Nutrigenomics Revisited: Separating the Hype from the Opportunity

Jeffrey Bland, PhD

Founder and Chairman Emeritus
The Institute for Functional Medicine

Founder & President
The Personalized Lifestyle Medicine Institute
My History with Personalized Nutrition Therapy

• 1983 Publication
  – The Nutrition-Disease Link
  – Nutrition for the Individual
    • Nutritional Needs and Biochemical Individuality
  – Preventive and Therapeutic Nutrition
  – Assessing Individual Nutritional Needs
Nutritional Pharmacology 1982

A “New” Concept?
The Birthing of Precision, Personalized Medicine
We are presently in the middle of a revolution in health care that is unprecedented in history.
It’s the lack of ambition that needs curing

It is a Revolutionary Time in Healthcare!

The Lancet 2016
“It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.”
Roger Williams and Linus Pauling

Biochemical Individuality Meets Molecular Medicine
The BIG Discovery of our time: YOUR BOOK OF LIFE IN 23 CHAPTERS
Expressed Differently in Different Environments
What Have We Learned?

Genes + Lifestyle + Diet + Toxins =

Disturbed Metabolism and Chronic Disease
Genes interact with nutritional components to signal change in expression (Nutrigenomics)

Nutrients can alter the way that genes regulate physiology through Epigenetic effects

Epigenetic effects are transferred from mother to offspring (Transgenerational)

Phytochemicals work through signal transduction

Specific nutrient effects work through hormesis
Macro and Micronutrients and Phytochemicals Influence Genomics

- Single Nucleotide Polymorphisms (SNPs)
  - Inducible or Constitutive
  - Regulatory or Functional
  - Correlation to Phenotype

- Nutrients influence:
  - Enzyme function based upon specific SNPs
  - Regulation of genetic expression, transcriptomics, proteomics, and metabolomics
  - Epigenetic regulation of promoter regions of genes and histone structure
How is genetic information clinically applied in the Functional Medicine system?
Functional Medicine and its Application to Nutrigenomics

- Seven Key Physiological Processes
  - Assimilation/Elimination
  - Detoxification
  - Cellular Communication
  - Immune Defense
  - Bioenergetics
  - Cellular Transport
  - Structure/Function
The Functional Medicine Tree

Genetic Potential

How?

Translates to Phenotype
Like all great mysteries, riddles, and puzzles, the human genome has layers of complexity, metaphoric trap doors and false walls, and amazing hidden treasures.
High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased $K_m$): relevance to genetic disease and polymorphisms\textsuperscript{1–3}

Bruce N Ames, Ilan Elson-Schwab, and Eli A Silver

**ABSTRACT** As many as one-third of mutations in a gene result in the corresponding enzyme having an increased Michaelis constant, or $K_m$, (decreased binding affinity) for a coenzyme, resulting in a lower rate of reaction. About 50 human genetic diseases due to defective enzymes can be remedied or ameliorated by the administration of high doses of the vitamin component of the corresponding coenzyme, which at least partially restores enzymatic activity. Several single-nucleotide polymorphisms, in which the variant amino acid reduces coenzyme binding and thus enzymatic activity, are likely to be remediable by raising cellular concentrations of the cofactor through high-dose vitamin therapy. Some examples include the alanine-to-valine substitution at codon 222 (Ala\textsuperscript{222}→Val) [DNA: C-to-T substitution at nucleotide 677 (677C→T)] in methylenetetrahydrofolate reductase (MTHFR) and the cofactor FAD (in relation to cardiovascular disease, migraines, and rages), the Pro\textsuperscript{187}→Ser (DNA: 609C→T) mutation in NAD(P):quinox oxidoreductase 1 (NAD(P)H dehydrogenase (quinone)) and FAD (in relation to cancer), the Ala\textsuperscript{44}→Gly (DNA: 131C→G) mutation in glucose-6-phosphate 1-dehydrogenase and NADP (in relation to favism and hemolytic anemia), and the Glu\textsuperscript{487}→Lys mutation (present in one-half of Asians) in aldehyde dehydrogenase (NAD\textsuperscript{+}) and NAD (in relation to alcohol intolerance, Alzheimer disease, and cancer). *Am J Clin Nutr* 2002;75:616–58.

**KEY WORDS** Genetic disease, therapeutic vitamin use, binding defect, favism, alcohol intolerance, autism, migraine headaches, single nucleotide polymorphisms, enzyme mutations, review the primary defect and remediates the disease. We show in this review that \textasciitilde 50 human genetic diseases involving defective enzymes can be remedied by high concentrations of the vitamin component of the coenzyme, and that this therapeutic technique can be applied in several other cases, including polymorphisms associated with disease risks, for which molecular evidence suggests that a mutation affects a coenzyme binding site.

The nutrients discussed in this review are pyridoxine (page 618); thiamine (page 625); riboflavin (page 627); niacin (page 632); biotin (page 637); cobalamin (page 638); folic acid (page 641); vitamin K (page 643); calciferol (page 645); tocopherol (page 645); tetrahydrobiopterin (page 646); S-adenosylmethionine (page 646); pantothenic acid (page 646); lipoic acid (page 647); carnitine (page 647); hormones, amino acids, and metals (page 648); and maxi B vitamins (page 649).

The proportion of mutations in a disease gene that is responsive to high concentrations of a vitamin or substrate may be one-third or greater (1–3). Determining the true percentage from the literature is difficult because exact response rates in patients are not always reported and much of the literature deals only with individual case reports. The true percentages depend on several factors, such as the nature of the enzyme, the degree of enzyme loss that results in a particular phenotype, how much a small conformational change disrupts the binding site of the particular enzyme, whether the binding site is a hot spot for mutations, and whether dietary administration of the biochemical raises its concentration in the cell. From what is known of enzyme structure, it seems plausible that, in addition to direct changes in the amino acids at the coenzyme binding site, some mutations affect the conformation of the protein, thus causing an indirect change in the binding site.
Examples of Specific B-Vitamin Responsive Polymorphisms

<table>
<thead>
<tr>
<th>Enzyme and EC no.</th>
<th>Cofactor</th>
<th>Nucleotide</th>
<th>Amino acid</th>
<th>Polymorphic frequency</th>
<th>Region where variant is found</th>
<th>Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylene tetrahydrofolate reductase (NADPH) (1.5.1.20)</td>
<td>FAD</td>
<td>677C→T</td>
<td>Ala222→Val</td>
<td>TT = 10–20</td>
<td>Worldwide</td>
<td>Human enzyme shows decreased affinity for FAD</td>
</tr>
<tr>
<td>NAD(P):quinone oxidoreductase 1 (1.6.99.2)</td>
<td>FAD</td>
<td>609C→T</td>
<td>Pro187→Ser</td>
<td>TT = 4–20</td>
<td>—</td>
<td>FAD affinity is lowered</td>
</tr>
<tr>
<td>Short-chain acyl-CoA dehydrogenase (1.3.99.2)</td>
<td>FAD</td>
<td>625G→A</td>
<td>Gly209→Ser</td>
<td>AA + AG = 35</td>
<td>Control population of an SCAD study</td>
<td>Mutation may affect FAD interaction</td>
</tr>
<tr>
<td>Aldehyde dehydrogenase (NAD+) (1.2.1.3)</td>
<td>NAD</td>
<td>—</td>
<td>Glu487→Lys</td>
<td>KK + EK = 50</td>
<td>Asians worldwide</td>
<td>K_m (NAD) is increased 150-fold</td>
</tr>
<tr>
<td>Glucose-6-phosphate 1-dehydrogenase (1.1.1.49)</td>
<td>NADP</td>
<td>131C→G</td>
<td>Ala44→Gly</td>
<td>G = 11^2</td>
<td>Rural south India</td>
<td>K_m (NADP) is increased 5-fold</td>
</tr>
<tr>
<td>Methionine synthase (2.1.1.13)</td>
<td>AdoCbl</td>
<td>2756A→G</td>
<td>Asp919→Gly</td>
<td>G = 15^2</td>
<td>Control population of an MS study</td>
<td>Mutation is in the AdoCbl binding site</td>
</tr>
<tr>
<td>Folylpoly-γ-glutamate carboxypeptidase (3.4.19.9)</td>
<td>Folylpoly-γ-glutamates (dietary folates)</td>
<td>1561C→T</td>
<td>His475→Tyr</td>
<td>HY = 7.7</td>
<td>Control population of a dementia study</td>
<td>Enzyme activity is lowered 53%</td>
</tr>
</tbody>
</table>

^1 AdoCbl, adenosylcobalamin; E, glutamate; H, histidine; K, lysine; K_m, Michaelis constant; MS, methionine synthase; SCAD, short-chain acyl-CoA dehydrogenase; Y, tyrosine.

^2 Allelic frequencies.
Difference Between Dietary Reference Intake (DRI) and Upper Level of Safety for Various Nutrients

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>DRI</th>
<th>UL</th>
<th>Mega-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridoxine (vitamin B-6)</td>
<td>1.3 mg</td>
<td>100 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Thiamine (vitamin B-1)</td>
<td>1.1 mg</td>
<td>—</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Riboflavin (vitamin B-2)</td>
<td>1.1 mg</td>
<td>—</td>
<td>400 mg</td>
</tr>
<tr>
<td>Niacin (vitamin B-3)</td>
<td>14 mg</td>
<td>35 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Biotin (vitamin B-7)</td>
<td>30 μg</td>
<td>—</td>
<td>100 000 μg</td>
</tr>
<tr>
<td>Cobalamin (vitamin B-12)</td>
<td>2.4 μg</td>
<td>—</td>
<td>1000 μg</td>
</tr>
<tr>
<td>Folic acid</td>
<td>400 μg</td>
<td>1000 μg</td>
<td>40 000 μg</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>90 μg</td>
<td>—</td>
<td>45 000 μg</td>
</tr>
<tr>
<td>Calciferol (vitamin D)</td>
<td>5 μg</td>
<td>50 μg</td>
<td>5000 μg</td>
</tr>
<tr>
<td>Tocopherol (vitamin E)</td>
<td>15 μg</td>
<td>1000 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Tetrahydrobiopterin</td>
<td>—</td>
<td>—</td>
<td>40 mg</td>
</tr>
<tr>
<td>S-Adenosylmethionine</td>
<td>—</td>
<td>—</td>
<td>800 mg</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>5 mg</td>
<td>—</td>
<td>150 mg</td>
</tr>
<tr>
<td>Lipoic acid</td>
<td>—</td>
<td>—</td>
<td>300 mg</td>
</tr>
<tr>
<td>Carnitine</td>
<td>—</td>
<td>—</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>—</td>
<td>—</td>
<td>1.75 mg</td>
</tr>
<tr>
<td>Serine</td>
<td>—</td>
<td>—</td>
<td>500 mg · kg⁻¹ · d⁻¹</td>
</tr>
<tr>
<td>Glycine</td>
<td>—</td>
<td>—</td>
<td>200 mg · kg⁻¹ · d⁻¹</td>
</tr>
<tr>
<td>Zinc</td>
<td>8 mg</td>
<td>40 mg</td>
<td>—</td>
</tr>
<tr>
<td>Potassium</td>
<td>2000 mg</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
B-Vitamin Polymorphisms and Cognitive Function

Review

B vitamin polymorphisms and behavior: Evidence of associations with neurodevelopment, depression, schizophrenia, bipolar disorder and cognitive decline

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Genetics
Memory
Mood

ABSTRACT

The B vitamins folic acid, vitamin B12 and B6 are essential for neuronal function, and severe deficiencies have been linked to increased risk of neurodevelopmental disorders, psychiatric disease and dementia. Polymorphisms of genes involved in B vitamin absorption, metabolism and function, such as methylene tetrahydrofolate reductase (MTHFR), cystathionine β synthase (CBS), transcobalamin 2 receptor (TCN2) and methionine synthase reductase (MTRR), have also been linked to increased incidence of psychiatric and cognitive disorders. However, the effects of these polymorphisms are often quite small and many studies failed to show any meaningful or consistent associations. This review discusses previous findings from clinical studies and highlights gaps in knowledge. Future studies assessing B vitamin-associated polymorphisms must take into account not just traditional demographics, but subjects’ overall diet, relevant biomarkers of nutritional status and also analyze related genetic factors that may exacerbate behavioral effects or nutritional status.

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The Tetrahydrofolate Cycle - Methylenetetrahydrofolate Reductase (MTHFR)
### Polymorphisms of B-Vitamin Dependent Enzymes and Psychiatric Diseases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Enzyme function</th>
<th>Mutation effect</th>
<th>Disease association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate hydrolase (FOLH1) C484T, C1561T</td>
<td>Catalyzes the hydrolysis of N-acetylaspartylglutamate to glutamate and N-acetylaspartate</td>
<td>Unknown</td>
<td>Depression, schizophrenia (Roffman et al., 2013), dementia (Kim et al., 2010)</td>
</tr>
<tr>
<td>Methylene tetrahydrofolate reductase (MTHFR) C677T</td>
<td>Converts CH$_3$ THF to CH$_2$ THF</td>
<td>T homozygote is less efficient, thus increased plasma homocysteine</td>
<td>Depression, schizophrenia, mental retardation, dementia, bipolar disorder</td>
</tr>
<tr>
<td>Methionine synthase (MTR) A2756G</td>
<td>Converts homocysteine into methionine</td>
<td>G allele may increase homocysteine levels</td>
<td>Dementia, depression</td>
</tr>
<tr>
<td>Fucosyltransferase 2 (FUT2) (rs492602)</td>
<td>Immune response protein which modulates B12 transport in the gut</td>
<td>GG carriers have higher plasma B12</td>
<td>Intelligence</td>
</tr>
<tr>
<td>Dihydrofolate reductase (DHFR) 19bp deletion in the intron1 (rs70991108)</td>
<td>Converts dihydrofolate into tetrahydrofolate, using NADPH (for purine synthesis)</td>
<td>Reduces protein expression by eliminating Sp1 transcription factor binding site</td>
<td>Intellectual ability</td>
</tr>
<tr>
<td>Methylenetetrahydrofolate dehydrogenase (MTHFD1) G1958A</td>
<td>Converts 5,10-methylenetetrahydrofolate and NADPH into 5,10-methenyltetrahydrofolate and NADPH</td>
<td>A allele increases plasma homocysteine</td>
<td>Dementia</td>
</tr>
<tr>
<td>Cystathionine β synthase (CBS) 844ins88</td>
<td>Converts serine and homocysteine (with B6) into cystathionine</td>
<td>Insert increases plasma homocysteine</td>
<td>Dementia, schizophrenia, mental retardation</td>
</tr>
<tr>
<td>Methionine synthase reductase (MTRR or MSR) A666G</td>
<td>Converts SAH into SAM (with B12)</td>
<td>G allele increases plasma homocysteine</td>
<td>Depression</td>
</tr>
<tr>
<td>Haptocorrin (TCN1) TC C776G</td>
<td>Protects cobalamin from degradation in the stomach</td>
<td>Unknown</td>
<td>Dementia</td>
</tr>
<tr>
<td>Transcobalamin II receptor (TCN2) G775C</td>
<td>Binds cobalamin in the portal circulation</td>
<td>More efficient vitamin B12 transport and binding mechanisms versus R allele homozygotes</td>
<td>Depression</td>
</tr>
<tr>
<td>Folate receptor 1 (FOLR1) G1816A and G1841A</td>
<td>Activated by folate to induce signaling cascade</td>
<td>Double mutation (1816A and 1841A) possibly increases homocysteine levels</td>
<td>Tendency of double mutation (1816A and 1841A) to coincide with dementia</td>
</tr>
</tbody>
</table>
Bland, J. What role has nutrition been playing in our health? The xenohormesis connection. *Integrative Medicine* 6(3); Jun/Jul 2007.
Macro and Micronutrients and Phytochemicals Influence Genetic Expression
The “Molecular Biology” of Food
Personalizing Nutrition Through Integrated Analytics

**SUMMARY**

Elevated postprandial blood glucose levels constitute a global epidemic and a major risk factor for complications and type II diabetes, but existing dietary methods for controlling them have limited efficacy. Here, we continuously monitored week-long glucose levels in an 800-person cohort, measured responses to 46,898 meals, and found high variability in the response to identical meals, suggesting that universal dietary recommendations may have limited utility. We devised a machine-learning algorithm that integrates blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota measured in this cohort and showed that it accurately predicts personalized postprandial glycemic response to real-world meals. We validated these predictions in an independent 160-person cohort. Finally, a blinded randomized controlled dietary intervention based on this algorithm resulted in significantly lower postprandial responses and consistent alterations to gut microbiota configuration. Together, our results suggest that personalized diets may successfully modify elevated postprandial blood glucose and its metabolic consequences.

**INTRODUCTION**

Blood glucose levels are readily measurable in the population, excelling by the steep rise in the prevalence of metabolic and impaired glucose tolerance estimated to affect 31% of the adult population (Bennet, 2013). Prediabetes, characterized by chronically impaired blood glucose responses, is a significant risk factor for type II diabetes mellitus (T2DM), with up to 70% of prediabetes eventually developing the disease (Bolton et al., 2013). It is also linked to other manifestations, collectively termed the metabolic syndrome, including obesity, hypertension, non-alcoholic fatty liver disease, hyperglycemia, and cardiovascular disease (Grundy, 2012). Thus, maintaining normal blood glucose levels is considered critical for preventing and controlling the metabolic impairments (Rudich and Ronen, 2009).

Dietary intake is a central determinant of blood glucose levels, and thus, in order to achieve normal glucose levels it is imperative to make food choices that include normal caloric, protein-metabolic glycemic responses (PDG) (Galili et al., 2013). Population hyperglycemia is an independent risk factor for the development of T2DM (American Diabetes Association, 2015), cardiovascular disease (Salmeron, 2009), and other conditions (Kahn et al., 2005) and is associated with obesity (Bennet et al., 2013) and severe mortality in both T2DM (Evans et al., 2013) and cancer (Garmar et al., 2020).

Despite their importance, no method exists for predicting PDGs to blood. The current practice is to use the most carbohydrate content (American Diabetes Association, 2015). Even though it is a poor predictor of the PPG (Coen and Holst, 1999). Other methodologies at estimating PDGs are the glycemic index, which quantifies PPG to consumption of a single tested food type, and the dietary glycemic load (Lorenc et al., 1993). It has limited applicability as assessing the PPG to real-life meals consisting of arbitrary food combinations and varying quantities. Coen et al. (2019) consumed a different time of the day and at different proximity to physical activity affector meals. Indeed, studies examining the effect of meals with similar glycemic index on T2DM risk, weight loss, and carotid artery risk factors mixed results (Eisenberg et al., 2013; Knip et al., 2013; Schwenke and Hoffman, 2013).
How the Gut Microbiome Influences Glycemic Response

- 800 people
- 46,898 meals
- Machine-learning algorithm
- Integrates blood parameters, dietary habits, anthropometrics, activity and microbiome
- Defines personalized diets that successfully modify elevated postprandial blood glucose and its metabolic consequences

SUMMARY

Elevated postprandial blood glucose levels constitute a global epidemic and a major risk factor for prediabetes and type II diabetes, but existing dietary methods for controlling them have limited efficacy. Here, we continuously monitored week-long glucose levels in an 800-person cohort, measured responses to 46,898 meals, and found high variability in the response to identical meals, suggesting that universal dietary recommendations may have limited utility. We devised a machine-learning algorithm that integrates blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota measured in this cohort and showed that it accurately predicts personalized postprandial glycemic response to real-life meals. We validated these predictions in an independent 100-person cohort. Finally, a blinded randomized controlled dietary intervention based on this algorithm resulted in significantly lower postprandial responses and consistent alterations to gut microbiota configuration. Together, our results suggest that personalized diets may successfully modify elevated postprandial blood glucose and its metabolic consequences.
AstraZeneca and Personalized Lifestyle and Diet for Diabetes

Fit2Me...what's in it for YOU?

Your customized plan is created around the choices that work best for you. For your food plan, you pick the ingredients, cuisines, and recipes you like. Your activity plan is based on your favorite activities and your activity level. Your plan will give you things like the “trade-off” between activity needed and the calories in what you’re planning to eat. It’s all stored in your personal file to access any time. And whether you prefer a printout or viewing on your mobile or tablet device, you can hold your plan in your hand.
How Dietary Preferences Influence Metabolomics

Metabolic profiles of male meat eaters, fish eaters, vegetarians, and vegans from the EPIC-Oxford cohort. 1,2

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1Cancer Epidemiology Unit, Nutritional Department of Population Health, University of Oxford, Oxford, United Kingdom. 2International Agency for Research on Cancer, Lyon, France, and Department of Epidemiology and Bioinformatics, School of Public Health, Imperial College London, London, United Kingdom.

ABSTRACT
Background: Human metabolism is influenced by dietary factors and lifestyle, environmental, and genetic factors; thus, men who exclude one or all animal products from their diet might have different metabolic profiles than meat eaters.

Methods: In this cross-sectional study, concentrations of metabolites were measured by mass spectrometry in plasma from 379 men categorized according to their diet group. Differences in mean metabolite concentrations across diet groups were tested by using ANOVA, and a false discovery rate-controlling procedure was used to account for multiple testing. Principal component analysis was used to investigate patterns in metabolic profiles.

Results: Concentrations of 70% of metabolites differed significantly by diet group. In the vast majority of cases, vegans had the lowest concentrations, whereas meat eaters often had the highest concentrations of the acylcarnitines, glycerophosphocholines, and sphingolipids, whereas vegetable or fruit eaters most often had the highest concentrations of the amino acids and a biogenic amine. A clear separation between patterns in the metabolic profiles of the 4 diet groups was seen, with vegans being more different from the other groups because of lower concentrations of some glycerophosphocholines and sphingolipids.

Conclusions: Metabolic profiles in plasma could effectively differentiate between men from different habitual diet groups, especially vegans compared with men who consume animal products. The differences in metabolic profiles were largely explained by dietary patterns. A more detailed analysis of the metabolites identified in this study is ongoing to better understand the differences observed in metabolic profiles of the 4 diet groups.

METHODS
Study population: From 1993 to 2000, 65,500 men and women 40-70 years of age were recruited from across the United Kingdom into the EPIC-Oxford cohort. 1,2

Keywords: EPIC-Oxford, mass spectrometry, metabolomics, vegan, vegetarian.

INTRODUCTION
Metabolic profiles are influenced by dietary, lifestyle, environmental, and genetic factors (1, 2), and individuals with different dietary habits might therefore have different metabolic profiles.

1518
Liver Detoxification Pathways & Supportive Nutrients

Endotoxins
- end products of metabolism
- bacterial endotoxins

Exotoxins
- drugs, (prescription, OTCs, recreational, etc)
- chemicals
  - agricultural
  - food additives
  - household
  - pollutants/contaminants
- microbial

PHASE I
[cytochrome P450 enzymes]
- nonpolar · lipid-soluble
- Reactions
  - oxidation
  - reduction
  - hydrolysis
  - hydration
  - dehalogenation
- Enzymes, Cofactors & Other Nutrients Used
  - riboflavin (vit. B2)
  - niacin (vit. B3)
  - pyridoxine (vit. B6)
  - folic acid
  - vitamin B12
  - glutathione
  - branched-chain amino acids
  - flavonoids
  - phospholipids
- more polar · more water-soluble
- Reactive Oxygen Intermediates
  - Superoxide
  - Free Radicals
  - Antioxidant/Protective Nutrients/Plant Derivatives
    - carotenes (vit. A)
    - ascorbic acid (vit. C)
    - tocopherol (vit. E)
    - selenium
    - copper
    - zinc
    - manganese
    - coenzyme Q10
    - thiols (found in garlic, onions & cruciferous vegetables)
    - bioflavonoids
    - silymarin
    - pycnogenol
- Secondary Tissue Damage

PHASE II
[conjugation pathways]
- sulphation
- glucuronidation
- glutathione conjugation
- acetylation
- amino acid conjugation
- glycine
- taurine
- glutamine
- ornithine
- arginine
- methylation
- N-acetylcysteine, cysteine, methionine are precursors

Intermediate metabolites

Excretory derivatives
- polar · water-soluble
- Serum
- Kidneys
- Bile
- Urine
- Faeces/stool
Review

Transactivation of Genes Encoding for Phase II Enzymes and Phase III Transporters by Phytochemical Antioxidants

Yoon Mee Yang, Kyoung Noh, Chang Yeob Han and Sang Geon Kim *

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Abstract: The induction of phase II enzymes and phase III transporters contributes to the metabolism, detoxification of xenobiotics, antioxidant capacity, redox homeostasis and cell viability. Transactivation of the genes that encode for phase II enzymes and phase III transporters is coordinately regulated by activating transcription factors in response to external stimuli. Comprehensive studies indicate that antioxidant phytochemicals promote the induction of phase II enzymes and/or phase III transporters through various signaling pathways, including phosphoinositol 3-kinase, protein kinase C, and mitogen-activated protein kinases. This paper focuses on the molecular mechanisms and signaling pathways responsible for the transactivation of genes encoding for these proteins, as orchestrated by a series of transcription factors and related signaling components.
Phytochemical Influence on Detoxification Gene Expression
Cruciferous Vegetable Sulfuraphane Influence on NrF2

Review Article

Sulforaphane and Other Nutrigenomic Nrf2 Activators: Can the Clinician’s Expectation Be Matched by the Reality?

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The recognition that food-derived nonnutrient molecules can modulate gene expression to influence intracellular molecular mechanisms has seen the emergence of the fields of nutrigenomics and nutrigenetics. The aim of this review is to describe the properties of nutrigenomic activators of transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2), comparing the potential for sulforaphane and other phytochemicals to demonstrate clinical efficacy as complementary medicines. Broccoli-derived sulforaphane emerges as a phytochemical with this capability, with oral doses capable of favourably modifying genes associated with chemoprevention. Compared with widely used phytochemical-based supplements like curcumin, silymarin, and resveratrol, sulforaphane more potently activates Nrf2 to induce the expression of a battery of cytoprotective genes. By virtue of its lipophilic nature and low molecular weight, sulforaphane displays significantly higher bioavailability than the polyphenol-based dietary supplements that also activate Nrf2. Nrf2 activation induces cytoprotective genes such as those playing key roles in cellular defense mechanisms including redox status and detoxification. Both its high bioavailability and significant Nrf2 inducer capacity contribute to the therapeutic potential of sulforaphane-yielding supplements.
NrF2 and its relationship to Expression of the Antioxidant Response Element
Activity and Bioavailability of Phytochemicals

**Figure 2:** CD values of popular phytochemicals used as supplements and a commonly prescribed pharmaceutical. CD values refer to the concentration of a compound required to double the activity of the Phase II detoxification enzyme, quinone reductase [83, 87–89, 91].

**Figure 3:** Comparative bioavailability of phytochemicals commonly used in supplements [90, 124, 127–129, 153].
Potential utility of natural products as regulators of breast cancer-associated aromatase promoters

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Abstract

Aromatase, the key enzyme in estrogen biosynthesis, converts androstenedione to estrone and testosterone to estradiol. The enzyme is expressed in various tissues such as ovary, placenta, bone, brain, skin, and adipose tissue. Aromatase enzyme is encoded by a single gene CYP19A1 and its expression is controlled by tissue-specific promoters. Aromatase mRNA is primarily transcribed from promoter I.4 in normal breast tissue and physiological levels of aromatase are found in breast adipose stromal fibroblasts. Under the conditions of breast cancer, as a result of the activation of a distinct set of aromatase promoters (I.3, II, and I.7) aromatase expression is enhanced leading to local overproduction of estrogen that promotes breast cancer. Aromatase is considered as a potential target for endocrine treatment of breast cancer but due to nonspecific reduction of aromatase activity in other tissues, aromatase inhibitors (AIs) are associated with undesirable side effects such as bone loss, and abnormal lipid metabolism. Inhibition of aromatase expression by inactivating breast tumor-specific aromatase promoters can selectively block estrogen production at the tumor site. Although several synthetic chemical compounds and nuclear receptor ligands are known to inhibit the activity of the tumor-specific aromatase promoters, further development of more specific and efficacious drugs without adverse effects is still warranted. Plants are rich in chemopreventive agents that have a great potential to be used in chemotherapy for hormone dependent breast cancer which could serve as a source for natural AIs. In this brief review, we summarize the studies on phytochemicals such as biochanin A, genistein, quercetin, isoliquiritigenin, resveratrol, and grape seed extracts related to their effect on the activation of breast cancer-associated aromatase promoters and discuss their aromatase inhibitory potential to be used as safer chemotherapeutic agents for specific hormone-dependent breast cancer.
Conversion of Androgens to Estrogens
Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women

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**IMPACT** Prospective studies linking shift work to coronary heart disease (CHD) have been inconsistent and limited by short follow-up.

**OBJECTIVE** To determine whether rotating night shift work is associated with CHD risk.


**EXPOSURES** Lifetime history of rotating night shift work (≥3 night shifts per month in addition to day and evening shifts) at baseline (updated every 2 to 4 years in the NHS2).

**MAIN OUTCOMES AND MEASURES** Incident CHD; ie, nonfatal myocardial infarction, CHD death, angiogram-confirmed angina pectoris, coronary artery bypass graft surgery, stents, and angioplasty.

**RESULTS** During follow-up, 7,303 incident CHD cases occurred in the NHS (mean age at baseline, 54.5 years) and 3,519 in the NHS2 (mean age, 34.8 years). In multivariable-adjusted Cox proportional hazards models, increasing years of baseline rotating night shift work was associated with significantly higher CHD risk in both cohorts. In the NHS, the association between duration of shift work and CHD was stronger in the first half of follow-up than in the second half (P=.02 for interaction), suggesting waning risk after cessation of shift work. Longer time since quitting shift work was associated with decreased CHD risk among ever shift workers in the NHS2 (P<.001 for trend).
Representative Biological Rhythms

**Testosterone**

Mean (±SD) total testosterone serum concentration vs time for PP Populations.

**Melatonin**

- Melatonin levels peak in the middle of the night.
- Melatonin production increases in the evening.
- Melatonin levels fall to normal daytime low by early morning.

**Cortisol**

- Circadian release of cortisol.

**Estrogen/Progesterone**

- Estradiol
- LH
- Progesterone
- FSH
- Menstruation
- Follicular Phase
- Ovulation
- Luteal Phase

Days of Menstrual Cycle:

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Clock Genes
*The Organizer of Metabolism*
Clock Genes and Chronobiology
Clock Gene Expression Regulates the Expression of Metabolic Genes
Diet Effect on Chronobiology
Interplay Between Clock Genes and Nutrition

Cell 2015; 161: 84-92
Time Restricted Feeding and Influence on Metabolism
High Palmitic Acid Intake Alters Clock Gene Expression and Risk to T2D

Palmitic Acid (C16:0) “jet-lag effect”
Interplay Between Microbiome and Gut Circadian Clock
• Enterolactone is an enterolignan produced by fermentation by gut microbiota of dietary lignans.

• Study of the genetic expression effect of administered enterolactone demonstrated interaction with both clock genes and estrogen metabolizing genes.

• This may indicate a link among diet, gut microbiota, and circadian signaling through specific phytochemical signal transduction.

J Nutrition 2011; 141: 1583-89
So what are the “Takeaways” from what has been learned about Chrononutrition?

• Do not eat anything that is calorie dense at night
• Try to fast from dinner to breakfast for 12 hours
• Get morning exercise to set parasympathetic system
• Regulate light-dark exposure time
• Stay away from excess caffeine
• Eat at regular times each day
• Limit intake of palmitic acid
• Do not rush eating
• Eat low glycemic load
• Eat high phytochemicals
• Consume prebiotics
Characteristics of a “Wellderly” Population

• Evaluated genes of healthy aging vs centenarians
• Only Apo E and FOXO3A found associated with longevity
• Genes related to carnitine metabolism associated with wellderly
• No difference in penetrance of monogenetic disorders
• No difference in genes for T2 diabetes or cancer suggesting environmental factors big drivers
• Mutation of COL25A1 found associated with Alzheimers
Clinical Applications to SNP Analysis?

• There are more than 3 million SNPs of which only a few have presently been identified to have stronger connection to phenotype

• Start with those SNPs that have the strongest known clinical utility concerning impact on **Physiological FUNCTION:**
  
  • Methylation network (eg. MTHFR, COMT, Cystathionase)
  • Pharmacogenomics/Detoxification (eg. CYP1A1, 1B1, Glucuronyl Transferase, Amino acid conjugases)
  • Insulin Regulation (eg. FOXO, Fatty Acid Synthase)
  • Inflammatory Signaling (eg. IL-1, IL-6, TNF alpha)
  • Coagulation (eg. Leiden Factor V, Prothrombin)
  • Immune Factors (eg. Transglutaminase, HLA-DQA1)
  • Cardiovascular (eg. PCSK9, CETP, ApoB)