Moderate Deficiency of an Essential Vitamin or Mineral Accelerates Diseases of Aging

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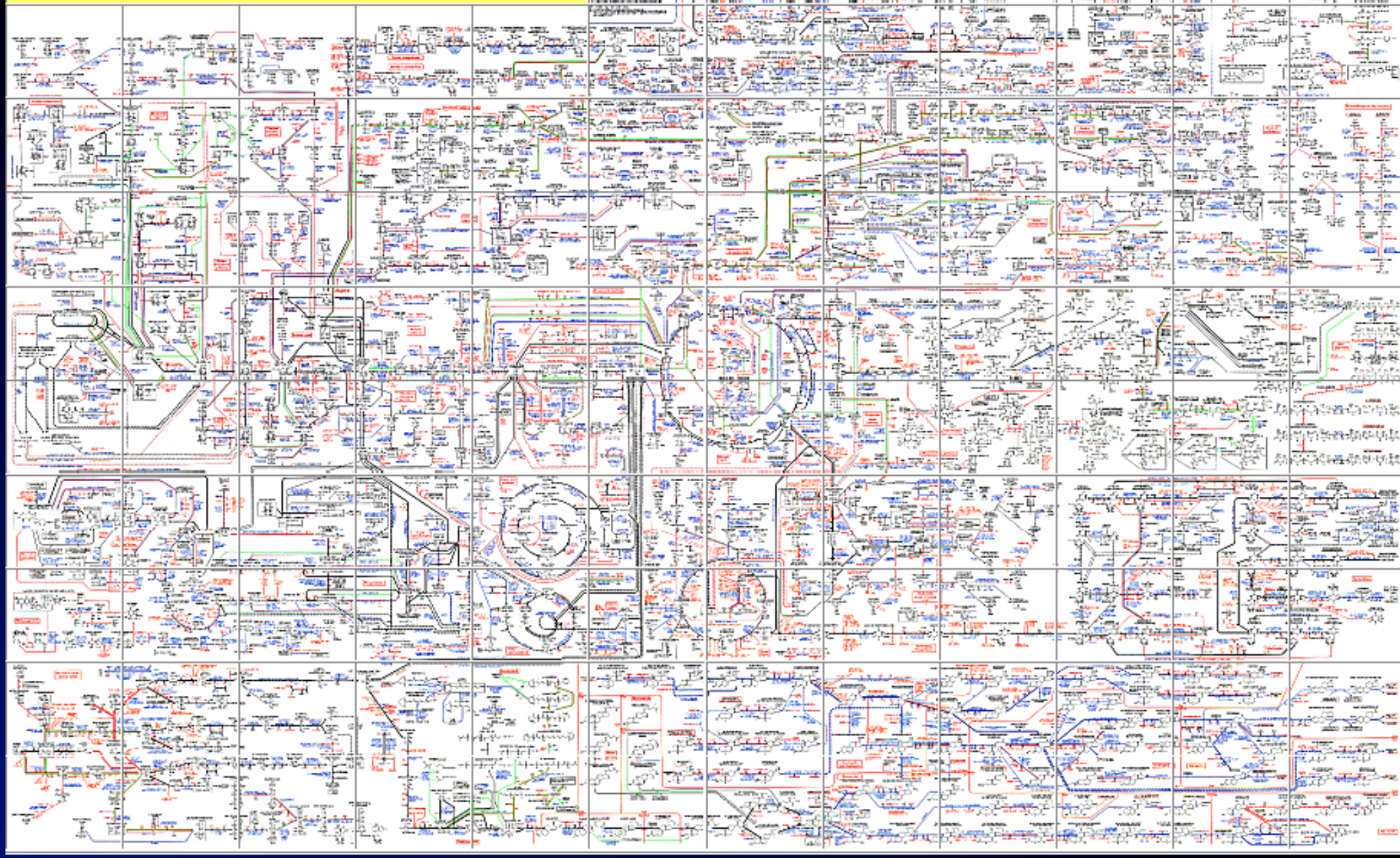
21 May 2015
Kann. NC

Biochemical Pathways



~40 Essential Micronutrients

- Biotin
- Folic acid
- Niacin
- Pantothenate
- Riboflavin
- Thiamine
- VitA
- VitB6
- VitB12
- VitC
- VitD
- VitE
- VitK

- Calcium
- Chloride
- Chromium
- Cobalt
- Copper
- Iodide
- Iron
- Magnesium
- Manganese
- Molybdenum
- Phosphorus
- Potassium
- Selenium
- Sodium
- Zinc

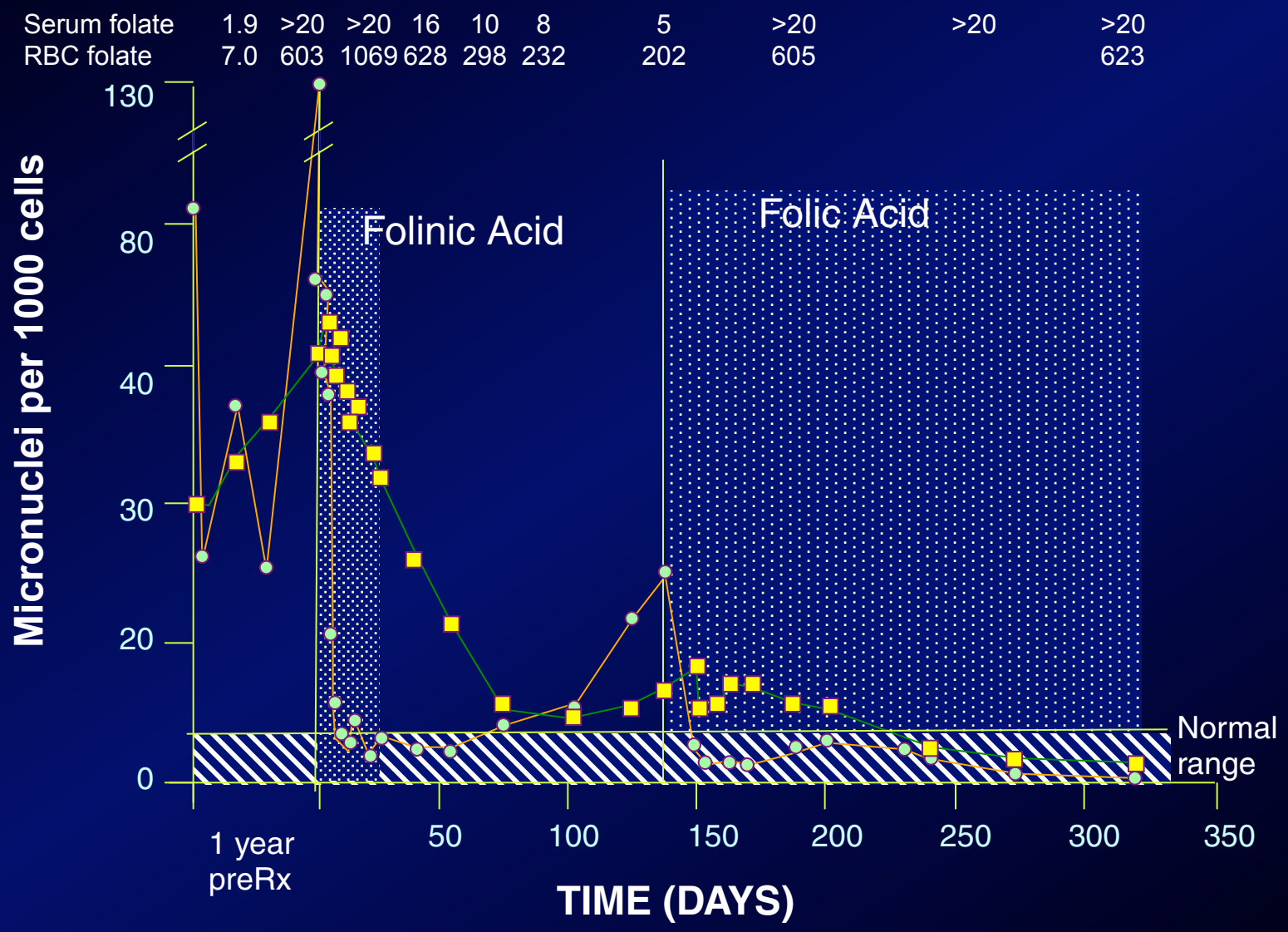
- Linolenic acid/DHA [ω-3]
- Linoleic acid [ω-6]
- Choline
- Isoleucine
- Leucine
- Lysine
- Methionine
- Phenylalanine
- Threonine
- Tryptophan
- Valine
- Histidine

Micronutrient Undernutrition in Americans

NUTRIENT	% Ingesting < EAR (food, fortif, suppl)
Vitamin D	70%
Vitamin E	60%
Magnesium	45%
Vitamin K	35 %
Calcium	35%
Vitamin A	34%
Vitamin C	25%
Omega-3	Very High %
Zinc	8%
etc.	

US Population (Fulgoni et al.2011)

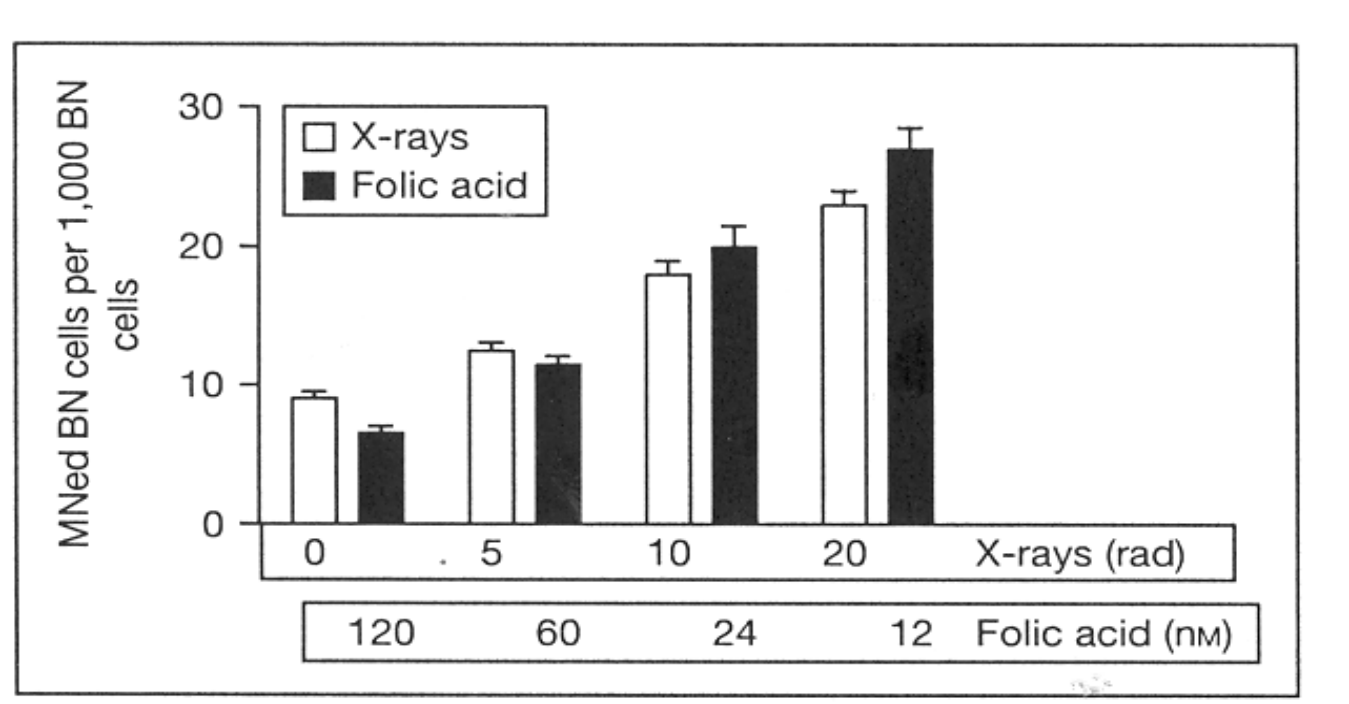
Micronuclei in: RNA positive erythrocytes
RNA negative erythrocytes



Everson RB, Wehr CM, Erexson GL, and MacGregor JT. (1988) *J Natl Cancer Inst* 80:525-9.

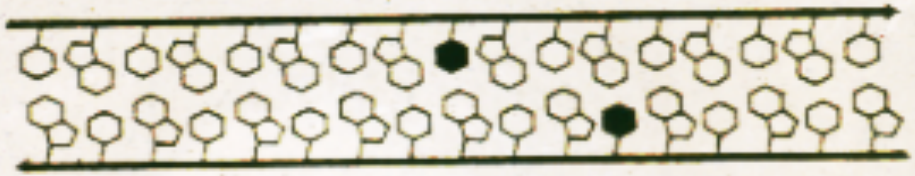
Dose-response on micronuclei induction in cultured lymphocytes

Acute exposure to X-rays vs. Folic Acid deficiency

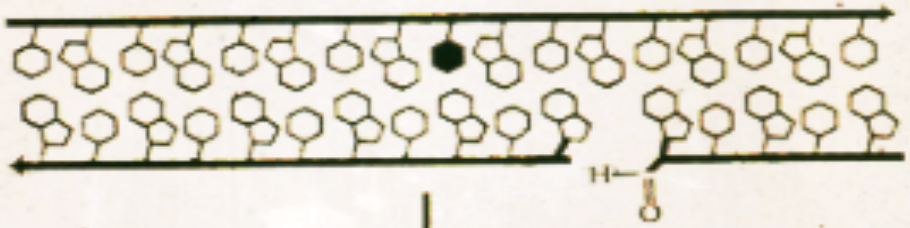


Fenech 2003, Nutrition Research Reviews

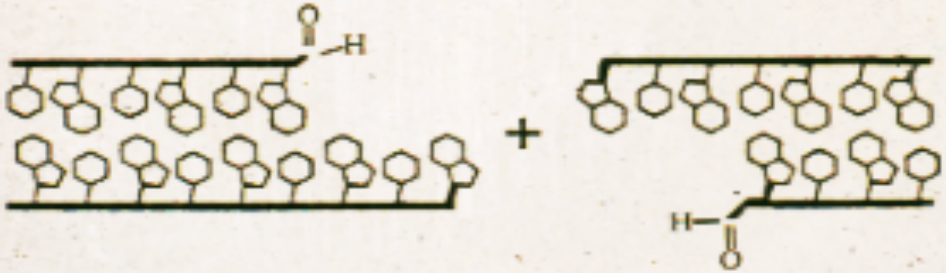
Base excision repair processing of opposed lesions



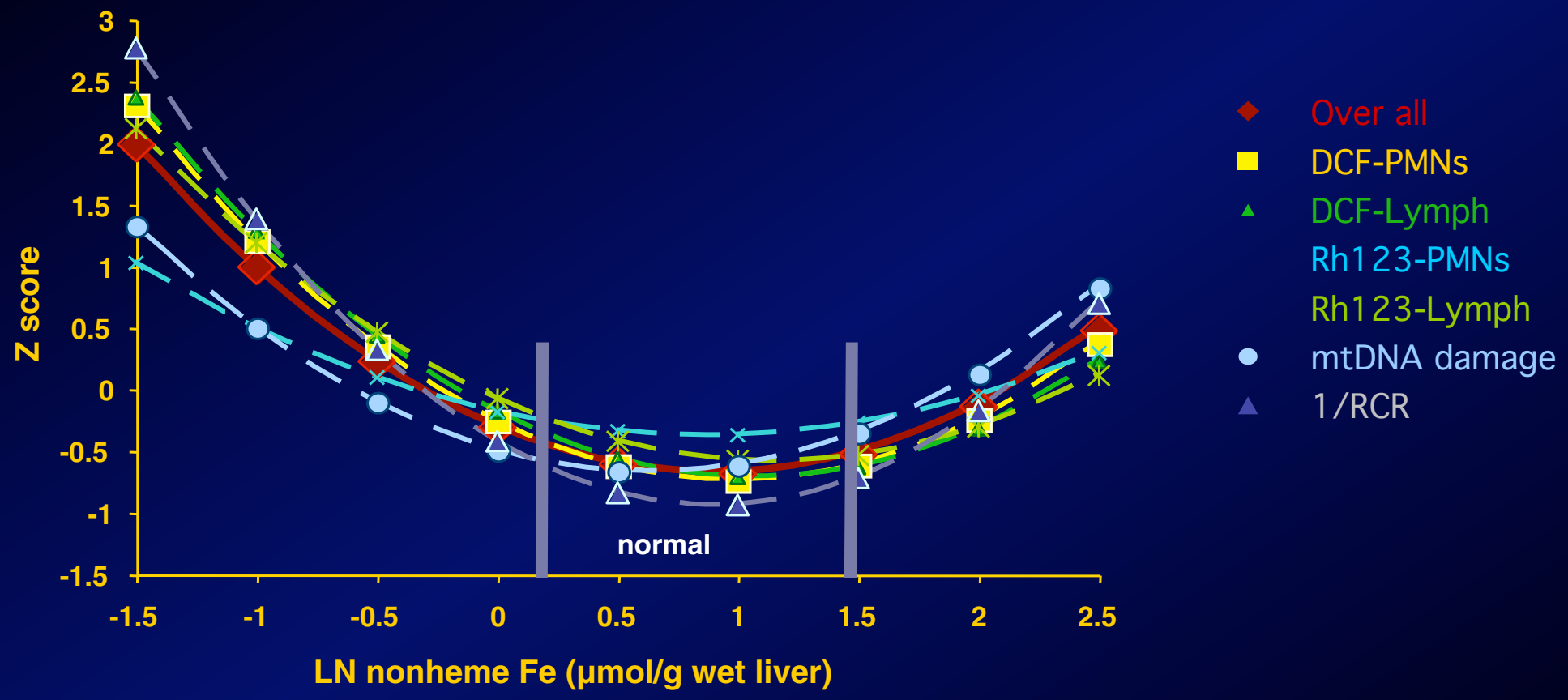
Gap three or more nucleotides away from base lesion



DNA double strand break formed by processing the second lesion

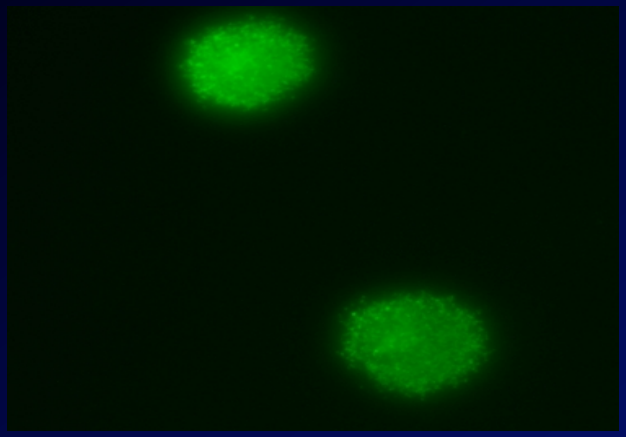


Analysis of nonlinear regression models: comparison of an overall model and individual models of Z-transformed values vs. ln- nonheme liver iron

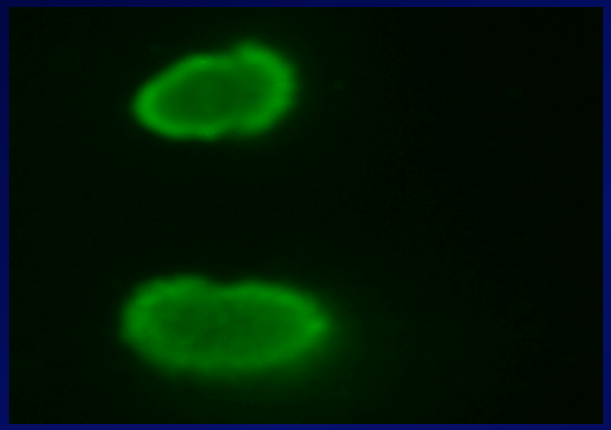


Each of the six dependent variables (that were analyzed by nonlinear regression in former figures) were transformed to Z scores and modeled as a quadratic function of the ln-liver nonheme iron as the independent variable. The equation for the RCR ratio's Z score was obtained from inverted RCR values (1/RCR) so that normal rats had the lower instead of the higher values. For presentation purposes each model line was obtained from 9 values of liver iron. All statistics were performed as in materials and methods.

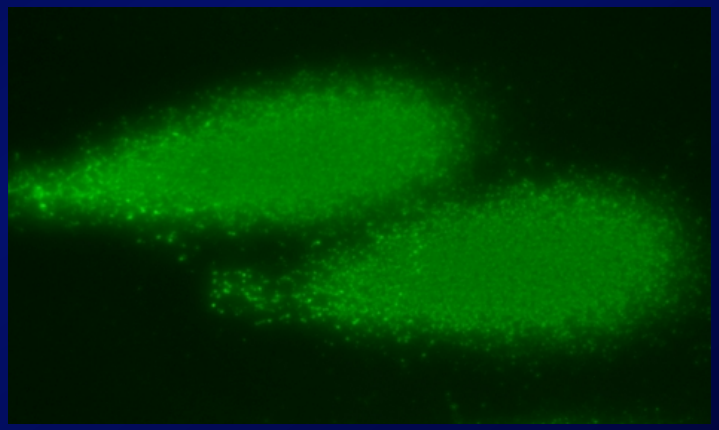
Zinc Deficiency Induces Fapy Glycosylase (Fpg)-sensitive Single Strand Breaks in Human Lung Fibroblasts



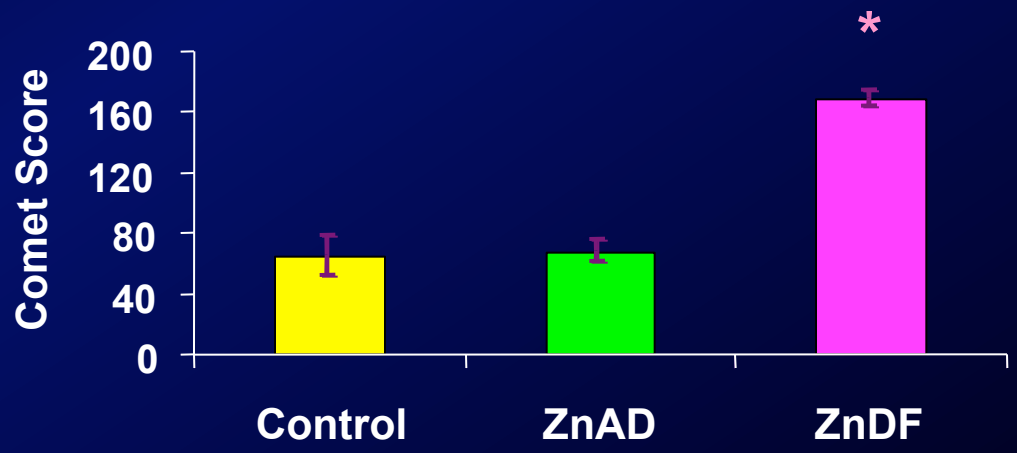
Control (+Fpg)



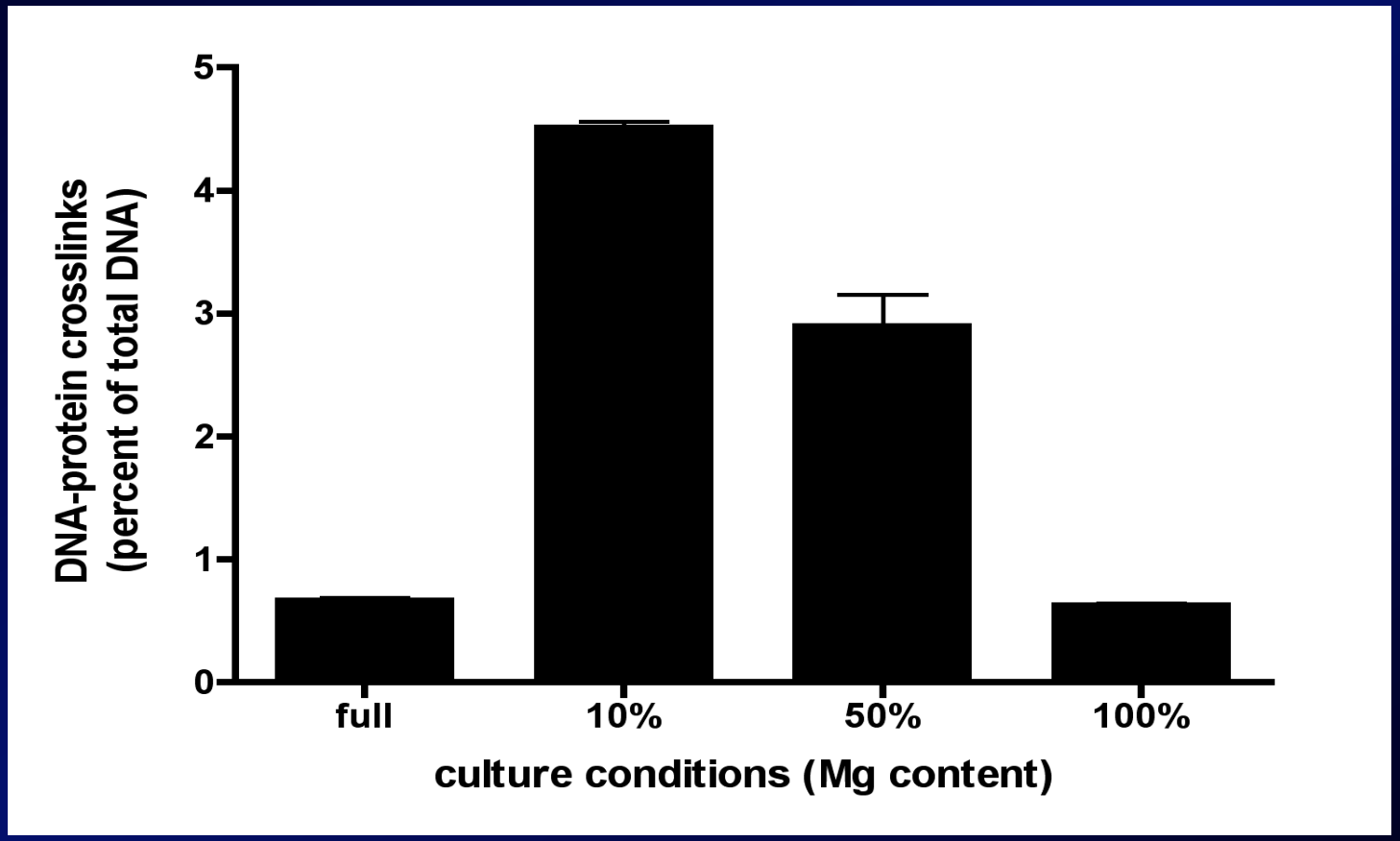
ZnAD (+Fpg)



ZnDF (+Fpg)



Magnesium Deficiency Induces mtDNA-Protein Crosslinks



Calcium Deficiency

Fenech: chromosome breaks

Lipkin: colon cancer mice

Folate Deficiency

MacGregor/Ames/Fenech: chromosome breaks mice/humans

Willett: epi colon cancer humans

Vitamin D Deficiency

Holick: epi many types of cancer

Magnesium Deficiency

Bell: chromosome breaks humans

Larsson: epi colorectal cancer humans

Zinc Deficiency

Fong: esophageal cancer humans/rodents

Potassium Deficiency

[Chang: Cardiovascular Disease]

Vitamin B12 Deficiency

Fenech: Chromosome breaks

Selenium Deficiency

Rao: DNA damage

Combs/Trumbo: Cancer humans

Omega-3 FA Deficiency

Denkins: Cancer

Niacin Deficiency

Kirkland/Depeint: DNA damage

Choline Deficiency

da Costa: DNA damage in humans

Proc. Natl. Acad. Sci. USA
Vol. 103, pp. 17589-17594, November 2006

Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage

Bruce N. Ames
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- Most of the world's population has inadequate intake of one or more micronutrients.
- Triage theory posits as a results of recurrent shortages of micronutrients during evolution, natural selection developed a metabolic rebalancing response to shortage.
- The rebalancing favors micronutrient-dependent protein needed for short term survival while those only required for long-term health are starved.
- This impairment results in insidious damage (e.g. increased DNA damage) that, over time, leads to the acceleration of age-associated diseases (e.g. increased cancer).

~30 Essential Minerals & Vitamins

- Biotin
- Folic acid
- Niacin
- Pantothenate
- Riboflavin
- Thiamine
- Vitamin A
- Vitamin B6
- Vitamin B12
- Vitamin C
- Vitamin D
- Vitamin E
- Vitamin K

- Calcium
- Chromium
- Cobalt
- Copper
- Fluoride
- Iodine
- Iron
- Magnesium
- Manganese
- Molybdenum
- Phosphorus
- Potassium
- Selenium
- Sodium
- Zinc

- Linolenic acid/DHA [ω-3]
- Linoleic acid [ω-6]
- Choline

16 Vitamin K Dependent Proteins

(γ-glutamyl-carboxylase, vitK quinone reductase and vitK epoxide reductase)

Coagulation Factors	*Other Proteins*
F2 (Prothrombin)	Osteocalcin
F7	Gas 6 protein
F9	Matrix Gla protein
F10	TGFBI
(Anticoagulant protein C)	Periostin
	(Anticoagulation Protein Z)

5 Lethal KO

6 nonlethal KO

Causes of Functional Deficiency of VKD-Proteins in Humans

Non-lethal VKD-protein	Function	Mouse Knockout Phenotypes	Human Mutants	Anticoagulant Therapy	Modest VitK deficiency
Osteocalcin	Bone struct. Glucose homeostasis	Fragile bones Insulin resistance	BMD loss (SNPs)	Bone health (men/children/rats)	Bone health Insulin resistance
Matrix Gla Protein (Mgp)	Negative regulator of vascular calcification	Arterial calcification	Abnormal soft tissue calcification (Keutel Syndrome; SNPS)	Arterial calcification (humans/rats)	Arterial calcification

McCann & Ames (2009) Vitamin K, an example of triage theory: is micronutrient inadequacy linked to diseases of aging? Am J Clin Nutr *90,889-907.*

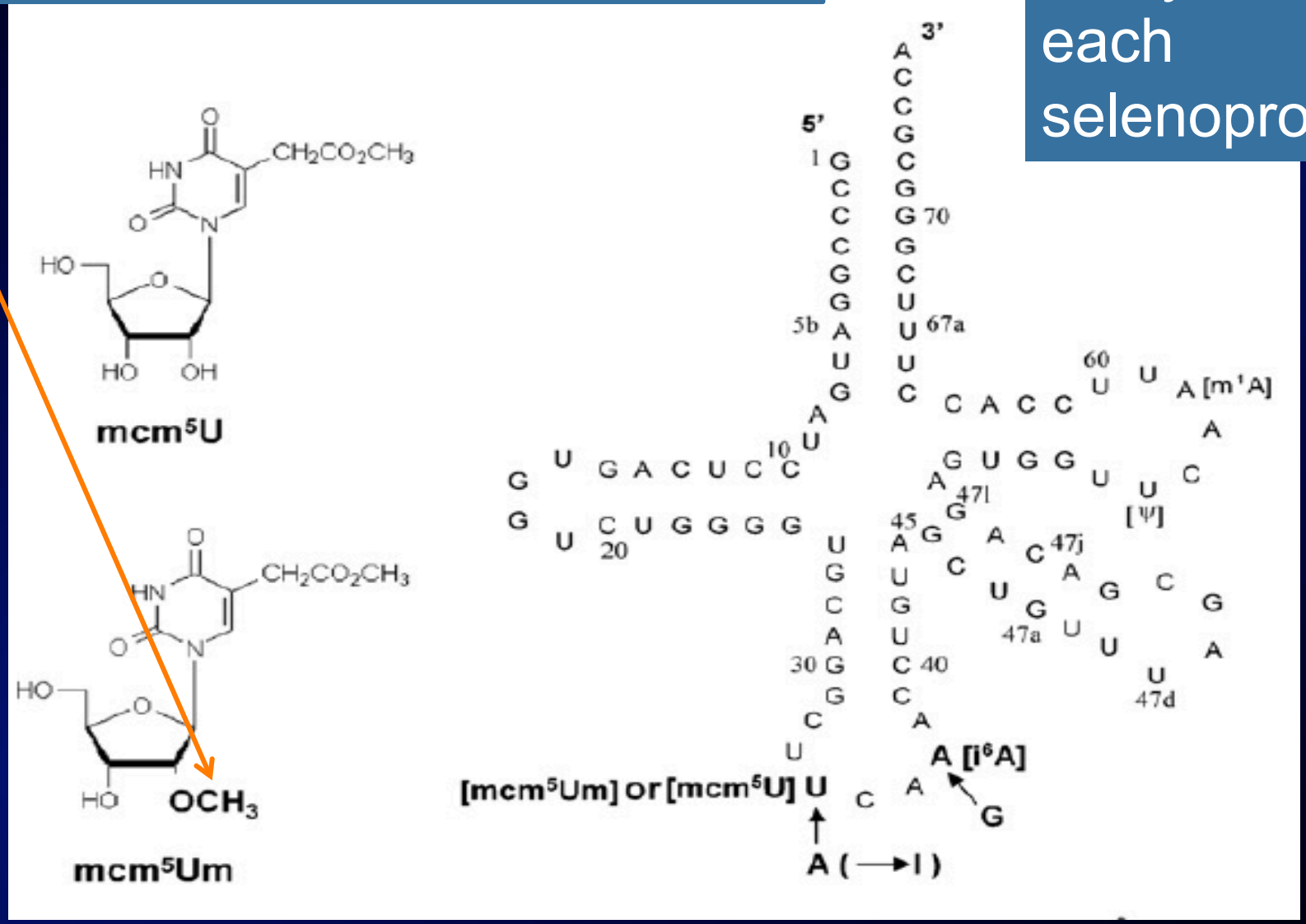
Selenium deficiency, genetic impairment of nonessential selenoproteins, and diseases or conditions associated with aging

Selenoprotein genetic loss		Se dietary loss
Rodent	Human	Human
Gpx1 KO: Senescence		Mortality
Gpx2 KO: UV-induced cancer	Gpx1 SNP, LOH, HYP: Various cancers	Cancer
Gpx1 Knockdown: UV-induced micronuclei		DNA damage
Gpx1 Heterozygote: Heart abnormalities	Gpx3 SNP: Stroke & thrombosis Dio2 SNP: Hypertension (mixed)	Heart disease, hypertension, mortality; *Keshan's disease*
Gpx1 KO: Viral induced myocarditis Gpx2 KO: Airway inflammation		Reduced resistance to infection (primarily viral)
	Dio1 SNP: Muscle weakness SELN Homozygote: Myopathy	*Muscle weakness/muscular dystrophy-like symptoms*
Dio2 KO: Bone fracture	Dio2 SNP: Osteoarthritis	*Kashin-Beck disease (osteoarthropathy)*
Gpx1 KO: Induced neurotoxicity	Dio2 SNP: Retardation (+ iodine def); psychological well-being	Poor cognitive function (1 study) *Mental retardation (+ iodine def)*
Gpx1 KO: Less fat-induced insulin resistance	Dio2 SNP: Insulin resistance (mixed)	Increased type 2 diabetes risk in older men (1 study)

McCann and Ames FASEB J 2011

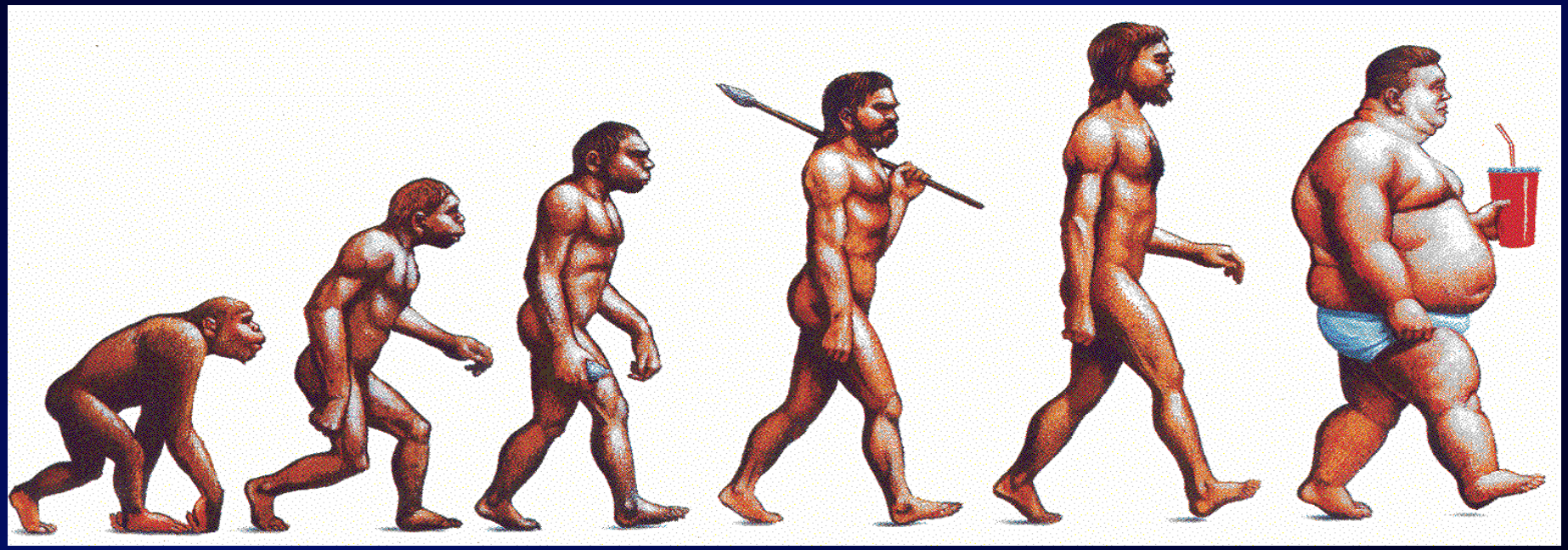
The methylation reaction is the last step in Sec tRNA synthesis; methylation dramatically changes the structure of Sec tRNA. This reaction is inhibited by Se deficiency.

One of two Sec tRNAs is used for synthesis of each selenoprotein



Benefits of a Triage Analysis

1. Provides a mechanism for how moderate V/M deficiency increases risk of a disease of aging, and suggests a prevention strategy.
2. Indicates about half of proteins analyzed are "longevity proteins" which suggests:
   a) biomarker assays for setting EARs; and
   b) a class of undiscovered "longevity V/Ms".



The Economist, December 13, 2003

Dr. Allen Spiegel, NIDDK/NIH

Top Sources of "Nutrition" for 20-30 year olds

	% total energy
1. Regular soft drinks	8.8
2. Pizza	5.1
3. Beer	3.9
4. Hamburgers, meat loaf	3.4
5. White bread	3.3
6. Cake, doughnuts, pastries	3.3
7. French fries, fried potatoes	3.0
8. Potato chips, corn chips, popcorn	2.7
9. Rice	2.6
10. Cheese or cheese spread	2.5
	38.6%

NHANES III (1988-1994) Wakimoto P & Block G. J Gerontol A Biol Sci Med Sci, 2001

CAUTION: HAZARDOUS WAIST

Visceral fat associated with risk of cancer, heart disease, cognitive dysfunction, diabetes, etc.

Start a waist disposal program today.

Supplementation Strategies

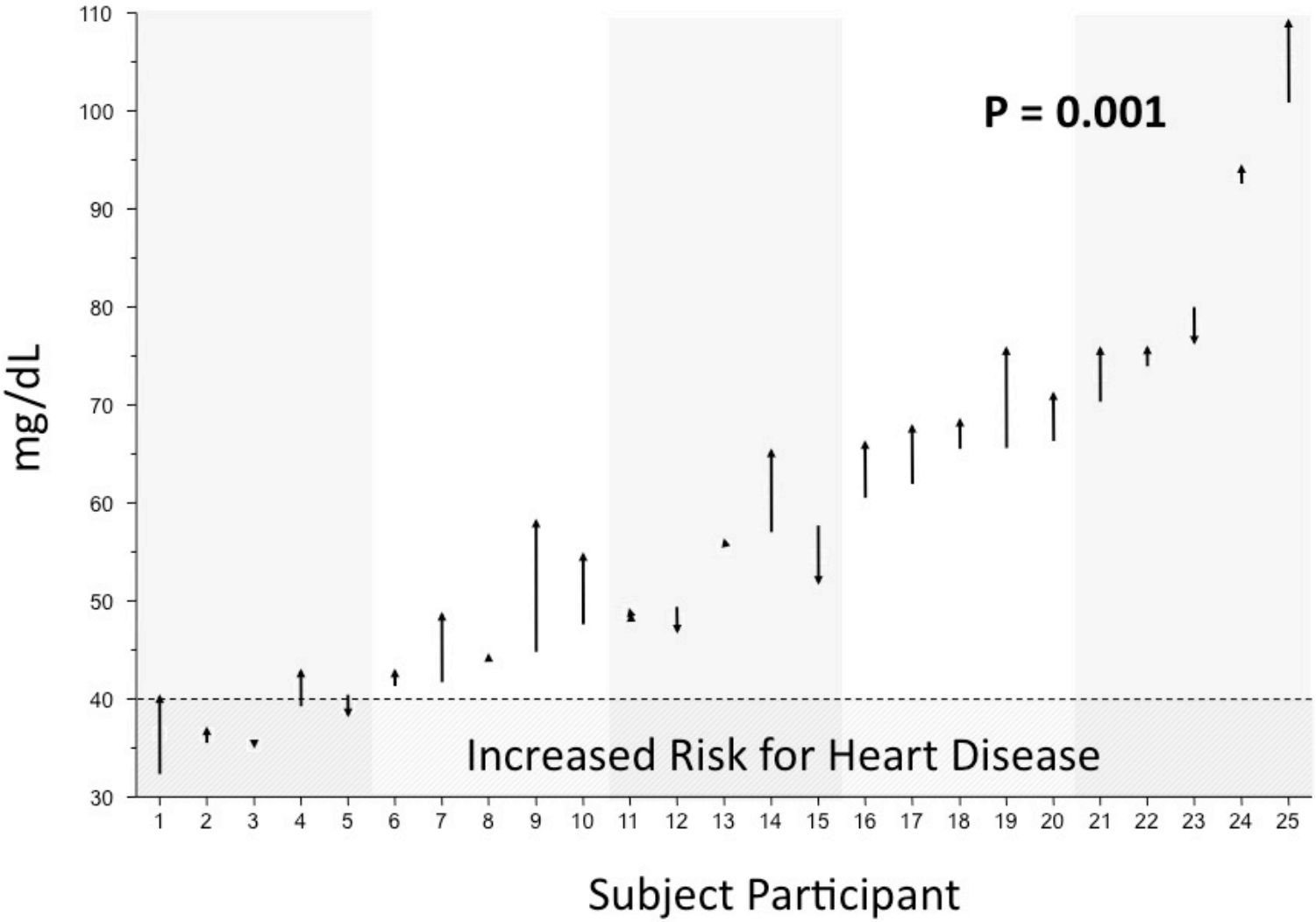
<u>Conventional</u>

- cumbersome
- compliance
- incomplete

<u>CHORI Bar</u>

- convenient
- complete

Figure 1: HDL-cholesterol



The FASEB Journal • Research Communication

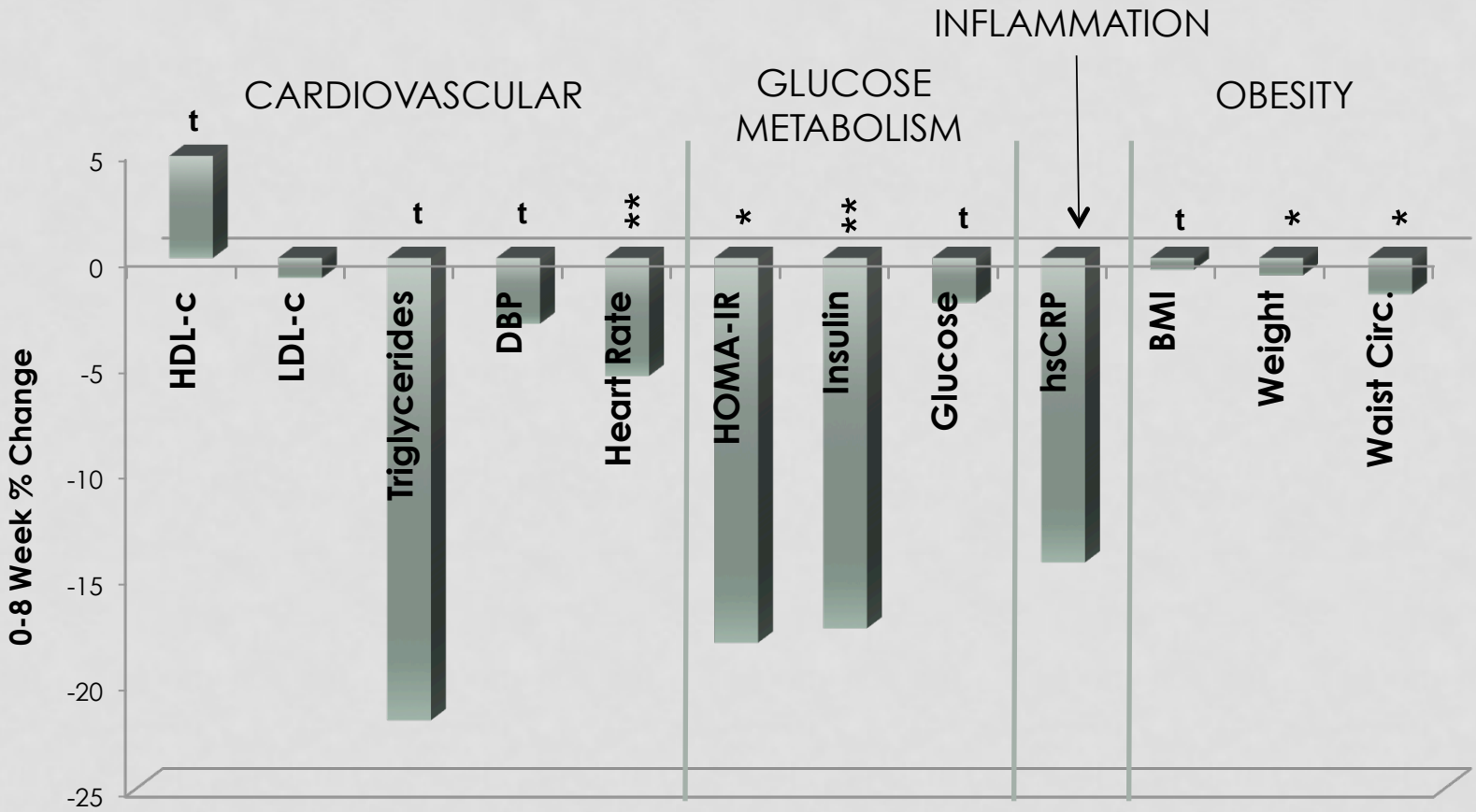
A multicomponent nutrient bar promotes weight loss and improves dyslipidemia and insulin resistance in the overweight/obese: chronic inflammation blunts these improvements

Joyce C. McCann,*,[1] Mark K. Shigenaga,*,[1] Michele L. Mietus-Snyder,*,† Ashutosh Lal,* Jung H. Suh,* Ronald M. Krauss,* Ginny L. Gildengorin,* Alisa M. Goldrich,* Devan S. Block,* Swapna V. Shenvi,* Tara H. McHugh, Don A. Olson, and Bruce N. Ames*

*Nutrition and Metabolism Center, Children's Hospital Oakland Research Institute, Oakland, California, USA; †Children's National Medical Center, Washington, DC, USA; and ‡Processed Foods Research Unit, U.S. Department of Agriculture-Agricultural Research Service-Western Regional Research Center, Albany, California, USA

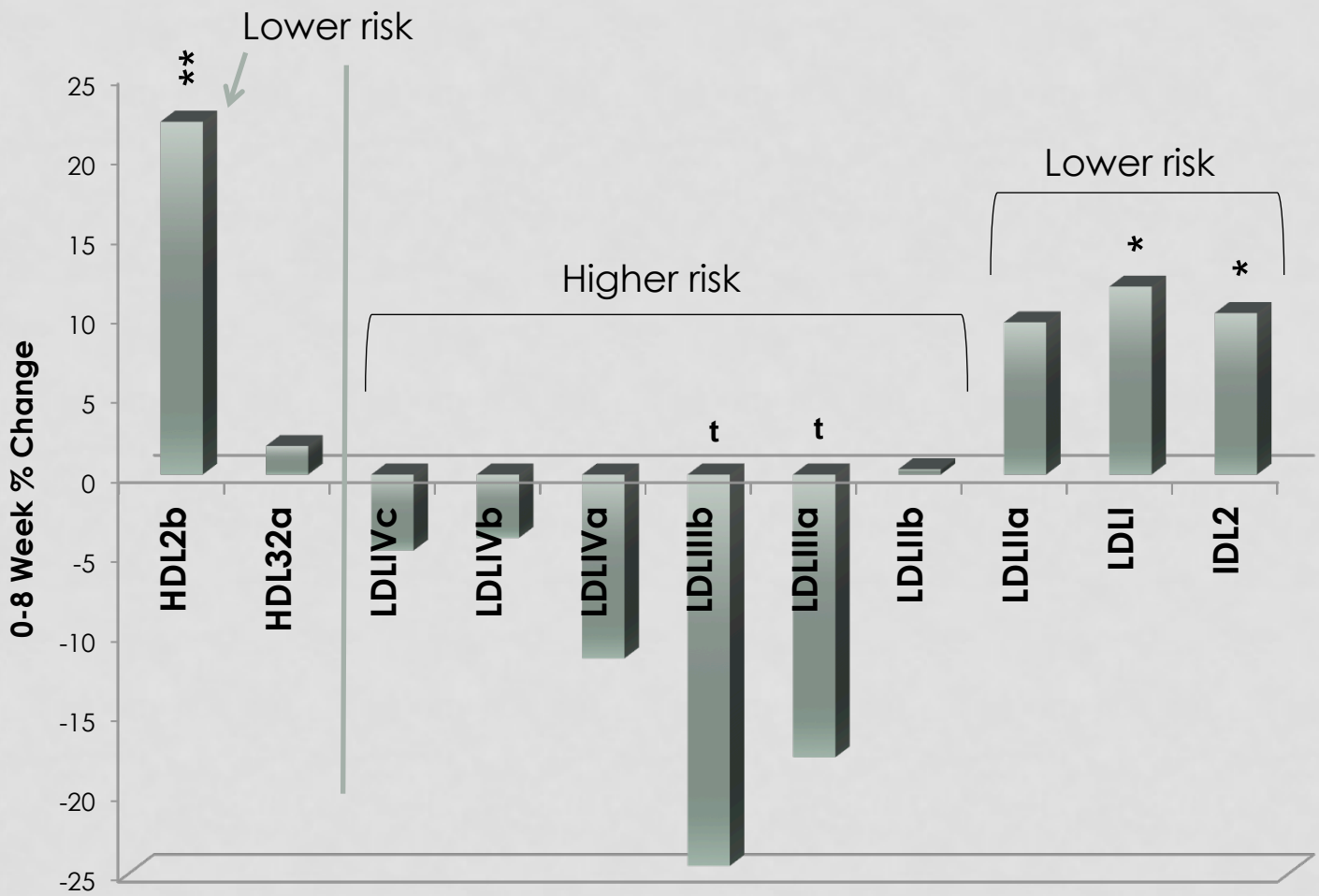
The FASEB Journal, *in press* (March, 2015)
To appear in the August print issue

Improvement in the Overweight/Obese of Standard Clinical Measures After 8 Weeks Consumption of 2 CHORI-bars a Day

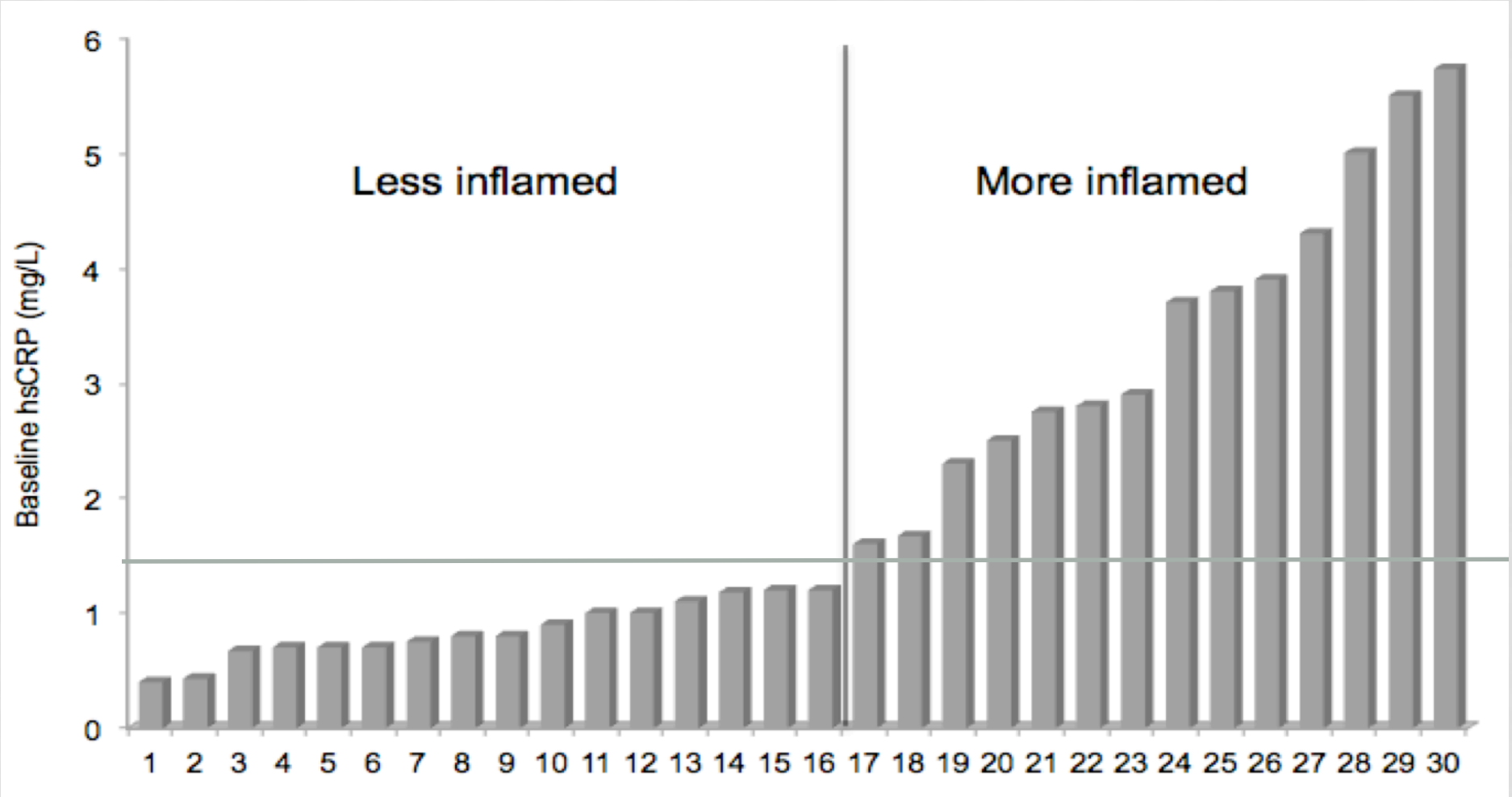


t = statistical trend
* ($p < 0.05$); ** ($p < 0.01$)

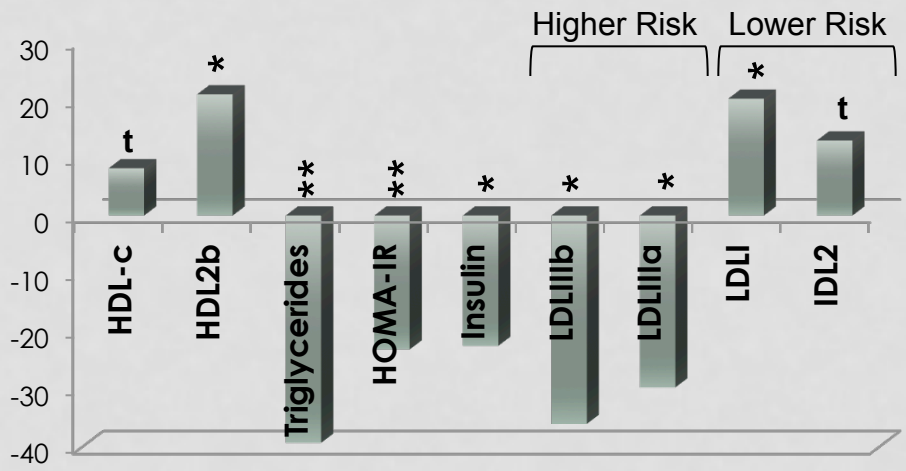
HDL and LDL Lipid Particles After 8 Weeks Consumption of 2 CHORI-bars a Day

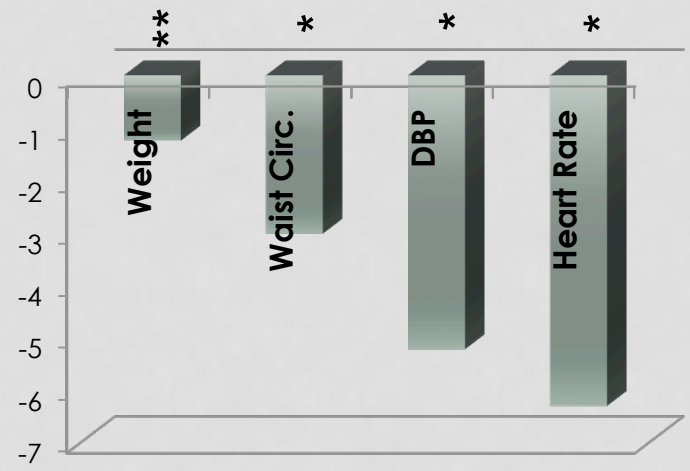


WIDE RANGE OF INFLAMMATION IN THE OVERWEIGHT/OBESE

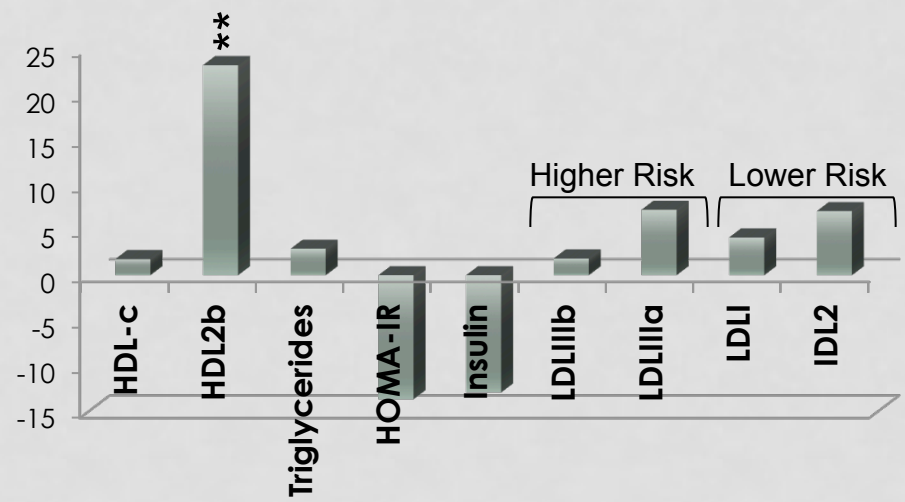


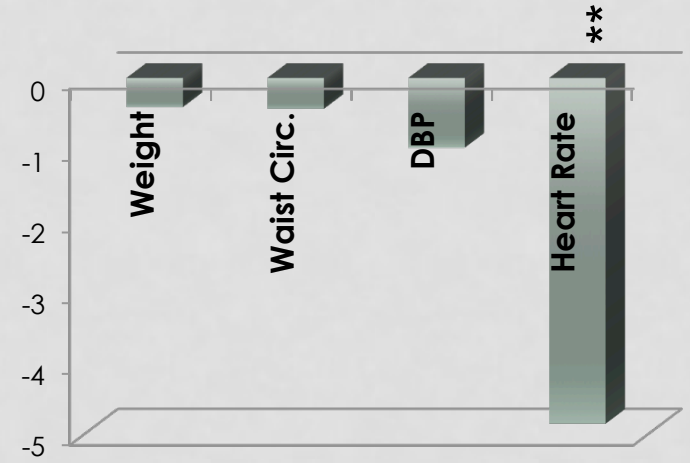
Lower Inflammation





Higher inflammation





The FASEB Journal • Review

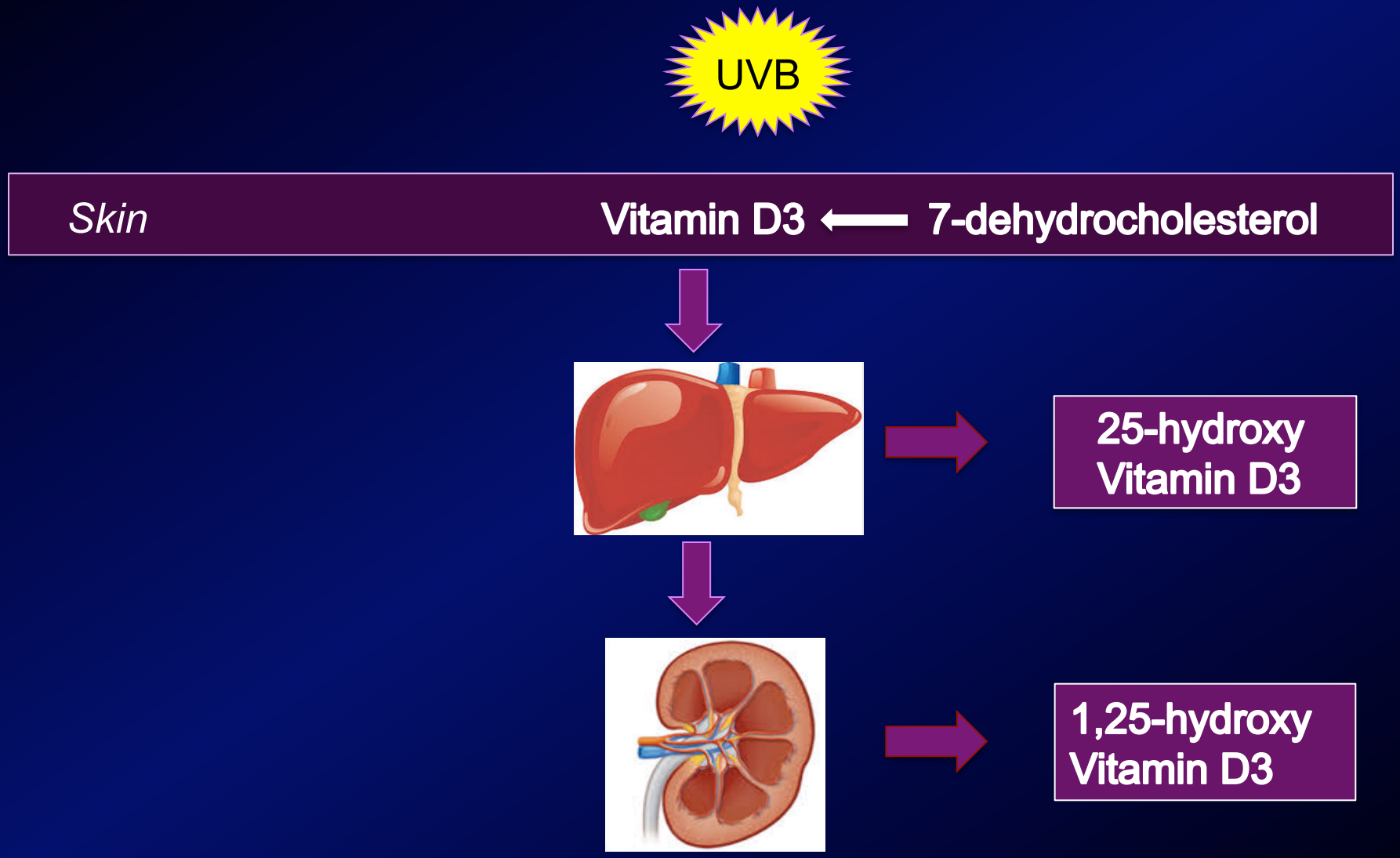
Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism

Rhonda P. Patrick[1] and Bruce N. Ames[1]

Nutrition and Metabolism Center, Children's Hospital Oakland Research Institute, Oakland, California, USA

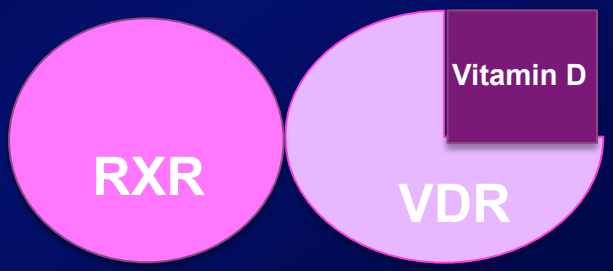
The FASEB Journal published online Feb. 20, 2014 [Jun;28(6):2398-413]

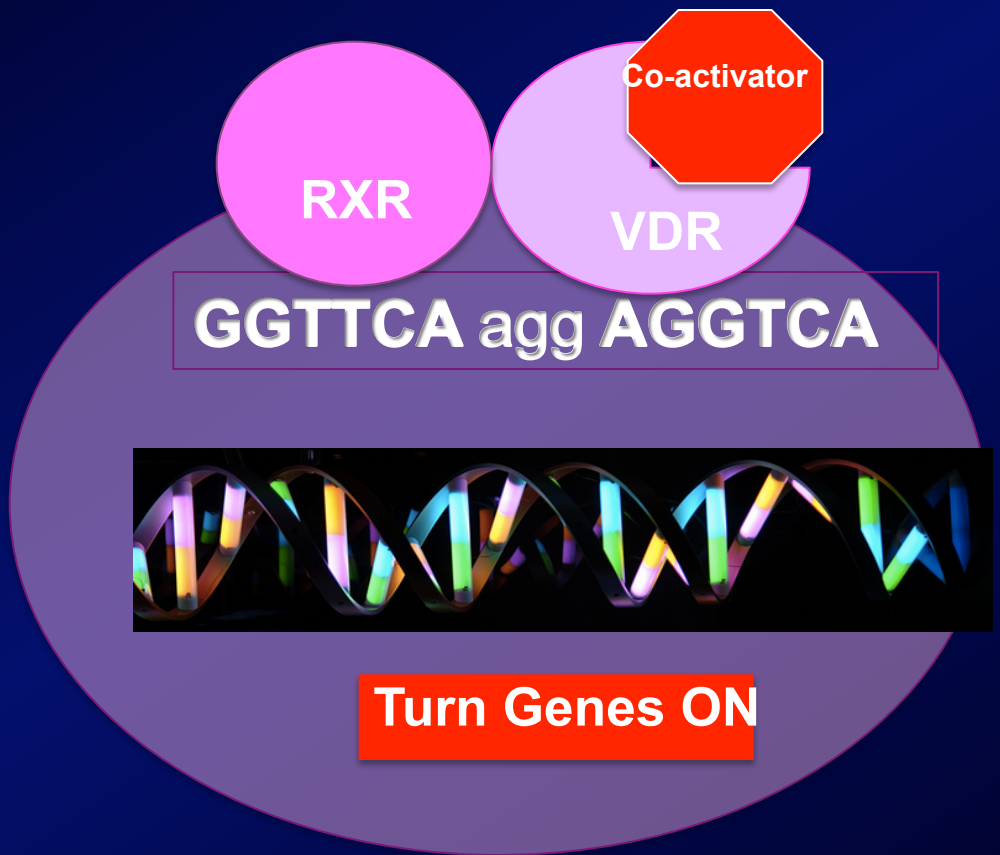
Vitamin D Hormone



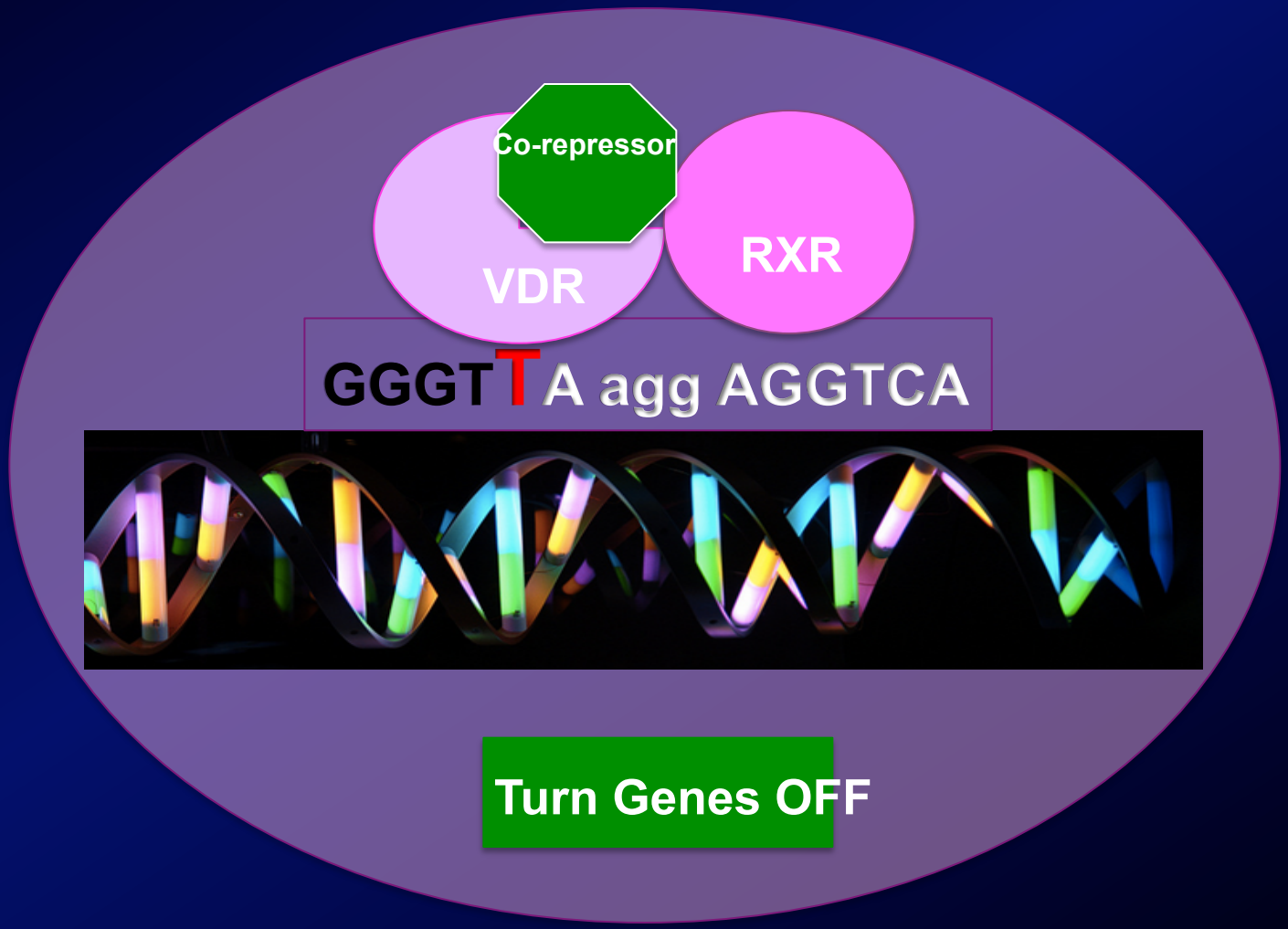
Vitamin D Hormone Regulates the expression of Over 1,000 genes

Vitamin D-Dependent Activation



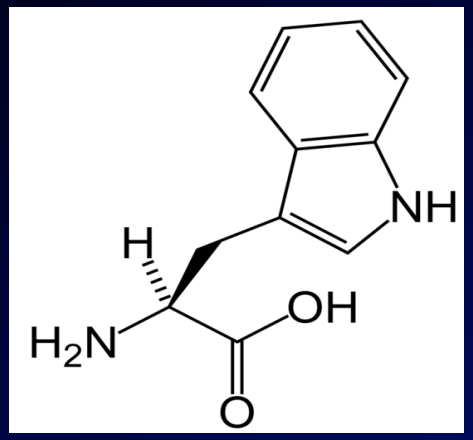


Vitamin D-Dependent Repression



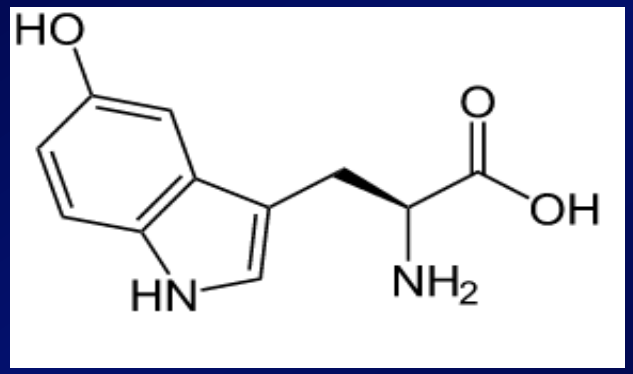
Receptor

Tryptophan Hydroxylase (TPH) contains VDREs



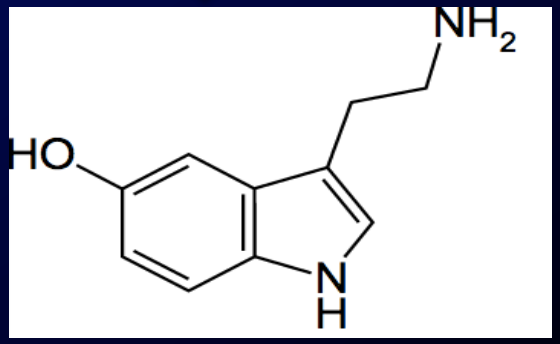
L-Tryptophan

Tryptophan Hydroxylase (TPH)



5-hydroxytryptophan (5-HTP)

Aromatic L-Amino Acid Decarboxylase



Serotonin (5-HT)

VDREs in *TPH1* and *TPH2*

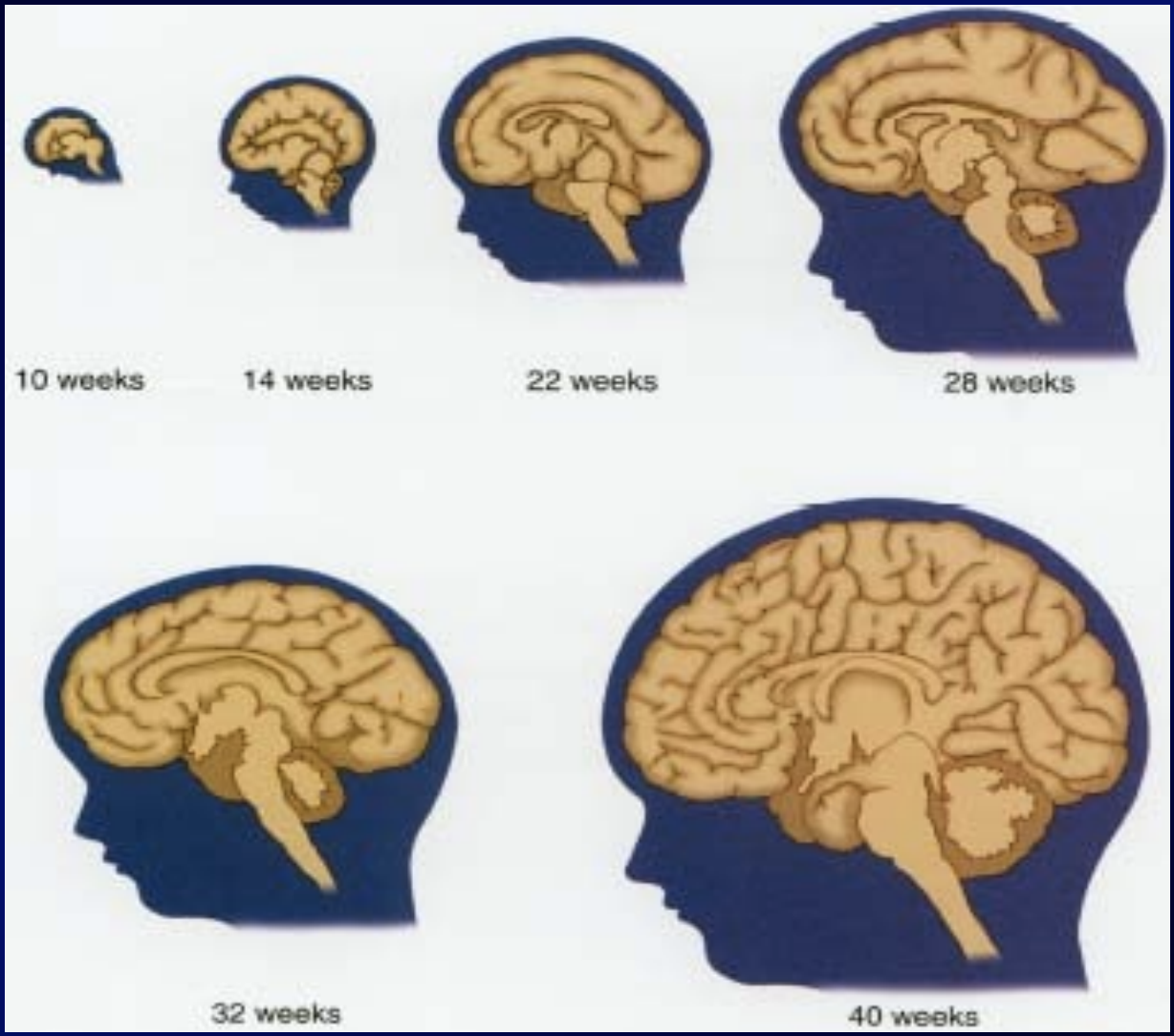
Human Gene	VDRE Type	VDRE Location	VDRE Sequence
TPH1	Repression	-4755	GGGTTA gca AGTTCA
TPH2	Activation	-9771	TGGTCA att AGTTCA

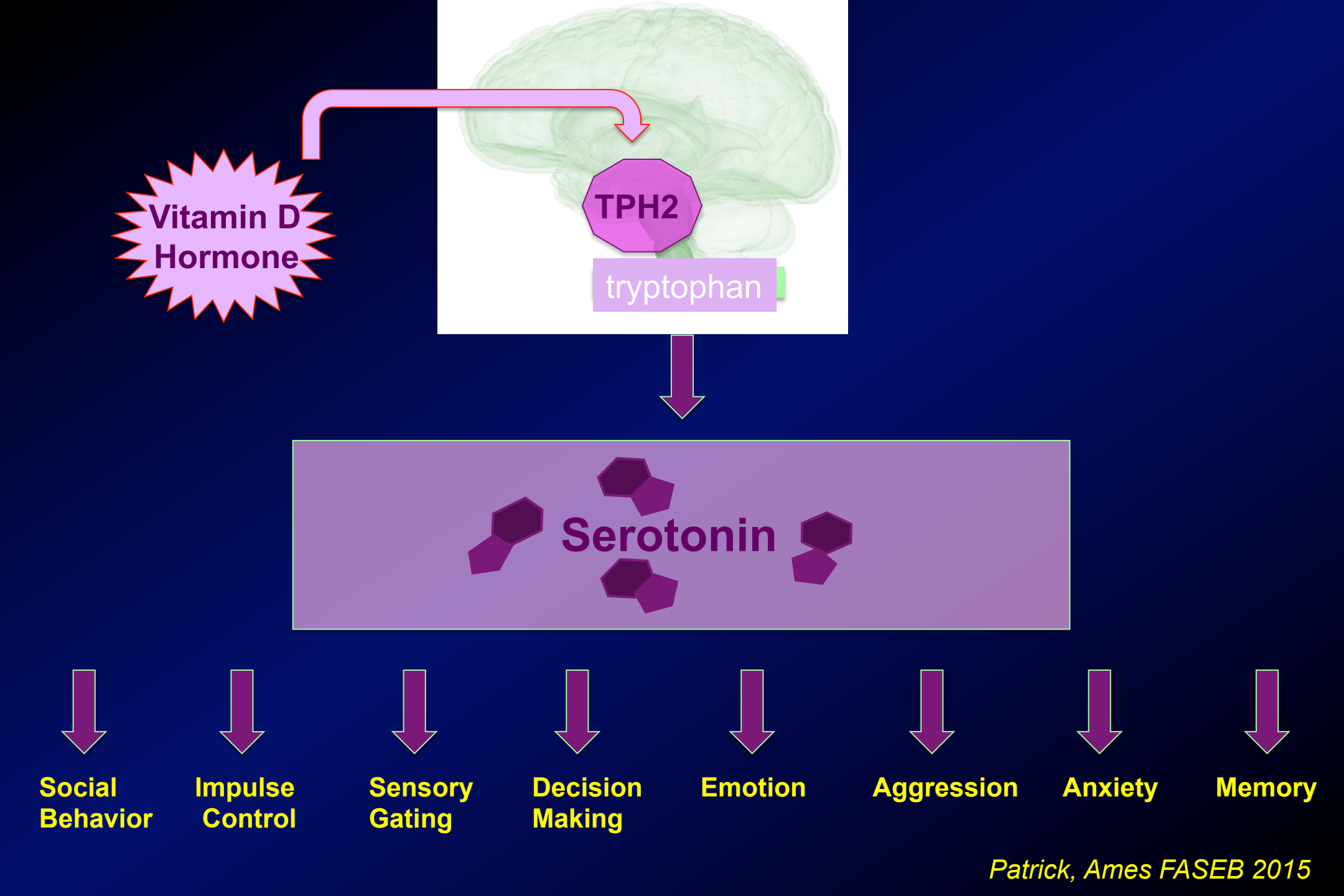
Patrick, Ames FASEB 2014

Explains Four Characteristics associated with Autism

- Low levels of serotonin in the brain and the high levels in blood cells (serotonin anomaly).
- High male prevalence.
- Associations with low vitamin D.
- Presence of maternal antibodies against fetal brain tissue.

Serotonin Shapes the Developing Brain





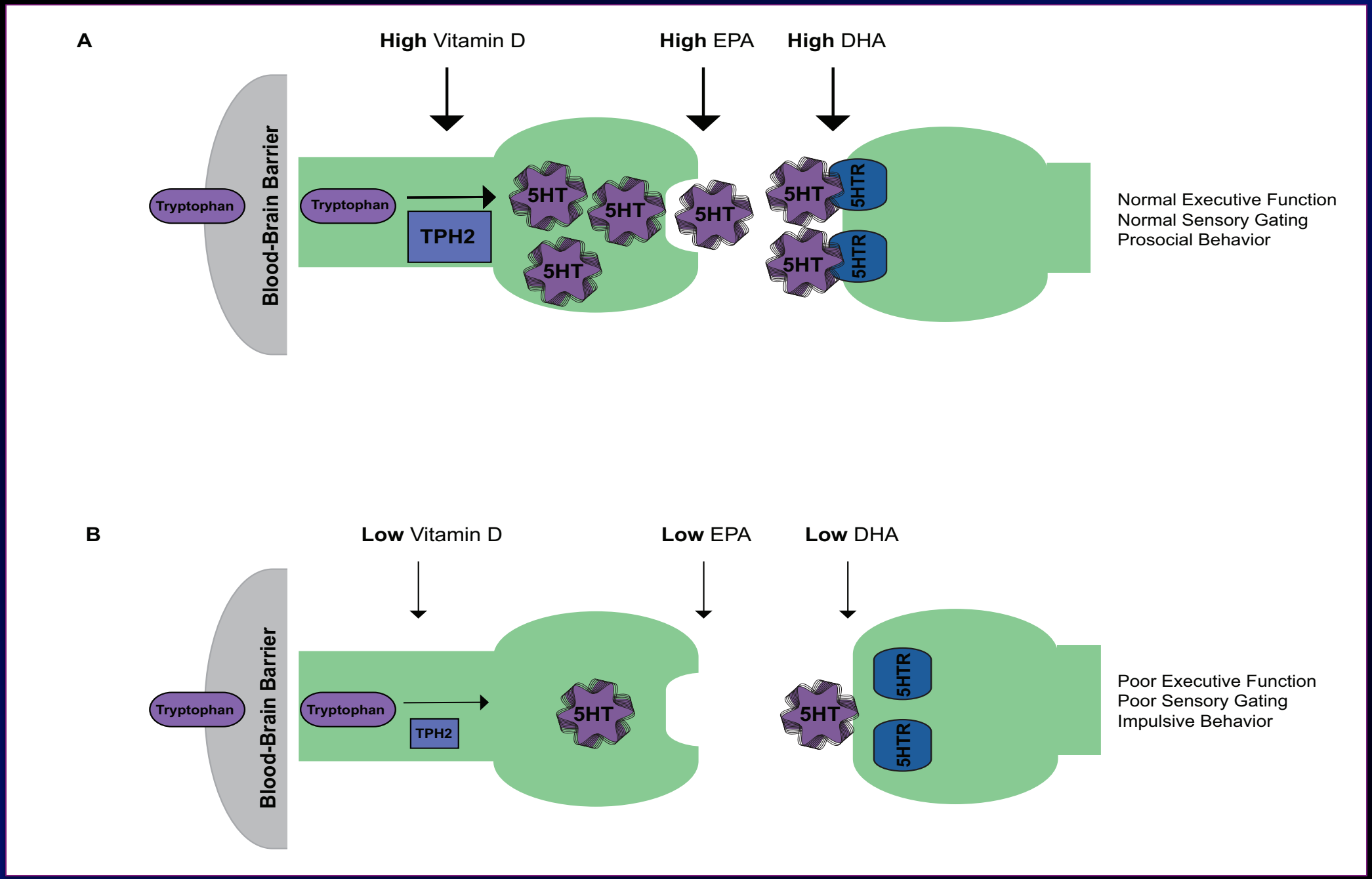
Patrick, Ames FASEB 2015

The FASEB Journal • Review

Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar, schizophrenia, and impulsive behavior

Rhonda P. Patrick[1] and Bruce N. Ames[1]
Nutrition and Metabolism Center, Children's Hospital Oakland Research Institute, Oakland, California, USA

The FASEB Journal published online Feb. 24, 2015 [Epub ahead of print]



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END