A, et al. Role of mitochondrial dynamics proteins in the pathophysiology of obesity and type 2 diabetes. Int J Biochem Cell Biol. 2009 Oct;41(10):1846-54.
Condò M, et al. Riboflavin prophylaxis in pediatric and adolescent migraine. J Headache Pain. 2009;10:361-5.

Key Mitochondrial Nutrients

- Creatine
  - Phosphocreatine participates in efficient recycling of ATP from ADP
  - Effective as part of a treatment for several neurodegenerative disorders, particularly Huntington's disease and Parkinson's disease
- Acetyl-L-carnitine & L-carnitine
  - Facilitates the uptake of acetyl-CoA into the mitochondria, and transports short, medium, and long-chain fatty acids toward or across the inner mitochondrial membrane, respectively. Carnitine also promotes gluconeogenesis.
  - Benefit for Alzheimer's dementia, chronic fatigue syndrome, depression, diabetic neuropathies, ischemia and reperfusion injury

Ryu H, etal. The therapeutic role of creatine in Huntington's disease. Pharmacol Ther. 2005 Nov;108(2):193-207.
Adhihetty PJ, Beal MF. Creatine and its potential therapeutic value for targeting cellular energy impairment in neurodegenerative diseases. Neuromolecular Med. 2008;10(4):275-90.
Calabrese V, et al. Acetylcarnitine and cellular stress response: roles in nutritional redox homeostasis and regulation of longevity genes. J Nutr Biochem. 2006 Feb;17(2):73-88.
Malaguarnera M, et al. Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. Arch Gerontol Geriatr. 2008 Mar-Apr;46(2):181-90.

Coenzyme Q10

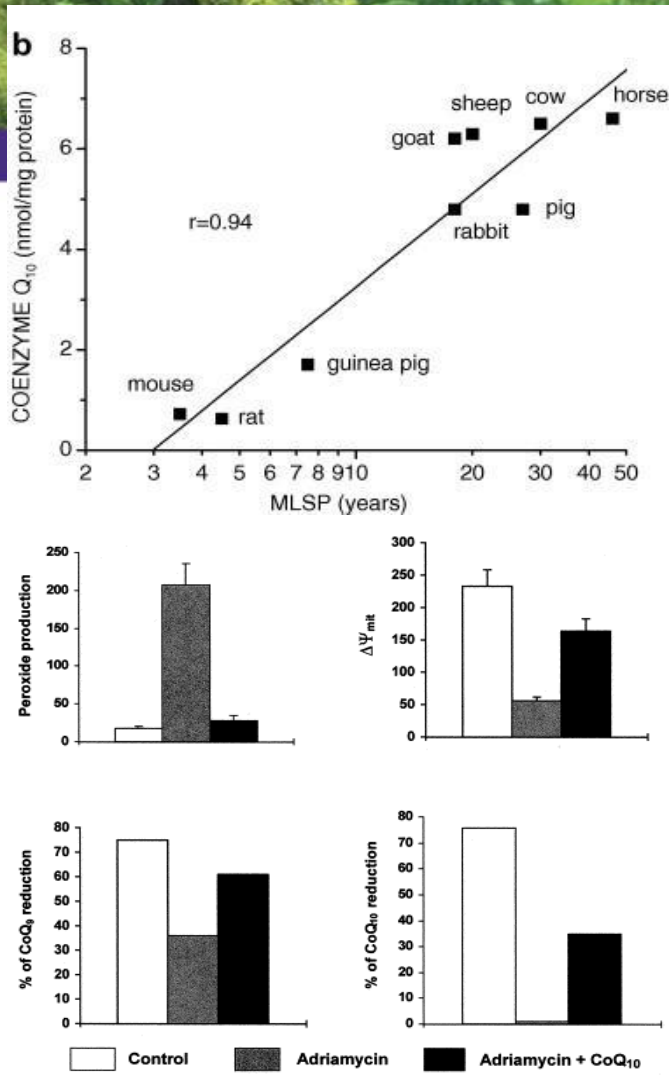
- Function:
  - Required for the production of ATP by mitochondria
  - Important mitochondrial and cellular antioxidant
- Primary clinical applications:
  - Heart disease (angina, cardiomyopathy, congestive heart failure, high blood pressure, etc.)
  - Neurodegenerative disease (e.g., Alzheimer's & Parkinson's)
  - Prevents statin-induced depletion and cardiotoxicity of chemotherapy drugs
  - Boost immune function, anti-aging, periodontal disease, macular degeneration, etc.

CoQ10 Levels in Humans

- Normal blood ranges:
  - 0.7 to 1.0 mcg.ml
  - Approximately 95% is ubiquinol
- Deficiency can be caused by:
  - Decreased dietary intake
    - Normal intake about 5 mg/day
  - Impaired biosynthesis
  - Increased need
    - Statin drugs
    - Oxidative stress
    - Aging, CV disease, cancer, diabetes, periodontal disease
    - Neurodegenerative disease

CoQ10

- Direct cross-species correlation between CoQ10 levels and longevity
- Statin drugs inhibit CoQ10 production
- Protects mitochondria from toxins and drugs
- Mitigated oxidative damage from reoxygenation following cardiac surgery
- May augment fat oxidation during exercise



Lenaz G, et al. Mitochondrial bioenergetics in aging. Biochim Biophys Acta. 2000;1459:397-404

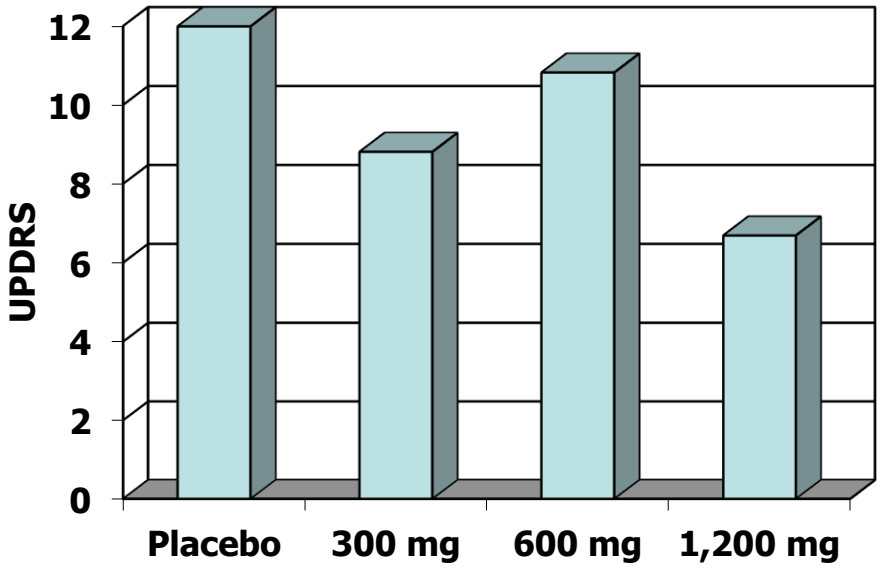
Sohal RS, Forster MJ. Coenzyme Q, oxidative stress and aging. Mitochon 2007;7:S103-11

Rosenfeldt F, et al. Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and in vitro contractility of myocardial tissue. J Thorac Cardiovasc Surg. 2005 Jan;129(1):25-32.

Zheng A, Moritani T. Influence of CoQ10 on autonomic nervous activity and energy metabolism during exercise in healthy subjects. J Nutr Sci Vitaminol (Tokyo). 2008 Aug;54(4):286-90.

CoQ10 and Parkinson's Disease

- Placebo-controlled, double-blind
- Followed for 16 months or until disability required L-dopa.
- Change in the total score on the UPDRS from baseline to last visit.
- It increased platelet mitochondrial function of complexes I, II, and III, compared with placebo
- Difference between the 1200-mg/d and placebo significant (P =.04)
- Earlier one month only showed positive trend, not significance

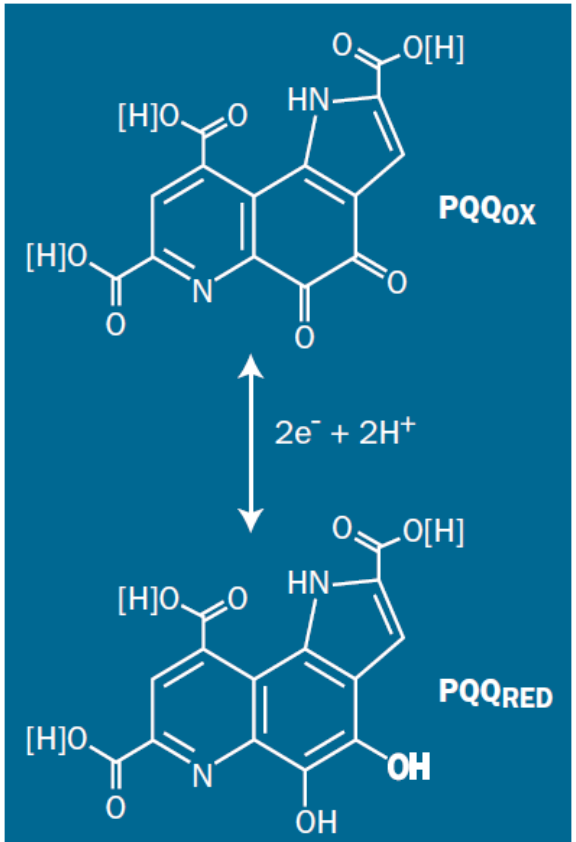


Shults CW, et al . Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol. 2002;59:1541-50

Shults CW, et al. Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients. Neurology 1998;50:793-5

Pyrroloquinoline Quinone (PQQ)

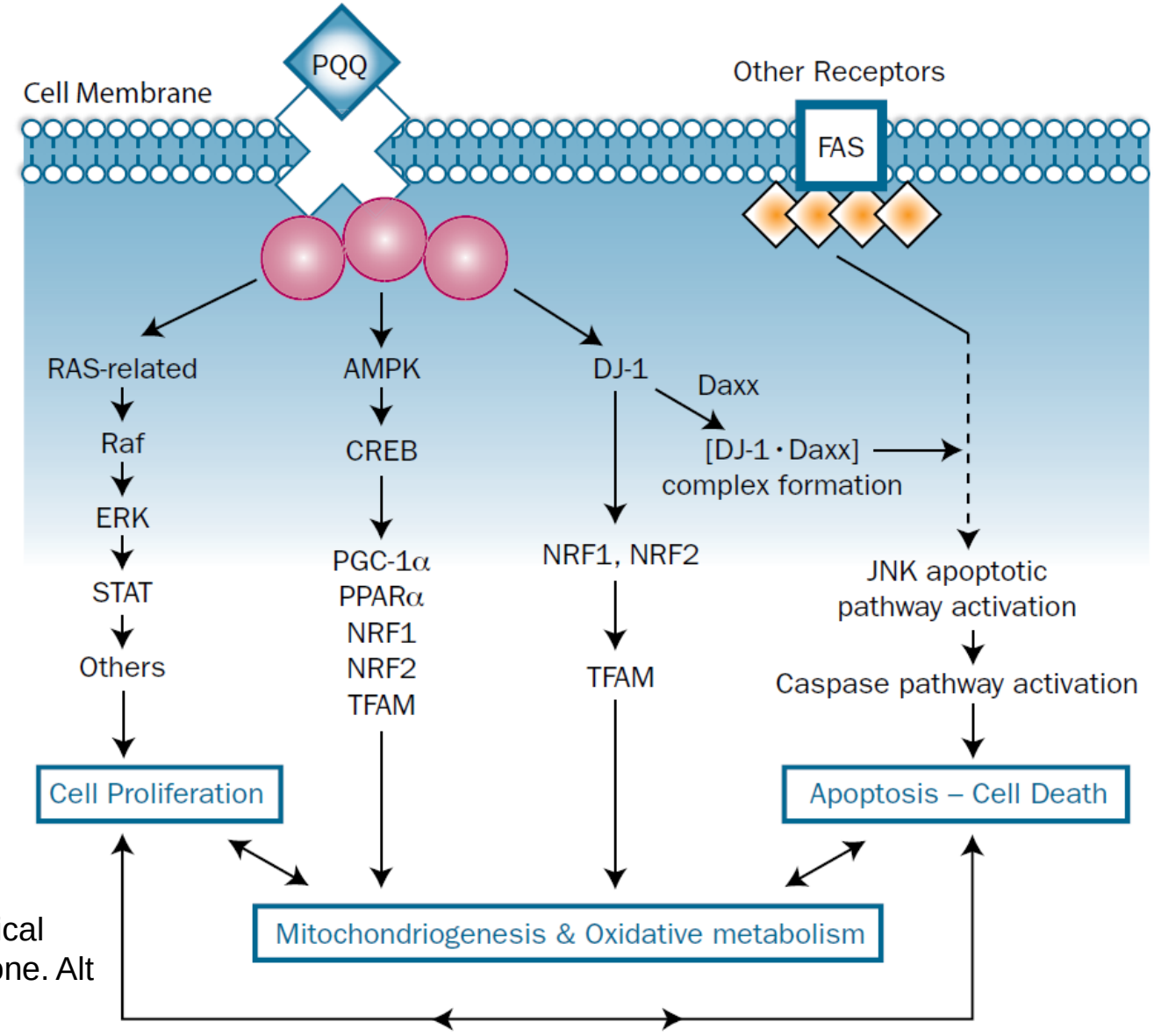
- Vitamin-like cofactor
- Shown to be essential in mammalian nutrition in 1994
- Physiological functions:
  - Vital for mitochondrial function
  - Neuroprotective, promotes NGF
  - Memory restorative in animal and human studies
- Synergistic effect with CoQ10



PQQ is depicted in its oxidized (OX) and reduced (RED) forms. Note at pH 7.0, PQQ is anionic (has a negative charge) owing to the dissociation of [H+] from its carboxylic acid moieties (–[C=O]-O[H]).

Rucker R, et al. Potential physiological importance of pyrroloquinolinequinone. Alt Med Rev 2009; 14: 268-77

PQQ and Cell Signaling



Rucker R, et al. Potential physiological importance of pyrroloquinolinequinone. Alt Med Rev 2009; 14: 268-77

PQQ: An Exceptional Antioxidant

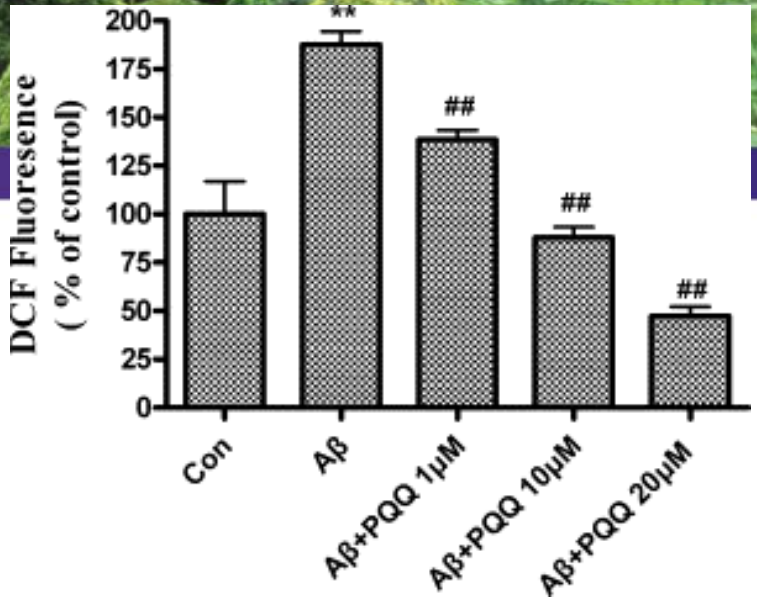
- Redox cycling systems result in repeated reactions in which molecules that act as catalysts are repeatedly oxidized and/or reduced.
- The potential number of catalytic cycles (repeated reactions) depends in part on chemical stability.
- PQQ is relatively stable; whereas, self-oxidation, polymerization, and/or changes in chemical structure are factors that compromise the chemical stability of many bioactive quinones or enediols (e.g., ascorbic acid).

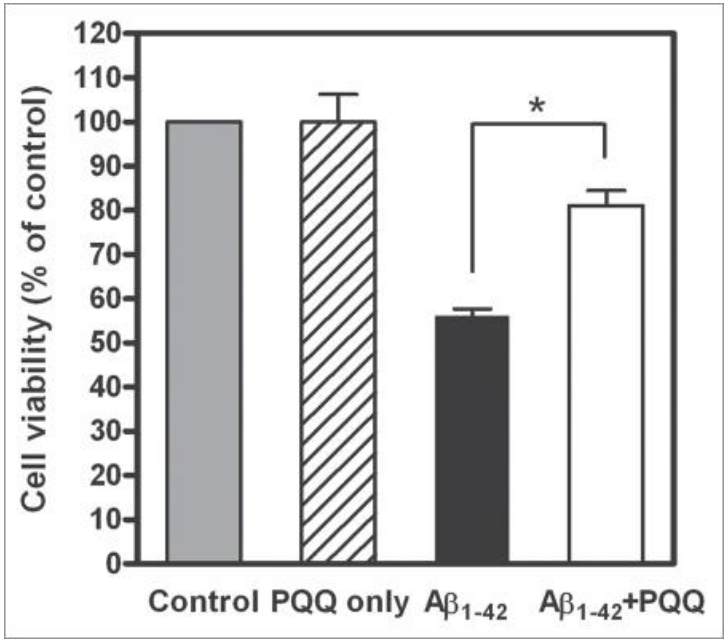
Compound	Potential Number of Catalytic Cycles
PQQ	20,000
Quercetin	800
Catechin	75
Epicatechin	700
Norepinephrine	200
Epinephrine	100
DOPA	20
6-OH-DOPA	20
Ascorbic Acid	4

Rucker R, et al. Potential physiological importance of pyrroloquinolinequinone. Alt Med Rev 2009; 14: 268-77

PQQ – Cell Data

- Inhibit production of beta-amyloid in mice neurons
- Protects human neurons from beta-amyloid



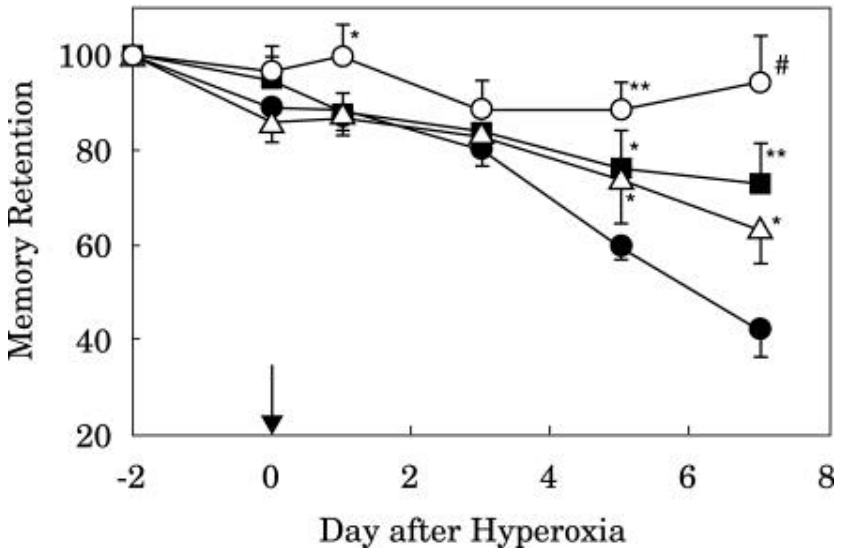


Zhang JJ, et al. Protective effect of pyrroloquinoline quinone against A-beta-induced neurotoxicity in human neuroblastoma SH-SY5Y cells. Neurosci Lett. 2009 Oct 30;464(3):165-9

Kim J, et al. Pyrroloquinoline quinone inhibits the fibrillation of amyloid proteins. Prion. 2010 Jan-Mar;4(1):26-31

PQQ and CoQ10 - Animal Data

- Together more effective than alone
- Protects brain from oxidative stress
  - ● Control
  - △ CoQ10
  - ■ PQQ
  - ○ CoQ10 + PQQ



Ohwada K, et al. Pyrroloquinoline quinone (PQQ) prevents cognitive deficit caused by oxidative stress in rats. J Clin Biochem Nutr. 2008 Jan;42:29-34

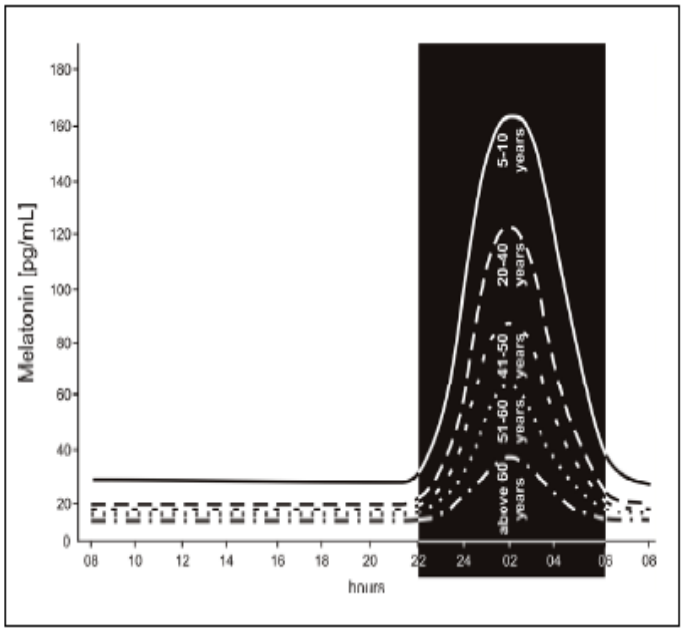
Sleep Enhancement – Delayed Onset

- LUX (phototherapy)
  - Although early trials suggested a 20-minute application was sufficient, more recent work suggests that 45 minutes has a greater effect and a longer lasting benefit
  - Bright morning light has also been used with success in the treatment of sleep-onset insomnia, while early morning awakening insomnia has been treated with bright light in the evening
- Melatonin
- Valerian/Kava kava

Kirisoglu C, et al. Twenty minutes versus forty-five minutes morning bright light treatment on sleep onset insomnia in elderly subjects. J Psychosom Res. 2004 May;56(5):537-42.
Lack L, et al. The treatment of sleep onset insomnia with bright morning light. Sleep Biol Rhythms 2007;5:173-9.
Lack L, et al. The treatment of early-morning awakening insomnia with 2 evenings of bright light. Sleep. 2005 May 1;28(5):616-23.

Melatonin

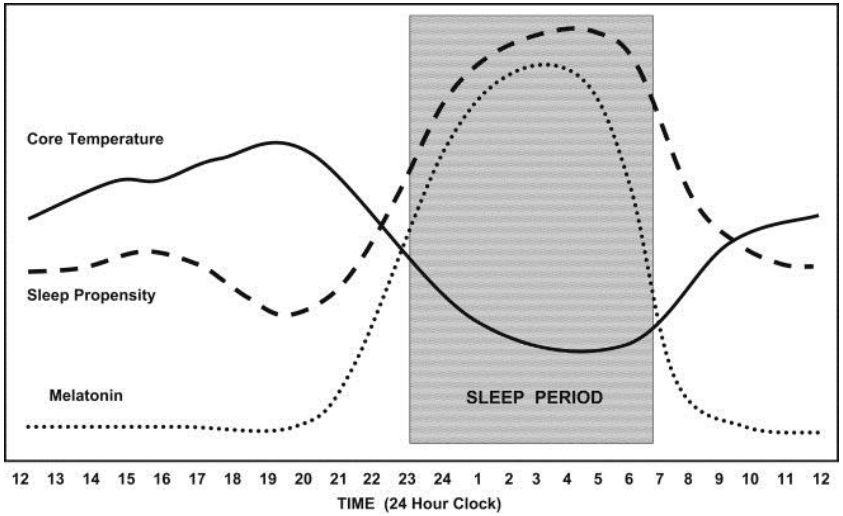
- Melatonin levels at night decrease with age
- Synthesized in pituitary from tryptophan
- Strictly controlled by light levels
- Potent free radical scavenger in brain
- Can counteract glucocorticoid damage
- May be related to sirtuin production



Karasek M. Does melatonin play a role in aging processes? J Physiol Pharmacol 2007;58s:105-13

Sleep Enhancement – Early Awakening

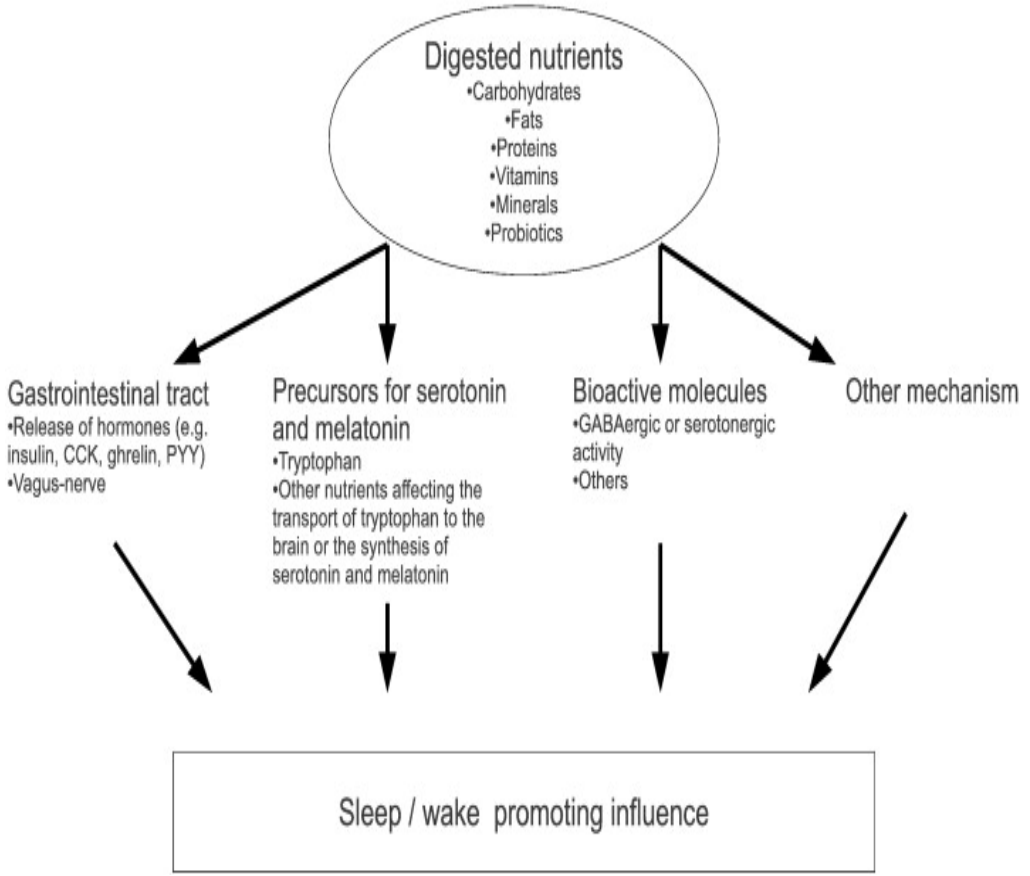
- Causes
  - Sleep apnea
  - Depression/anxiety
  - Alcohol rebound (leave 2 hrs/oz)
  - Caffeine rebound (leave 12 hours if slow CYP1A2)
  - Restless leg syndrome
  - Room environment too active (light, noise, heat)
- Interventions
  - Cooler temperature:
  - Melatonin (elderly & young)
  - Magnesium
  - GABA
  - 5-HTP
  - Theanine



Lack LC, Gradisar M, Van Someren EJ, et al. The relationship between insomnia and body temperatures. Sleep Med Rev. 2008 Aug;12(4):307-17

Diet Also Influences Sleep Patterns

- Emerging evidence suggests a link between nutrients and sleep’
- Ex: 5-HTP is converted to serotonin by AADC, which needs pyridoxine
- Ex: Arylalkylamine-N-acetyltransferase (NAT) needs n-3 fatty acids to convert serotonin to melatonin



Peuhkuri K, et al. Diet promotes sleep duration and quality. Nutr Res. 2012 May;32(5):309-19.

2. Neurological Hyper-Excitability

- Hyper-Excitability
  - Reduced threshold for neuronal activation increases susceptibility to sudden intense neuronal activity
- Signs and symptoms
  - Irritability
  - Tetany syndrome (muscle spasms, cramps, hyperarousal, hyperventilation, and asthenia)
- Lab tests
  - Increased plasma glutamic acid
- Typical diseases
  - Migraine (with aura)
  - Epilepsy
  - Dizziness/Vertigo

Neurological Hyper-Excitability: Causes

- Excess excitatory neurotransmitter glutamate
- Decreased activity of the inhibitory neurotransmitter GABA, which normally inhibits the activity of serotonin and glutamate
- Head injury
- Hypoxia
- Toxic exposure
  - Neurotoxins
  - Barbituates
  - Benzodiazapenes
- Magnesium deficiency
- Decreased neuronal mitochondrial activity

Neurological Hyper-Excitability: Treatment

- Eliminate
  - Toxin exposure
  - Neurotoxic drugs
  - Food allergens
- Supplement with
  - Magnesium
  - Zinc
  - Glycine
  - GABA

3. Neuronal Hypo-Excitability

- Hypo-Excitability
  - Impaired neuronal function
  - Decreased neuronal activity
  - Decreased neurotransmitters
- Symptoms
  - Fatigue
  - Lethargy
- Diseases
  - Depression
  - SAD (seasonal affective disorder)

Neuronal Hypo-Excitability: Causes

- Hormonal
- Environmental toxins
- Lifestyle
- Nutritional deficiencies

Neuronal Hypo-Excitability Causes - Hormonal

- Low thyroid function
  - Decreases all cellular metabolic activity
  - Blood thyroid hormone levels not reliable
- Elevated cortisol, often associated with low DHEA
  - Increases tryptophan oxygenase, shunting of tryptophan to the kynurenine pathway at the expense of serotonin and melatonin synthesis

  $\Rightarrow$ Sleep disruption

Neuronal Hypo-Excitability Causes – Environmental Toxins

Toxic Metals

- Lead
- Mercury
- Cadmium
- Arsenic
- Nickel
- Aluminum

Solvents

- Cleaning materials
- Formaldehyde
- Toluene
- Benzene

Pesticides

- OC pesticides

Herbicides

Neuronal Hypo-Excitability Causes - Lifestyle

- Smoking
  - Elevates cortisol levels
    - Activates of tryptophan oxygenase (kynurine path)
    - Down-regulates" serotonin receptors
- Alcohol
  - Brain depressant
  - Increases cortisol production
- Caffeine + sugar
  - Depressed subjects consume more

Leibenluft E, et al. Depressive symptoms and the self-reported use of alcohol, caffeine, and carbohydrates in normal volunteers and four groups of psychiatric outpatients. Am J Psychiatry 1993;150:294-301

Neuronal Hypo-Excitability Causes – Nutritional Deficiencies

- Folic acid and vitamin B12
  - Deficient in 31–35% of depressed patients
  - Required for SAMe production
  - Required for neurotransmitter methylation (serotonin and dopamine)
- Vitamin B6
  - Essential in the manufacture of all monoamines
- Omega-3 fatty acids
  - Phospholipid composition of neuron membranes
  - Directly influences neurotransmitter synthesis, signal transmission, uptake of neurotransmitters, and the activity of monoamine oxidase

In Conclusion

1. Neurodegeneration is common, preventable and, to some degree, reversible
2. Protect neurological system from damage
   - Neurotoxic POPs, Hg
   - Antioxidants
   - Adequate rest
   - Stress reduction
   - Reduce AGE content of foods
3. Utilize appropriate nutrients to support mitochondrial and neuron health
4. Promote glutathione production
5. Get adequate sleep