OXIDATIVE STRESS:
The effect on mitochondria & energy production

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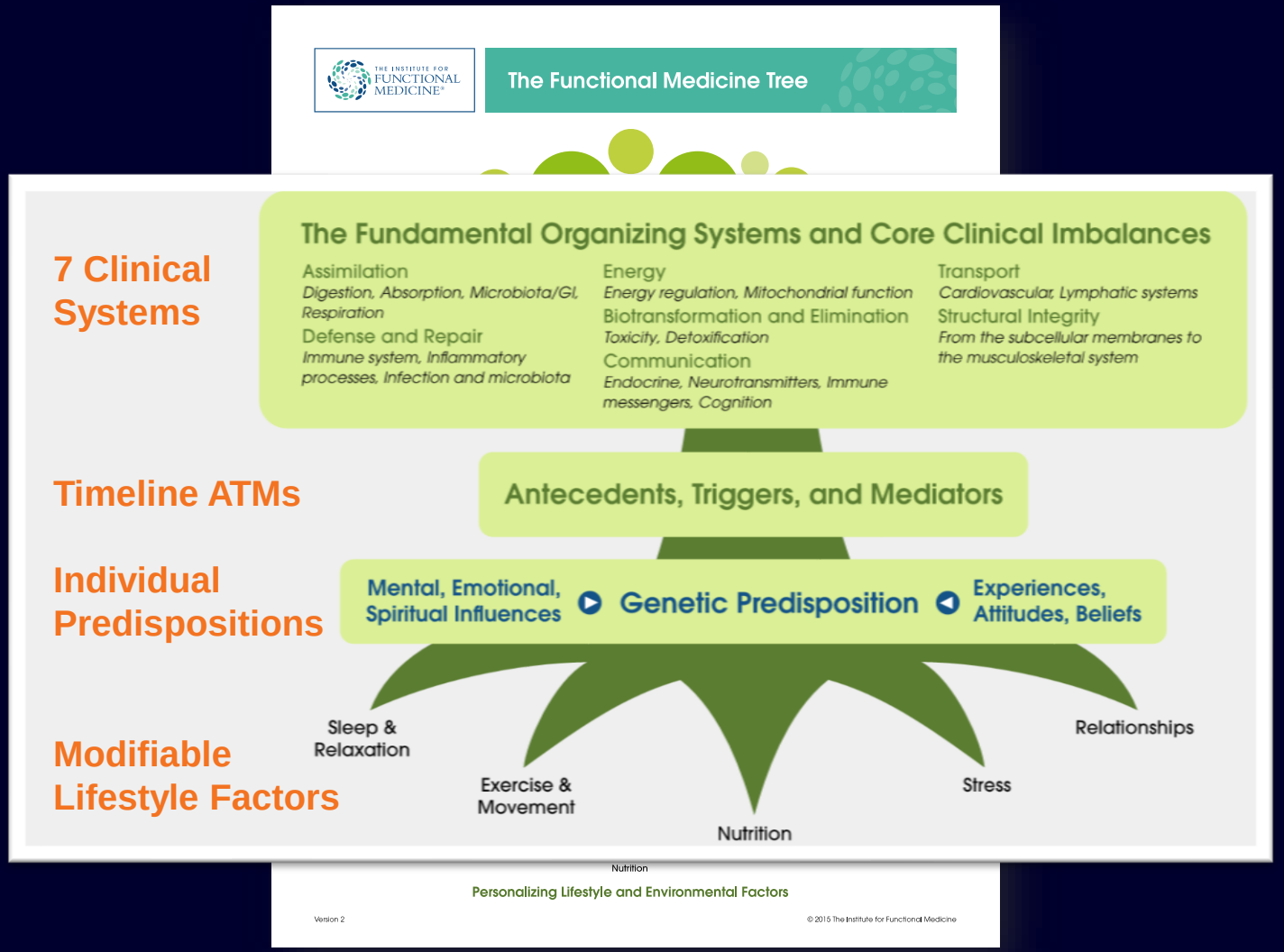
Disclosures

- None


The Functional Medicine Tree
7 Clinical Systems
The Fundamental Organizing Systems and Core Clinical Imbalances
Assimilation
Digestion, Absorption, Microbiota/GI, Respiration
Defense and Repair
Immune system, Inflammatory processes, Infection and microbiota
Energy
Energy regulation, Mitochondrial function
Biotransformation and Elimination
Toxicity, Detoxification
Communication
Endocrine, Neurotransmitters, Immune messengers, Cognition
Transport
Cardiovascular, Lymphatic systems
Structural Integrity
From the subcellular membranes to the musculoskeletal system
Timeline ATMs
Antecedents, Triggers, and Mediators
Individual Predispositions
Mental, Emotional, Spiritual Influences
Genetic Predisposition
Experiences, Attitudes, Beliefs
Modifiable Lifestyle Factors
Sleep & Relaxation
Exercise & Movement
Nutrition
Stress
Relationships
Nutrition
Personalizing Lifestyle and Environmental Factors
Version 2
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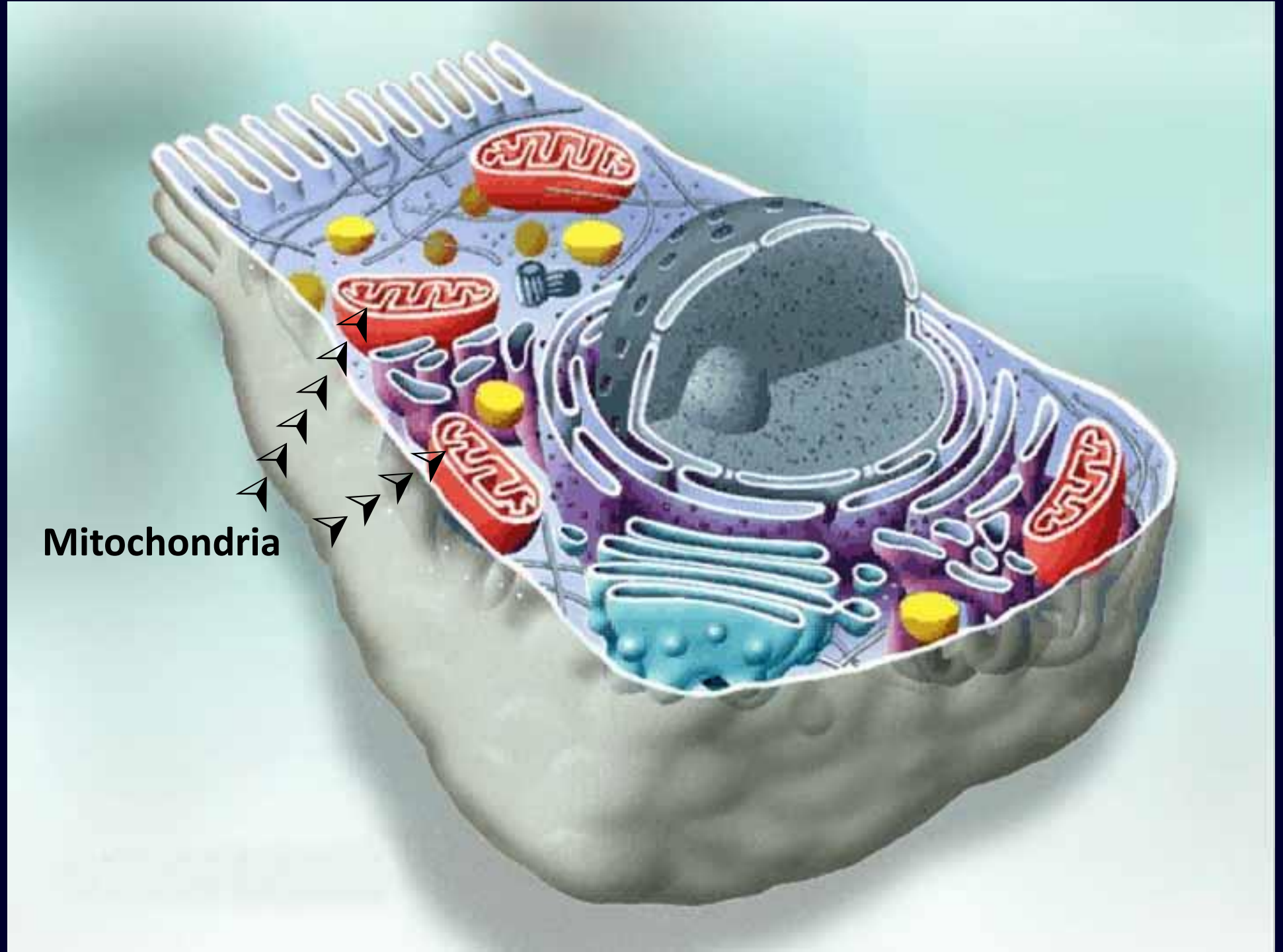
Objectives

- Review mitochondrial structure, energy production and metabolism
- Discuss the pathophysiology of oxidative stress and mitochondrial damage; including dietary factors, ROS, and toxins
- Review ways to support mitochondria with diet, nutrients, and phytochemicals


Mitochondria

Mitochondrial distribution

- Approximately 10 million billion total: ~10% of body weight
- Average of 200 to 2000 per somatic cell

  ~5000 in cardiac cells -- 50% of myocardial cytoplasm -- there is complete turnover of myocardial ATP pool every 10 seconds

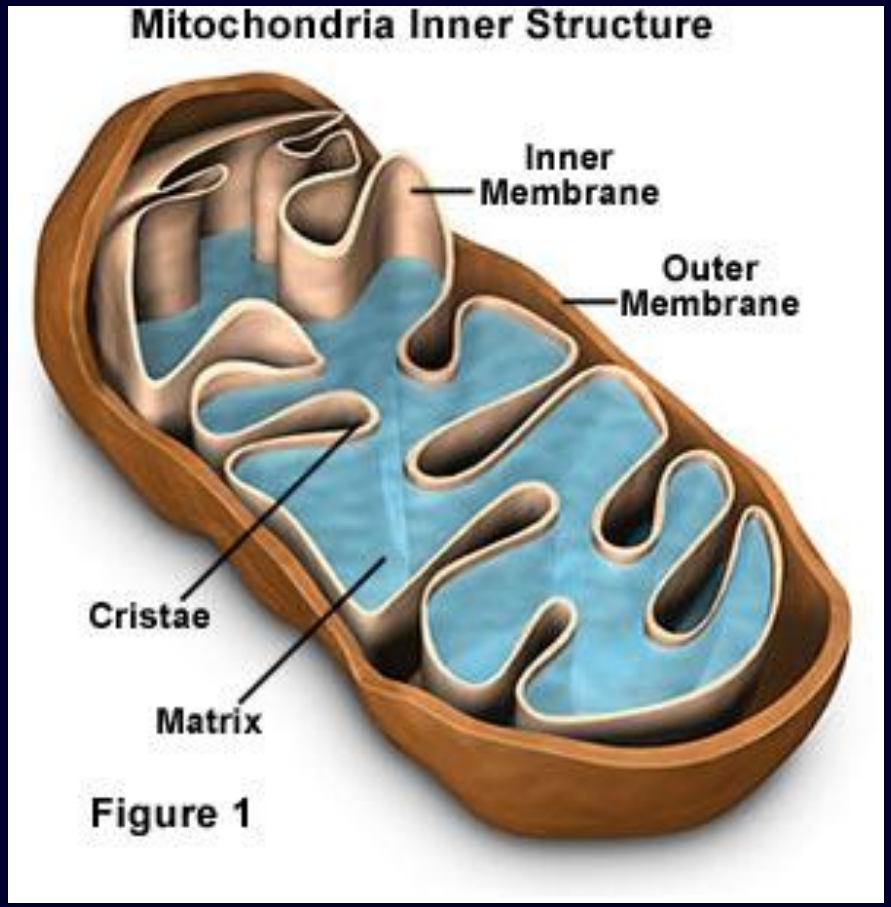
  ~800 in hepatocytes

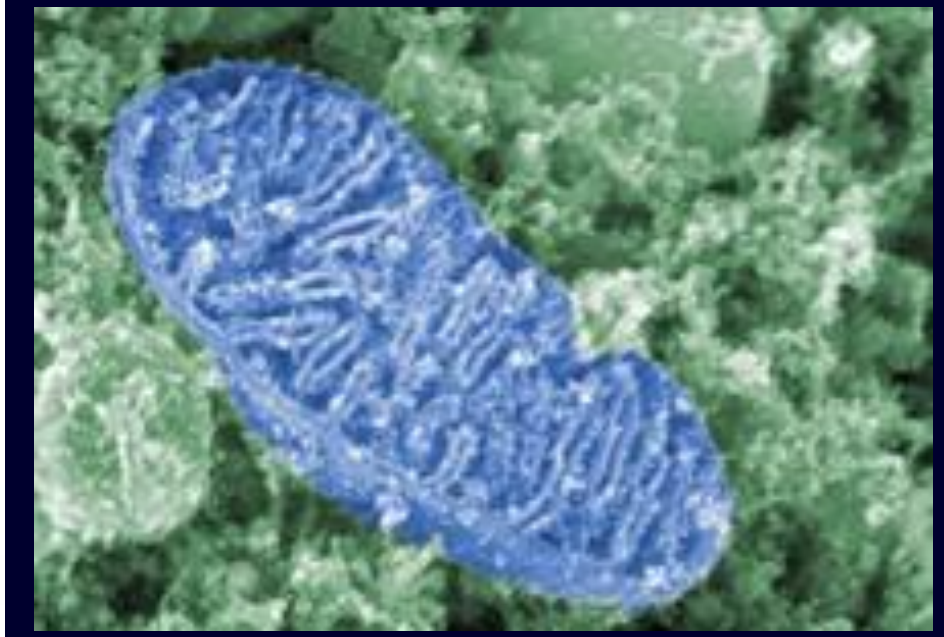
  ~300-400 in neurons (filamentous)
- **Mitochondria generate and consume the body's weight in ATP every day**

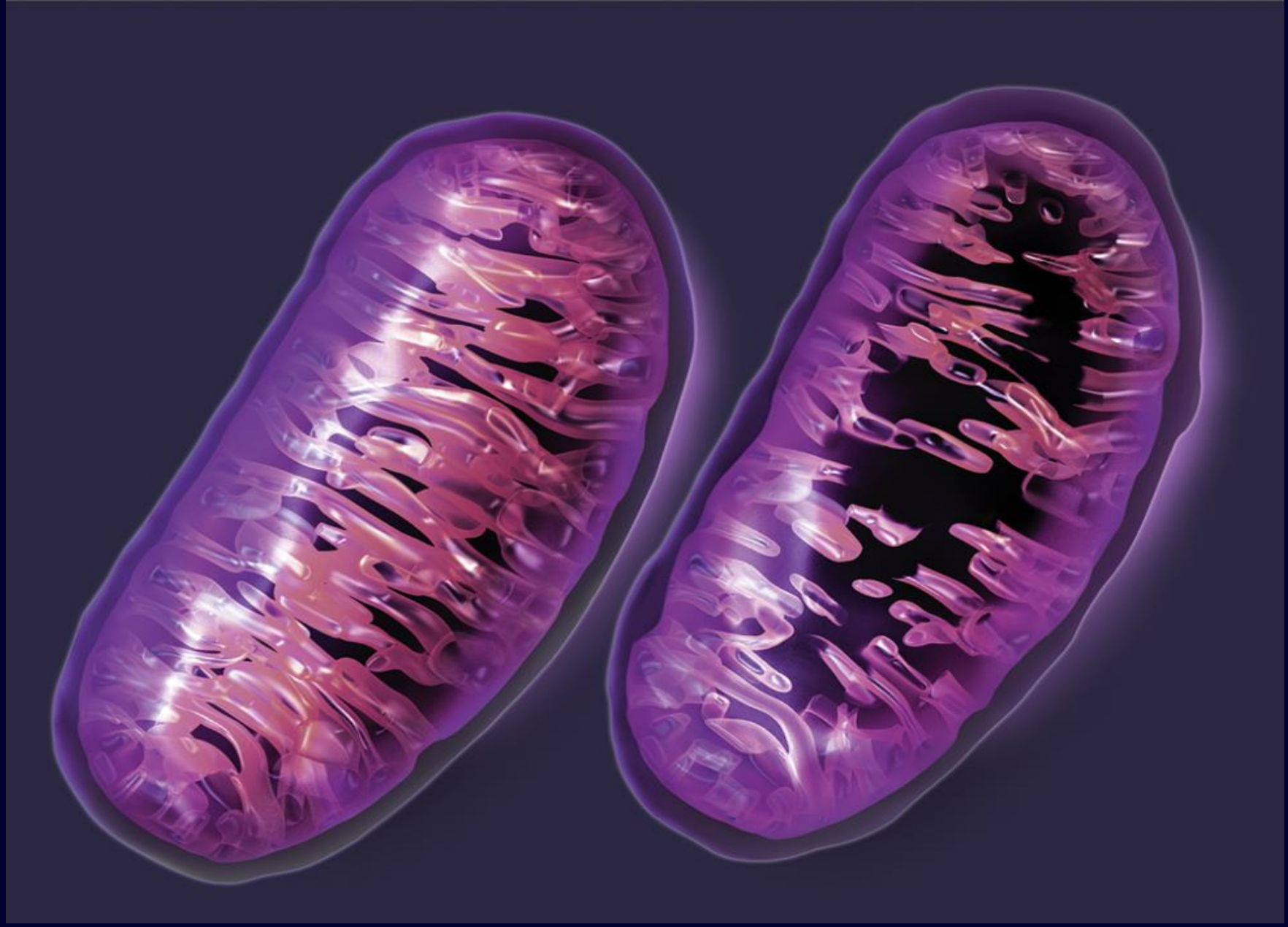
Mitochondria: powerhouse of the cell

- Mitochondria consume about 90% of the oxygen used by the body for oxidative phosphorylation
- The oxygen serves as the ultimate electron receptor from the electron transport chain, allowing ATP to be generated

Mitochondrial anatomy







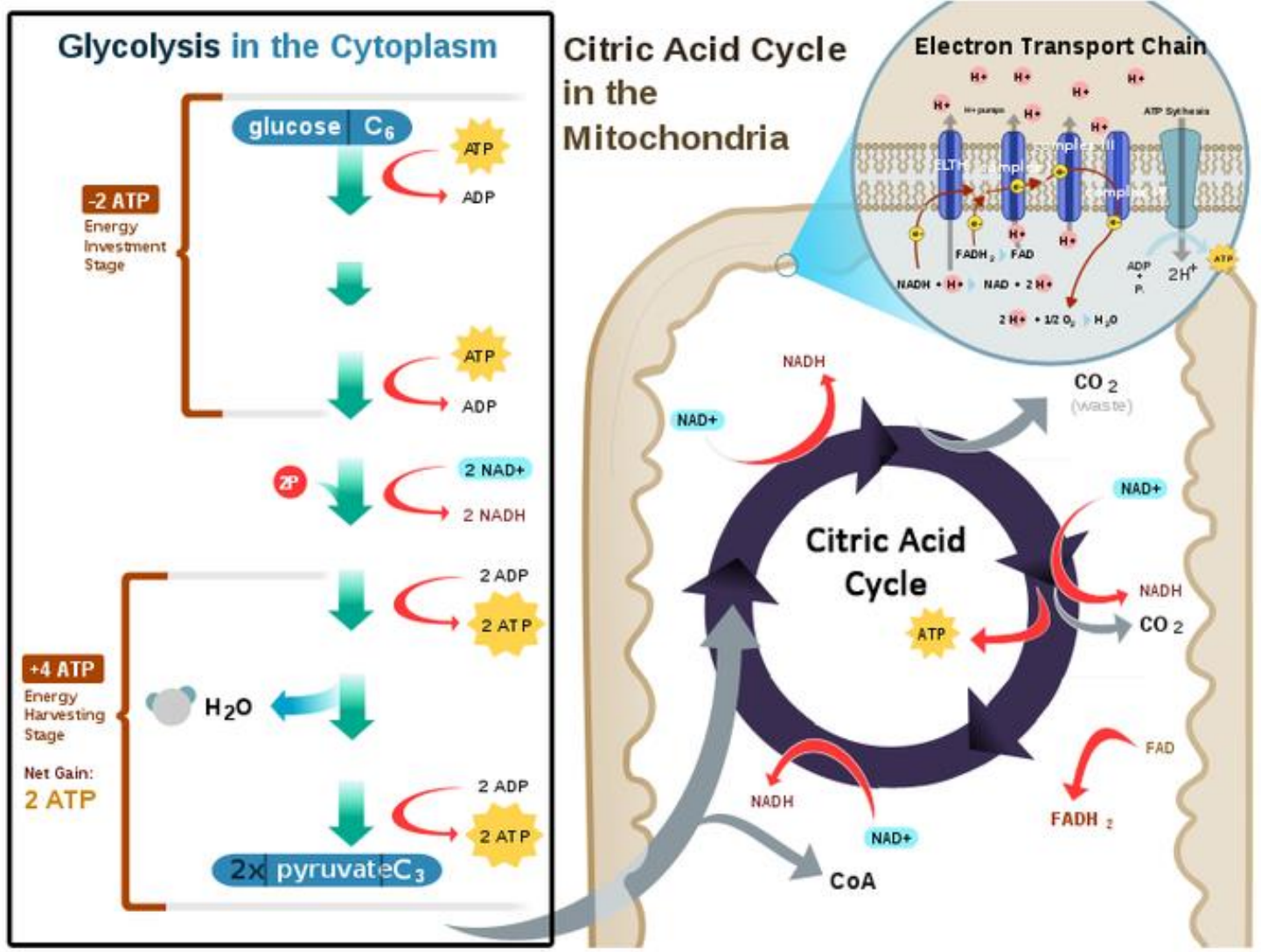
Healthy cristae (left) vs damaged (right)

Mitochondrial functions

- ATP synthesis
- Buffering Ca^{++} flux (from endoplasmic reticulum & plasma membrane)
- Maintenance of ion gradients (polarized cells)
- Generation of reactive oxygen species (ROS)
- Regulation of cell growth, cell cycle, metabolism

Mitochondrial bioenergetics

- Catabolism of CHO, fats, & amino acids into *carbon skeletons*
- Extraction of energy released via catabolism:
  - Glycolysis
  - Citric acid cycle (Krebs)
  - β-oxidation
  - Oxidative phosphorylation
- 36-38 molecules of ATP per molecule of glucose



Net ATP: 30 to 32 ATP per glucose

Glycolysis: +2 ATP via substrate-level phosphorylation

Citric Acid Cycle: +2 ATP via substrate level phosphorylation (1 per pyruvate)

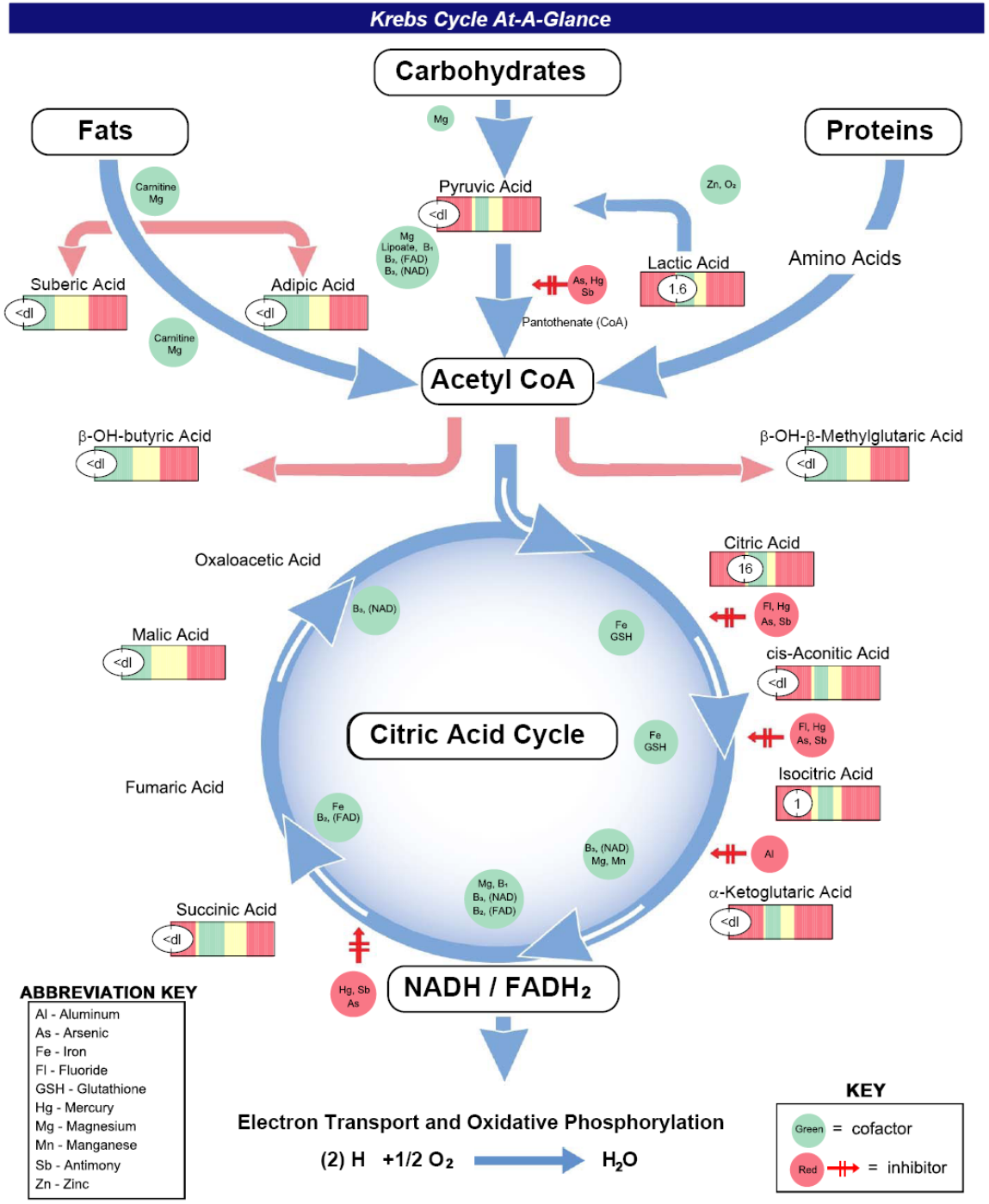
Electron Transport Chain: +26 to 28 ATP via oxidative phosphorylation

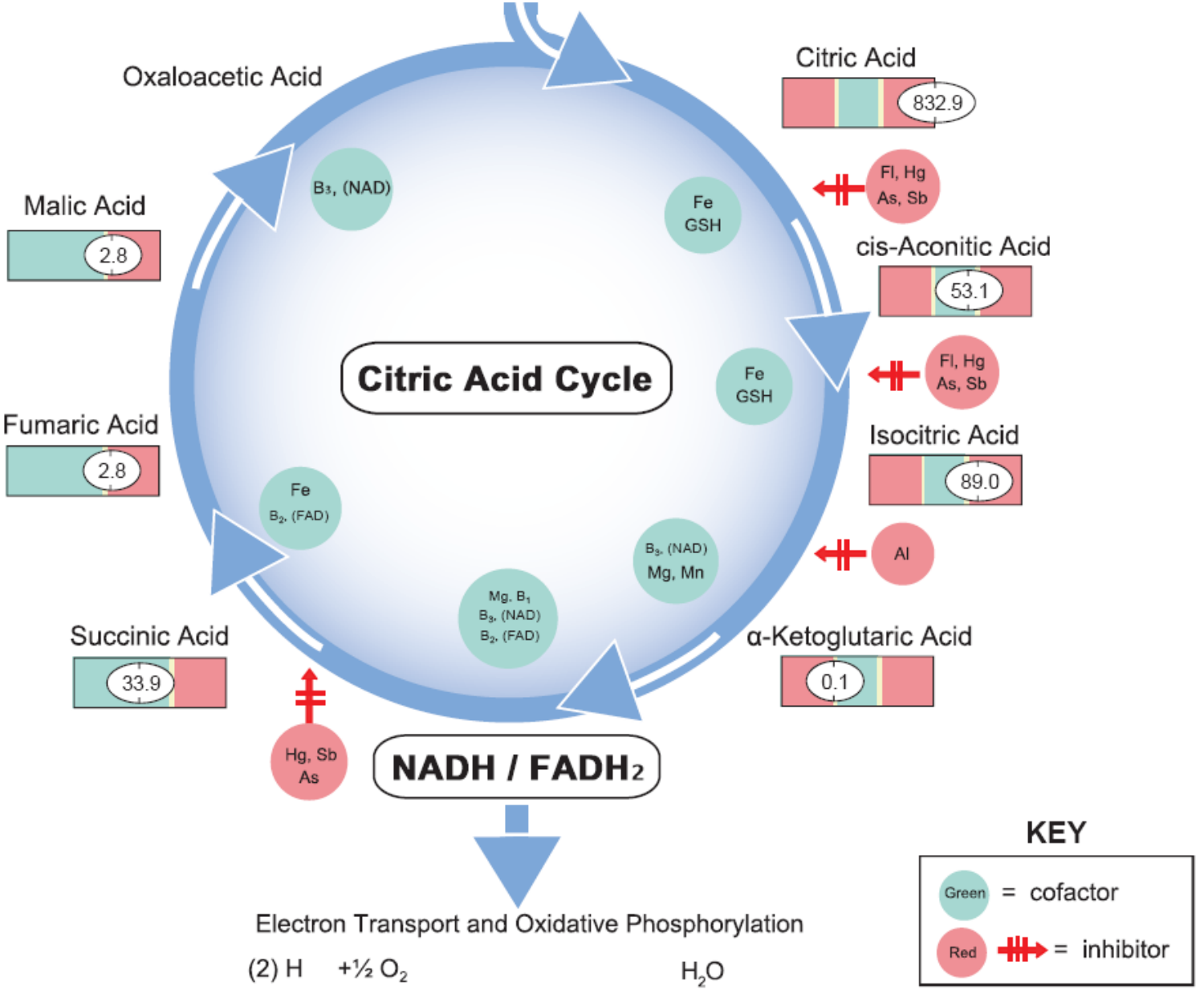
Glycolysis

- Ancient metabolic pathway -- in cytosol of most living organisms

- Glucose (6C): initial electron donor
  - Reduces NAD^+ into NADH x 2
  - Generates ATP x 2
    (very rapid but inefficient energy production)
  - Splits into pyruvate x 2

- Pyruvate (3C)
  - Actively transported into matrix for aerobic respiration by mitochondrial pyruvate carrier
  - When mitochondrial metabolism inhibited (anaerobic conditions, etc.), converted into lactate by LDH, which regenerates NAD^+


Krebs Cycle At-A-Glance
Carbohydrates
Fats
Proteins
Mg
Carnitine
Mg
Pyruvic Acid
<dl
Zn, O₂
Mg
Lipoate, B₁
B₂, (FAD)
B₃, (NAD)
Lactic Acid
1.6
As, Hg
Sb
Amino Acids
Suberic Acid
<dl
Adipic Acid
<dl
Carnitine
Mg
Pantothenate (CoA)
Acetyl CoA
β-OH-butyric Acid
<dl
β-OH-β-Methylglutaric Acid
<dl
Oxaloacetic Acid
Citric Acid
16
B₃, (NAD)
Fe
GSH
Fl, Hg
As, Sb
Malic Acid
<dl
cis-Aconitic Acid
<dl
Citric Acid Cycle
Fe
GSH
Fl, Hg
As, Sb
Isocitric Acid
1
Fumaric Acid
Fe
B₂, (FAD)
B₃, (NAD)
Mg, Mn
Al
α-Ketoglutaric Acid
<dl
Mg, B₁
B₃, (NAD)
B₂, (FAD)
Succinic Acid
<dl
Hg, Sb
As
NADH / FADH2
ABBREVIATION KEY
Al - Aluminum
As - Arsenic
Fe - Iron
Fl - Fluoride
GSH - Glutathione
Hg - Mercury
Mg - Magnesium
Mn - Manganese
Sb - Antimony
Zn - Zinc
Electron Transport and Oxidative Phosphorylation
(2) H +1/2 O2
H2O
KEY
Green = cofactor
Red = inhibitor


Oxaloacetic Acid
Citric Acid
832.9
Fl, Hg
As, Sb
B₃, (NAD)
Fe
GSH
Malic Acid
2.8
cis-Aconitic Acid
53.1
Citric Acid Cycle
Fe
GSH
Fl, Hg
As, Sb
Fumaric Acid
2.8
Isocitric Acid
89.0
Fe
B₂, (FAD)
B₃, (NAD)
Mg, Mn
Al
Mg, B₁
B₃, (NAD)
B₂, (FAD)
Succinic Acid
33.9
α-Ketoglutaric Acid
0.1
Hg, Sb
As
NADH / FADH2
Electron Transport and Oxidative Phosphorylation
(2) H +½ O2
H2O
KEY
Green = cofactor
Red = inhibitor

Conventional wisdom has been that mitochondria prefer carbohydrates (glucose) as the primary source of energy, however, fatty acids (ketones), and amino acids can also be readily utilized by mitochondria

Tricarboxylic Acid (Krebs) Cycle

- Final common catabolic pathway for all nutrients (protein, fat, carbohydrates)
- Enzymes located in mt matrix (except for complex II - succinate dehydrogenase)
- Acetyl-CoA oxidized to CO_2
- Produces
  - Metabolic byproducts: amino acid precursors
  - NADH, $FADH_2$, GTP

Long chain fatty acids: mitochondrial metabolism

- Most dietary fatty acids undergo β-oxidation in mitochondria
- High carbohydrate intake impairs β-oxidation, resulting in accumulation of intracellular lipid intermediates and triglycerides, causing insulin resistance
- Fasting, starvation, and low carbohydrate/high fat diets increase hepatic β-oxidation, resulting in ketogenesis

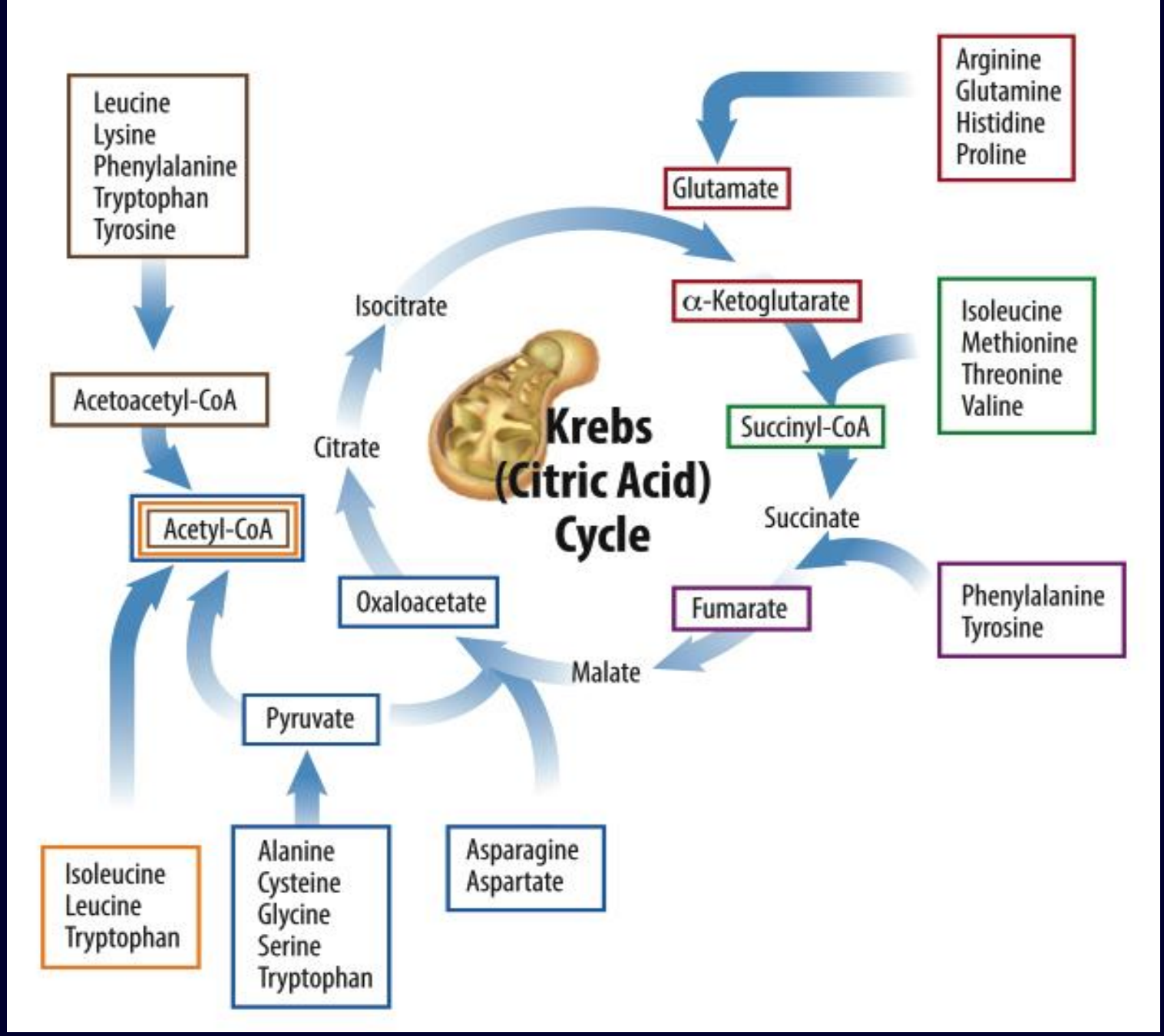
Ketone bodies

- Ketones soluble in water—no protein carriers required
- Plasma levels increase with fasting, high fat/low CHO diets, and uncontrolled diabetes
- Ketones are preferred fuel (vs glucose) for cardiac muscle and renal cortex
- Used in brain (after crossing blood brain barrier) proportionate to concentration in blood, provide energy when glucose availability is limited

J Med Food 16 (11) 2013, 965–967

Amino acids as fuel sources

- Can be oxidized, degraded into pyruvate, used as citric acid cycle intermediates, or converted into ketone bodies
- Oxidative degradation of AAs produces 10-15% of total metabolic energy
- Act as precursors for gluconeogenesis when glucose supply is low



Amino acid precursors for TCA cycle

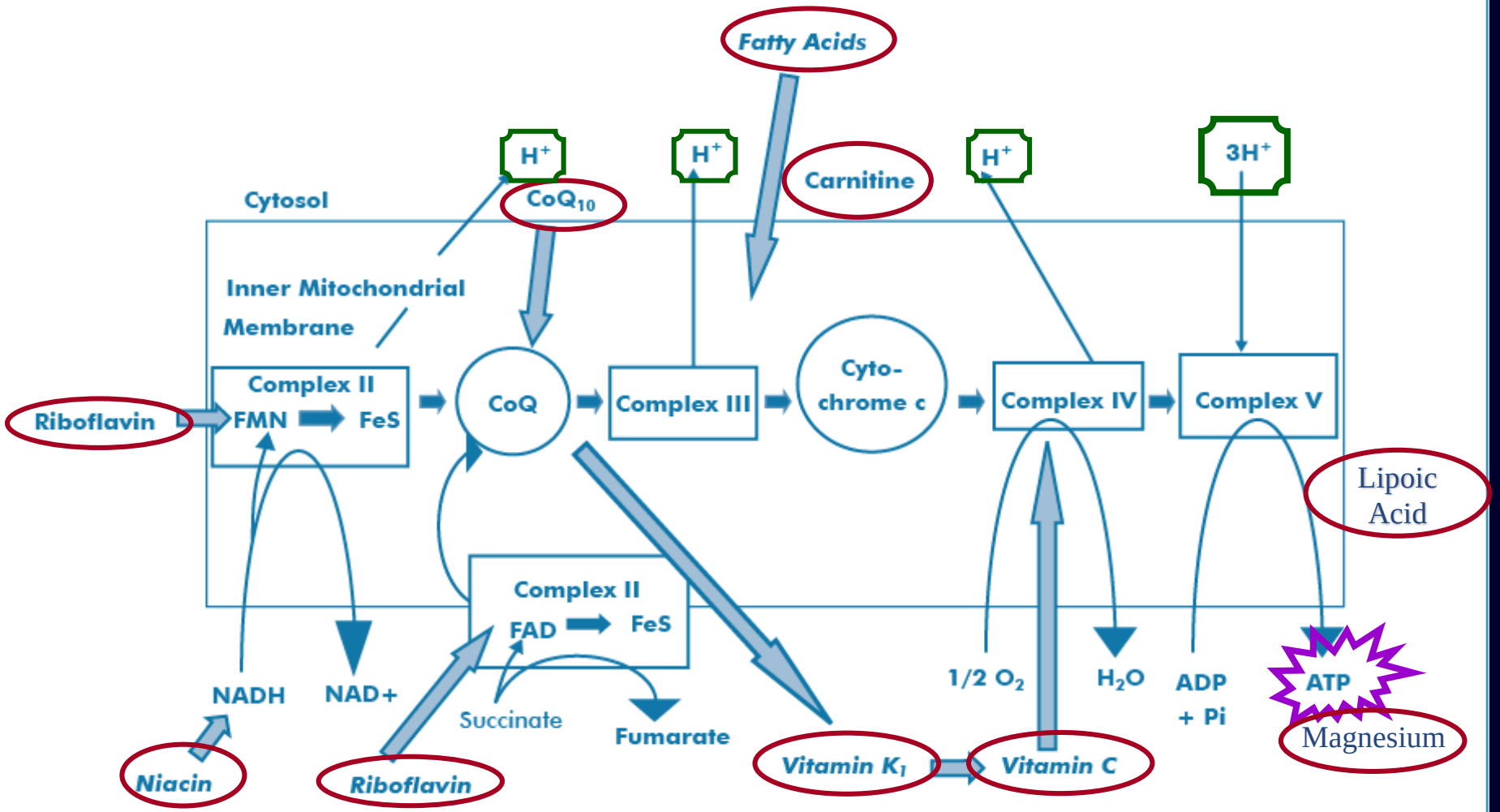
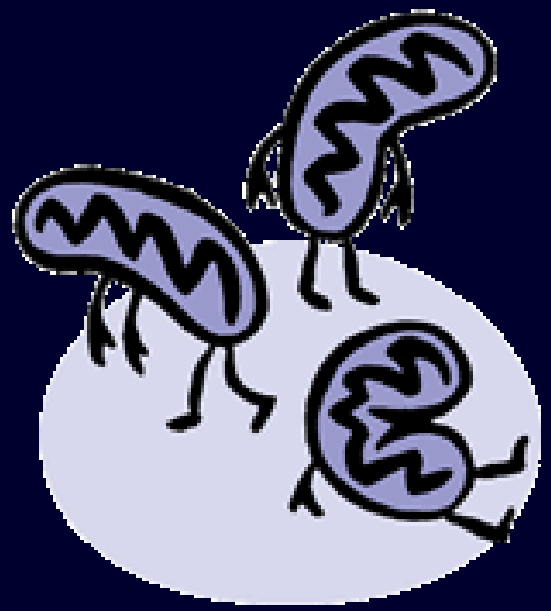
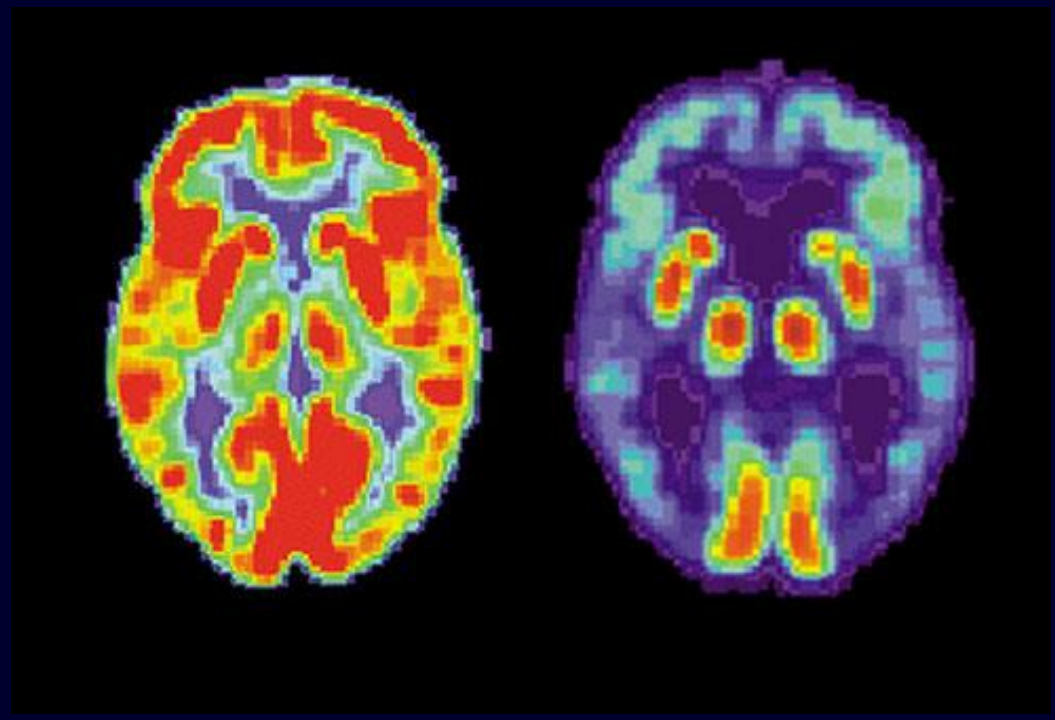


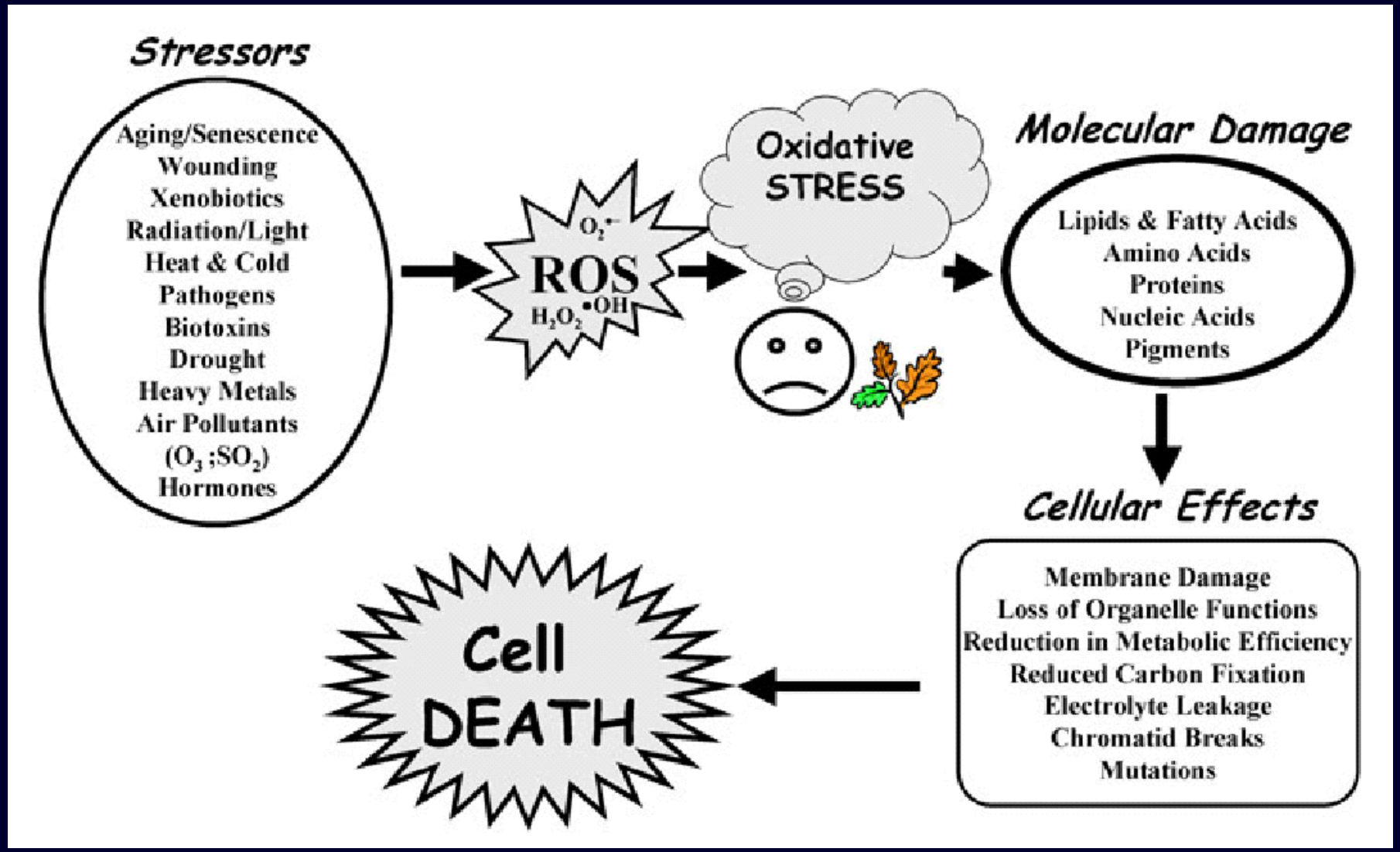
FIG. *Mitochondrial Respiratory Chain. Protons (H^+) are pumped from the mitochondrial matrix to the intermembrane space through complexes I,III, and IV. Complex V utilizes the proton gradient as a source of energy to produce ATP. Coenzyme Q_{10} transfers electrons from complexes I and II to complex III. Riboflavin is a precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The amide form of niacin, (nicotinamide) is a precursor for nicotinamide adenine dinucleotide (NAD). Vitamin K_3 in combination with vitamin C serce as electron acceptors to bypass a deficiency in complex III. Carnitine function to transfer long chain fatty acids across the mitochondrial membrane.*

Introducing: The Electron Transport Chain

Mitochondrial energy production






Stressors
Aging/Senescence
Wounding
Xenobiotics
Radiation/Light
Heat & Cold
Pathogens
Biotoxins
Drought
Heavy Metals
Air Pollutants
(O_3 ;SO_2)
Hormones
$O_2^{\bullet-}$
ROS
H_2O_2 $^{\bullet}OH$
Oxidative STRESS
Molecular Damage
Lipids & Fatty Acids
Amino Acids
Proteins
Nucleic Acids
Pigments
Cellular Effects
Membrane Damage
Loss of Organelle Functions
Reduction in Metabolic Efficiency
Reduced Carbon Fixation
Electrolyte Leakage
Chromatid Breaks
Mutations
Cell DEATH

Objectives

- Review mitochondrial structure, function and metabolism
- **Discuss the pathophysiology of mitochondrial damage, including dietary factors, ROS, and toxins**
- Review ways to support mitochondria with diet, nutrients, and phytochemicals

An individual produces about 1 kg of oxygen radicals per year. The consequence is about 100,000 oxidative attacks on mDNA per cell per day.

Causes of increased mitochondrial ROS

- Caloric excess
- Hyperglycemia (endothelial)
- Inflammatory mediators (TNFα)
- Hypoxia
- Environmental pollutants & toxicants
- Toxic metals (mercury, arsenic)
- Ionizing radiation

Denham Harman

- First proposed the idea of “free radicals” in 1956 and postulated that these compounds play a role in aging through cross-linking reactions.
- Free radicals covalently modify lipids, proteins, cellular and mitochondrial DNA.

Harman D. Role of free radicals and radiation chemistry. *J Gerontol* 1956;11:298-300.
Harman D. Free radical theory of aging: consequences of mitochondrial aging. *Age* 1983;6:86-94.

Free radical theory of aging

- Increased oxidant generation
- Declining defenses and repair
- Accumulation of the end products of oxidative damage
  - ✓ **Advanced Glycosylated End Products (AGEs)**
  - ✓ **Protein Oxidation (NitroTyrosine)**
  - ✓ **Oxidized LDL, Isoprostane F2, Lipid Peroxides, MDA**
  - ✓ **DNA damage (8-OH dG)**

Free radicals, ROS, and RNS…

React with and damage structural and functional components of cells

- Membranes & Receptors
- Enzymes & other proteins
- Cellular DNA & RNA
- Mitochondrial DNA & Membranes

Mitochondria & free radicals

- About 1-2% of oxygen consumed by our mitochondria is converted to superoxide and hydrogen peroxide
- One rat liver mitochondrion produces ~$3X10^{7}$ superoxide radicals per day
- Each liver cell contains ~1000 mitochondria

NK-kB mediated cellular damage

⇑ Oxidative Stress

↓

Activation of NF-KB

↓

Up-regulation of stress and inflammation genes including inducible NOS (iNOS)

↓

⇑ RNS, NO, *$ONO2^-$

↓

Increased Cellular Damage

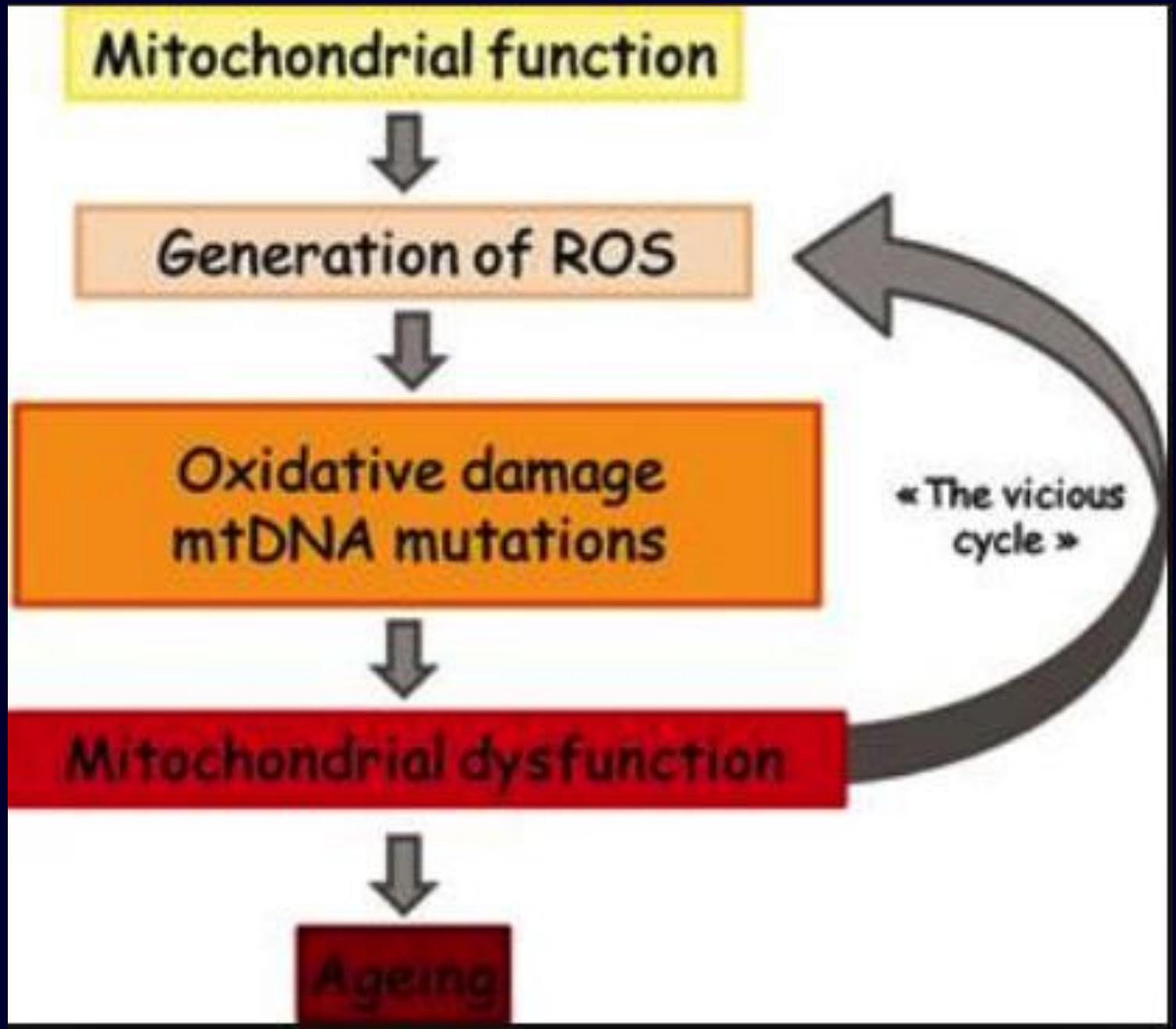
How does the body protect itself from ROS?

1. Enzymes
   - Catalase *(Fe)*
   - Superoxide dismutase-SOD *(Zn, Cu, Mn)*
   - Glutathione peroxidase *(Se)* and glutathione reductase
2. Dietary Anti-Oxidants
   - Vitamin C for aqueous compartments
   - Vitamin E for lipid compartments
   - Carotenoids, flavonoids, etc.
3. Endogenous Anti-Oxidant Molecules
   - Glutathione, cysteine, CoQ_{10}, lipoic acid, uric acid, cholesterol.

Understanding oxidative stress

To have a comprehensive understanding of the body's red-ox potential and level of total oxidative stress, you need to know:

1. What is the antioxidant reserve or total antioxidant capacity?
2. What is the throughput of reactive oxygen species and free radicals?
3. What damage to cellular components is being done?


Mitochondrial function
Generation of ROS
Oxidative damage
mtDNA mutations
Mitochondrial dysfunction
Ageing
« The vicious cycle »

What's the damage?

Oxidative stress from free radicals, ROS, and RNS can damage many cellular components

- Damaged Fats
- Damaged Sugars
- Damaged Proteins
- Damaged DNA

One can evaluate with:

- Damaged Fats → Lipid Peroxides, oxidized LDL, Isoprostane F2
- Damaged Sugars → HgbA1c, AGEs
- Damaged Proteins → 3-Nitrotyrosine
- Damaged DNA → 8-OH Deoxyguanosine

Therapies to ↓ lipid peroxides

Consider fat-soluble antioxidants:

- Vitamin E (interrupts rapid propagation of lipid peroxides)
- CoQ10
- Lipoic Acid

For lowering serum lipid peroxides, the combination of Curcumin, cayenne, and garlic is effective

Kempaiah RK, Srinivasan K. Ann Nutr Metab 2004;48:314-320.

Damaged DNA (8-OHdG)
8-hydroxy-deoxyguanosine

- When an activated oxygen species reacts with the nucleotide guanosine, 8-hydroxy-deoxyguanosine is created
- 8-OHdG is the most frequent mutagenic lesion in our DNA
- Damage can be triggered by chemical toxicity, inflammation, or radiation

8-OHdG as a marker of oxidative stress

Journal of Environmental Science and Health Part C, 27:120–139, 2009
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ISSN: 1059-0501 (Print); 1532-4095 (Online)
DOI: 10.1080/10590500902885684

Taylor & Francis

8-hydroxy-2′-deoxyguanosine (8-OHdG): A Critical Biomarker of Oxidative Stress and Carcinogenesis

Athanasios Valavanidis, Thomais Vlachogianni, and Constantinos Fiotakis

Department of
Greece

There is exten
to lipids of cel
DNA, 8-hydrox
(8-oxodG) is or
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ment of variou
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chemical detect
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Oxidative DNA
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The biomarker
fect of endoger
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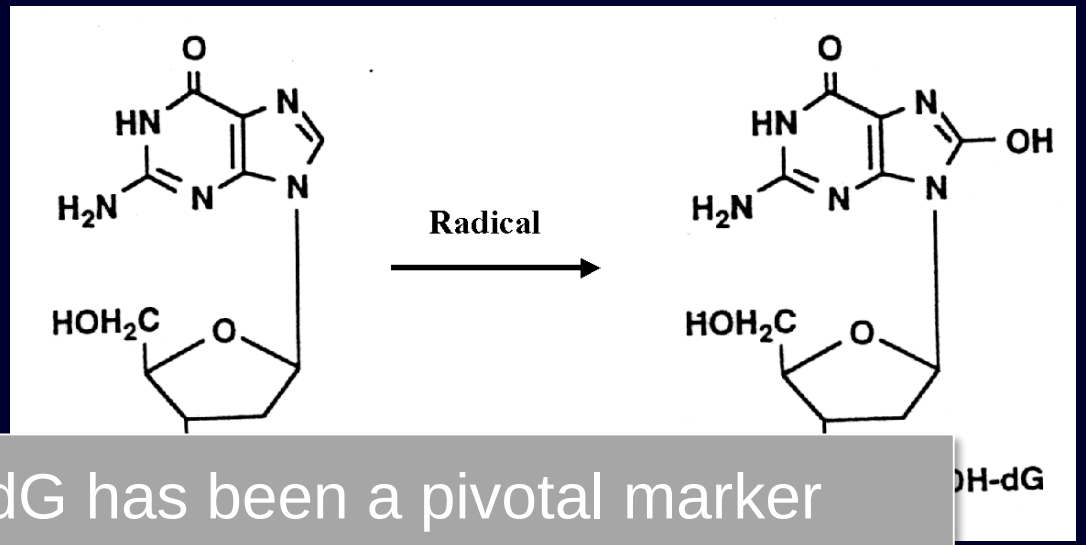
in humans afte
fibers, heavy m
has been used
endogenous oxi
cancer.

Key Words: Reactive oxygen species; biomarker; oxidative damage; DNA; 8-OHdG; 8-oxodG; carcinogenic substances; carcinogenesis

Received January 24, 2009; accepted March 11, 2009.
Address correspondence to Assoc. Prof. A. Valavanidis, Department of Chemistry, Uni-



"The biomarker 8-OHdG has been a pivotal marker for measuring the effect of endogenous oxidative damage to DNA and as a factor of initiation and promotion of carcinogenesis."

J Environ Science & Health Part C;27:120-139, 2009

Therapies to treat damaged DNA

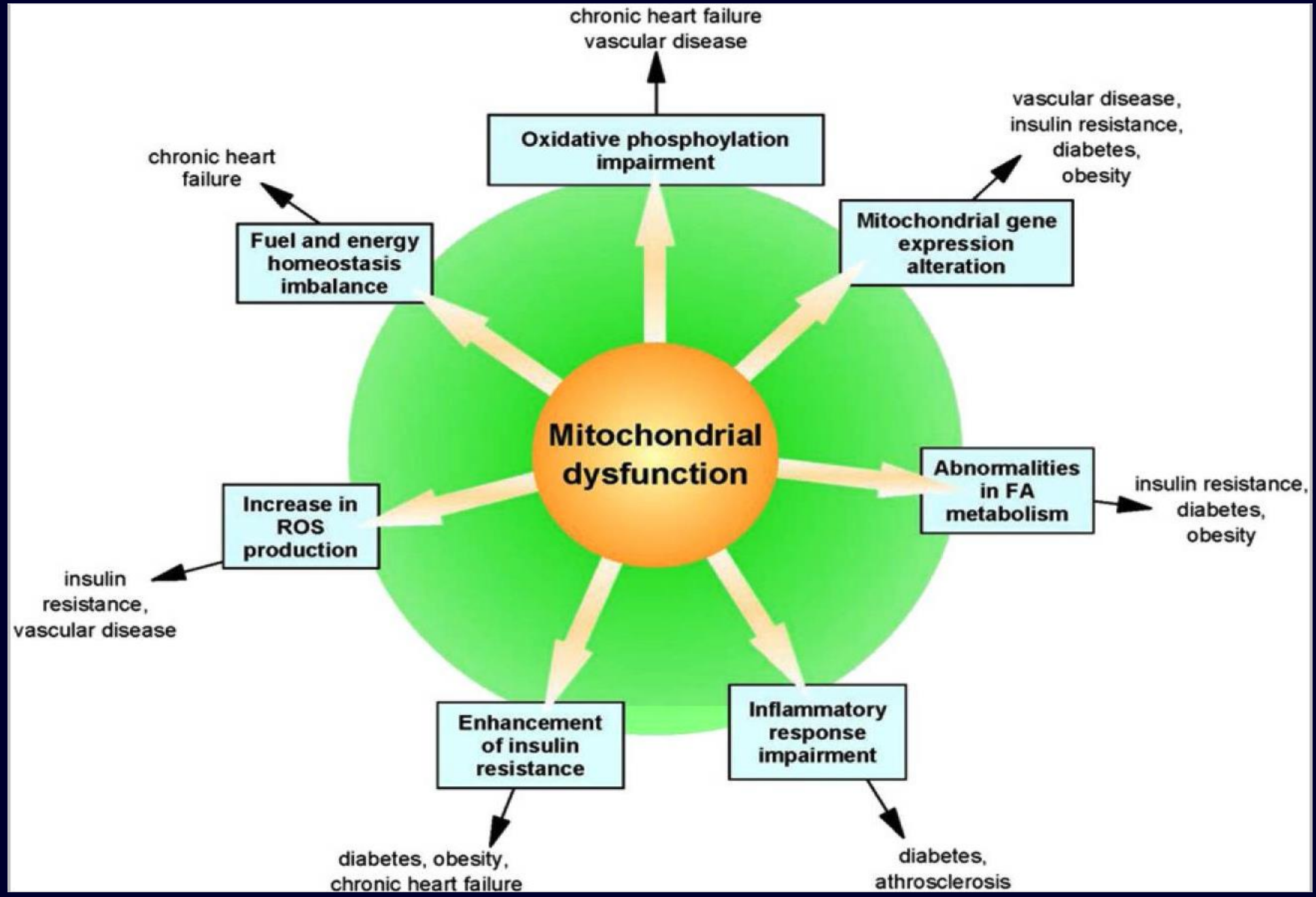
- Carotene supplementation has been found to decrease DNA oxidation
- Reduce iron overload, if present
- Combination antioxidant support is most effective
- Methylation is critical for DNA synthesis

Griffiths HR. Mol Aspects Med. 2002;23:101-108.

Wu LL et al. Clin Chim Acta. 200;339:1-9.

Effective treatment

- Nutritional Anti-Oxidants (Vit A, C, E)
  - Glutathione, alpha-Lipoic Acid
  - CoEnzyme Q-10 (CoQ-10)
- Plant-based Anti-Oxidants
  - Resveratrol
  - EpiGalloCatechinGallate (EGCG)
  - Many, many, many others
- Proper Methylation Function (B-Vitamins)
- Mineral Co-Factors (Mg, Mn, Fe, Zn)
- Amino Acid Balance and Protein Digestion
- Eat Your Vegetables!



Transl Res. 2013, Vol 161(2): 73–84

Mitochondrial dysfunction & disease

- Metabolic syndrome: insulin resistance, type 2 diabetes, obesity, non-alcoholic fatty liver disease
- Cardiovascular disease (congestive heart failure)
- Cancer
- Neurodegenerative & neuromuscular disorders
- Mood disorders; bipolar disorder
- Chronic fatigue; fibromyalgia
- Multiple chemical sensitivity
- Premature aging

Common mediators of neurodegeneration

- Reactive species and oxidative/nitrative damage – which offending species?
- Mitochondrial dysfunction
- Abnormal protein aggregates
- Inflammation

Common types of neurodegeneration

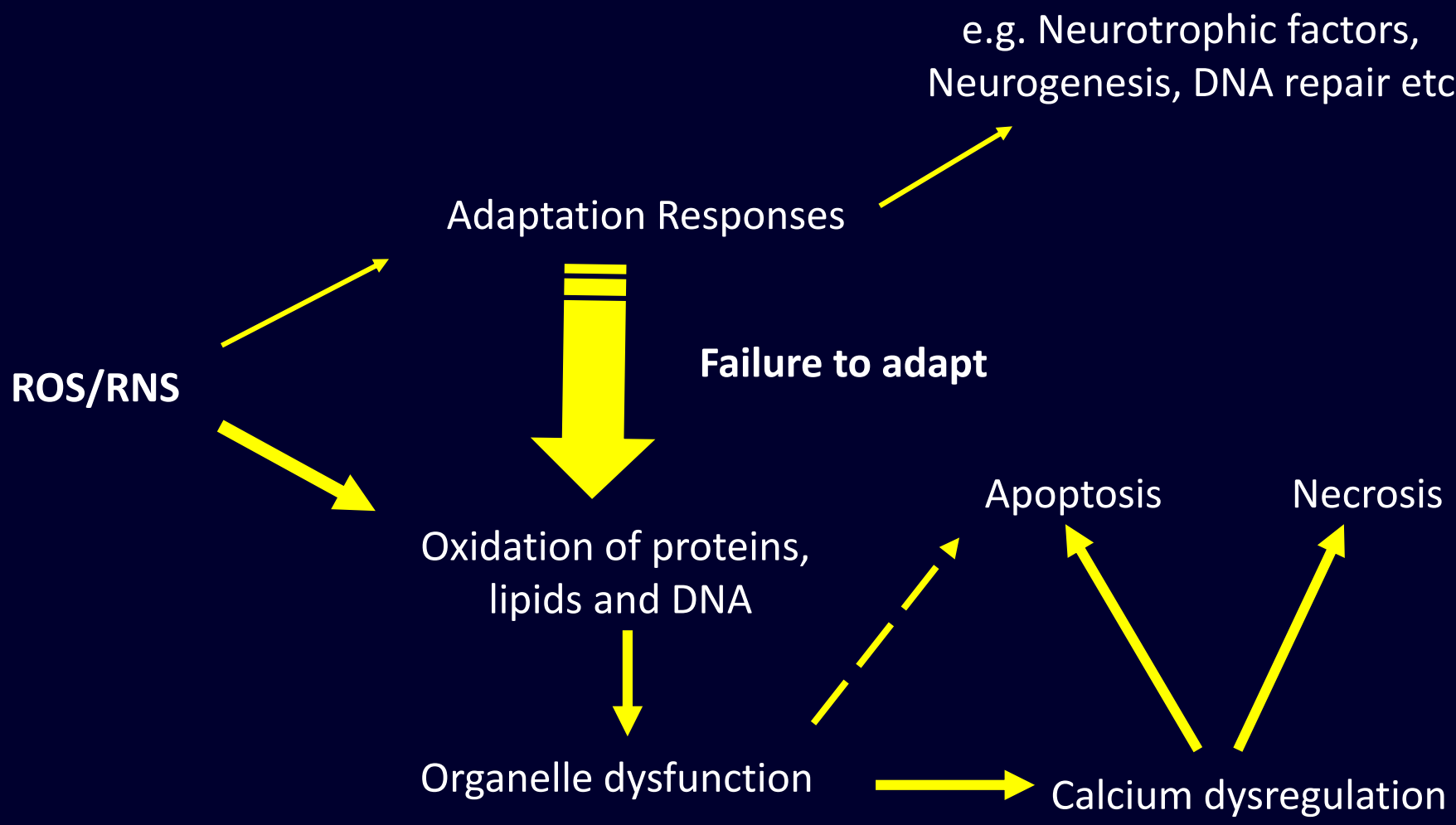
- Alzheimer's Disease
  - (a.k.a. Senile Dementia of the Alzheimer's Type – SDAT)
- Cognitive Impairment
- Memory Loss
- Parkinson's Disease
- Stroke/ CVA

Damage to lipids, proteins, DNA, & RNA in mild cognitive impairment

"These studies establish *oxidative damage* as an *early event* in the pathogenesis of Alzheimer disease that can serve as a therapeutic target to slow the progression or perhaps the onset of the disease."

Markesbery, W., Arch Neurol. 64(7):954-956; July, 2007

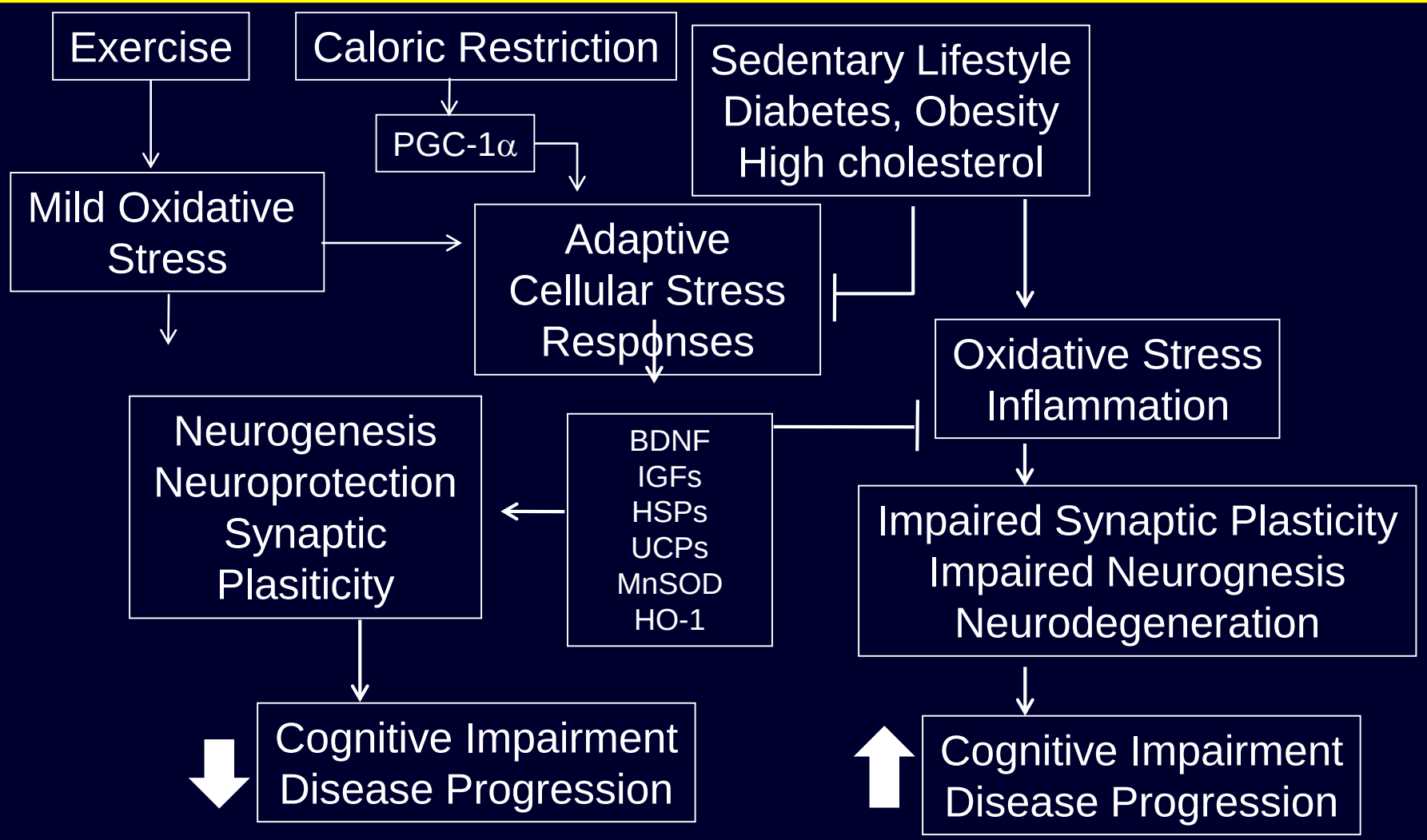
Oxidative stress response



Metabolic regulation of cognitive dysfunction

- Diabetes aggravates, and energetic challenges attenuate, CNS inflammation.
- Exercise and caloric restriction ameliorate, and diabetes exacerbates, Alzheimer’s disease models.
- Cognitive impairment associated with trauma or ischemia can be modified by caloric intake and exercise.

Regulation of cognitive function



Adapted from: Stranahan and Mattson, 2011

Is oxidative stress a useful target for brain disorders?

Dual roles of ROS:

Signaling vs damage → Xenohormesis

- Are ROS merely associated with the disease process or play a causative role?
- Do antioxidant compounds interfere with physiological processes?
- Does redox signaling role interfere with antioxidant efficacy?

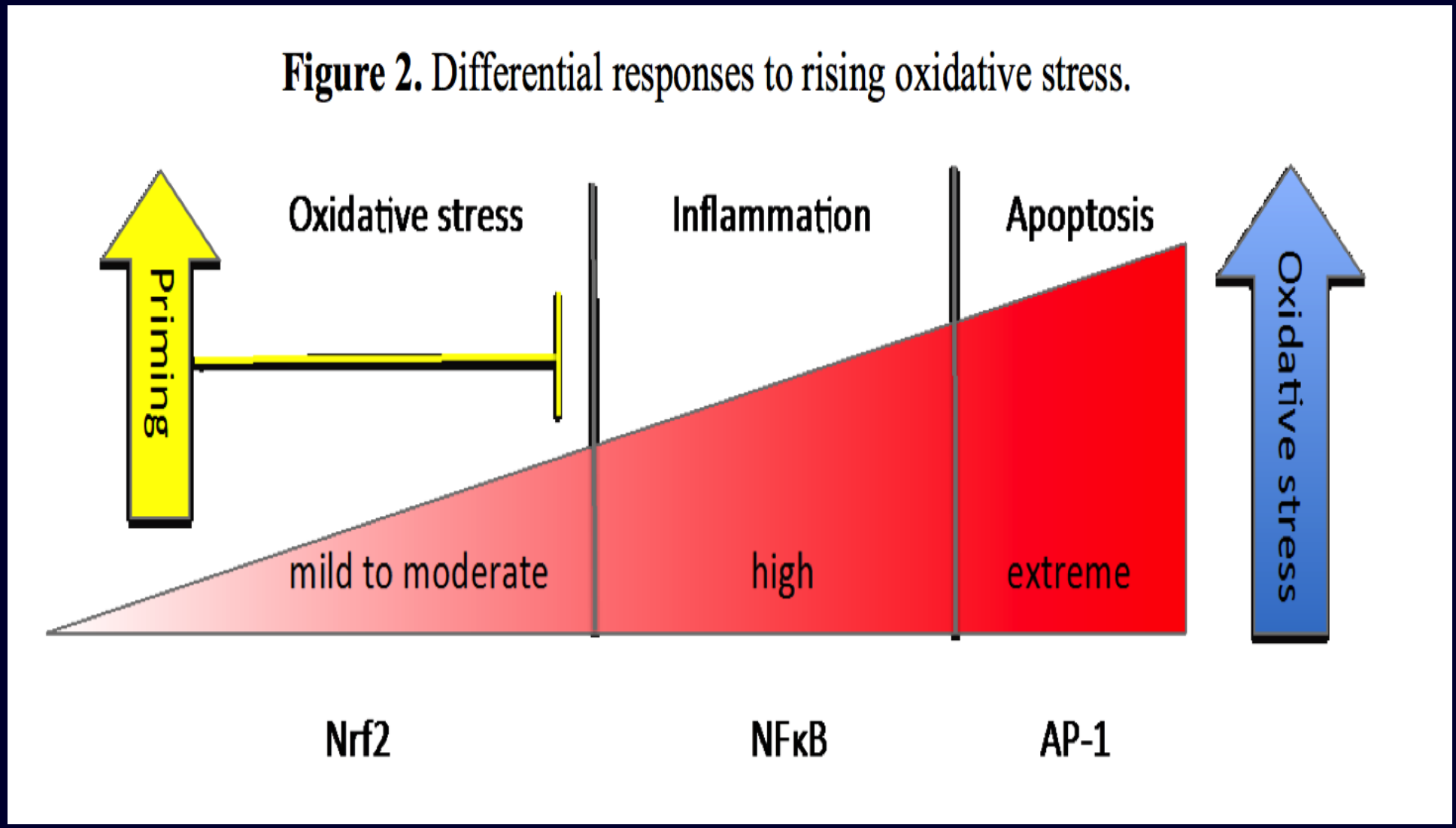
Goal of antioxidant therapy in disease states
is to normalize elevated ROS levels
and decrease oxidative damage

Xenohormesis

All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and remedy.

Paracelsus (1493–1541)

“What doesn’t kill you, makes you stronger!”



Nutrients 2014, Vol 6: 3777-3801

Xenohormesis

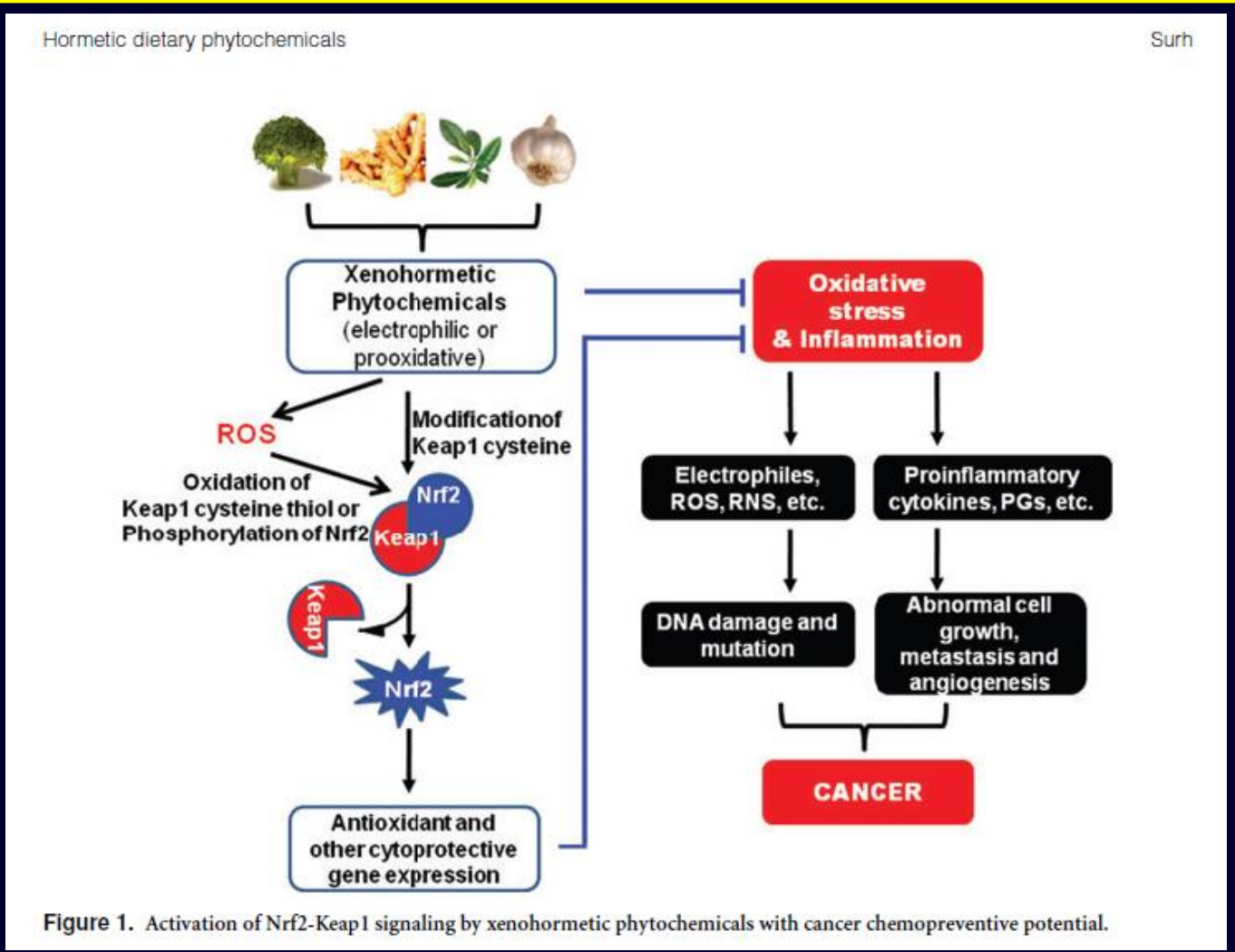
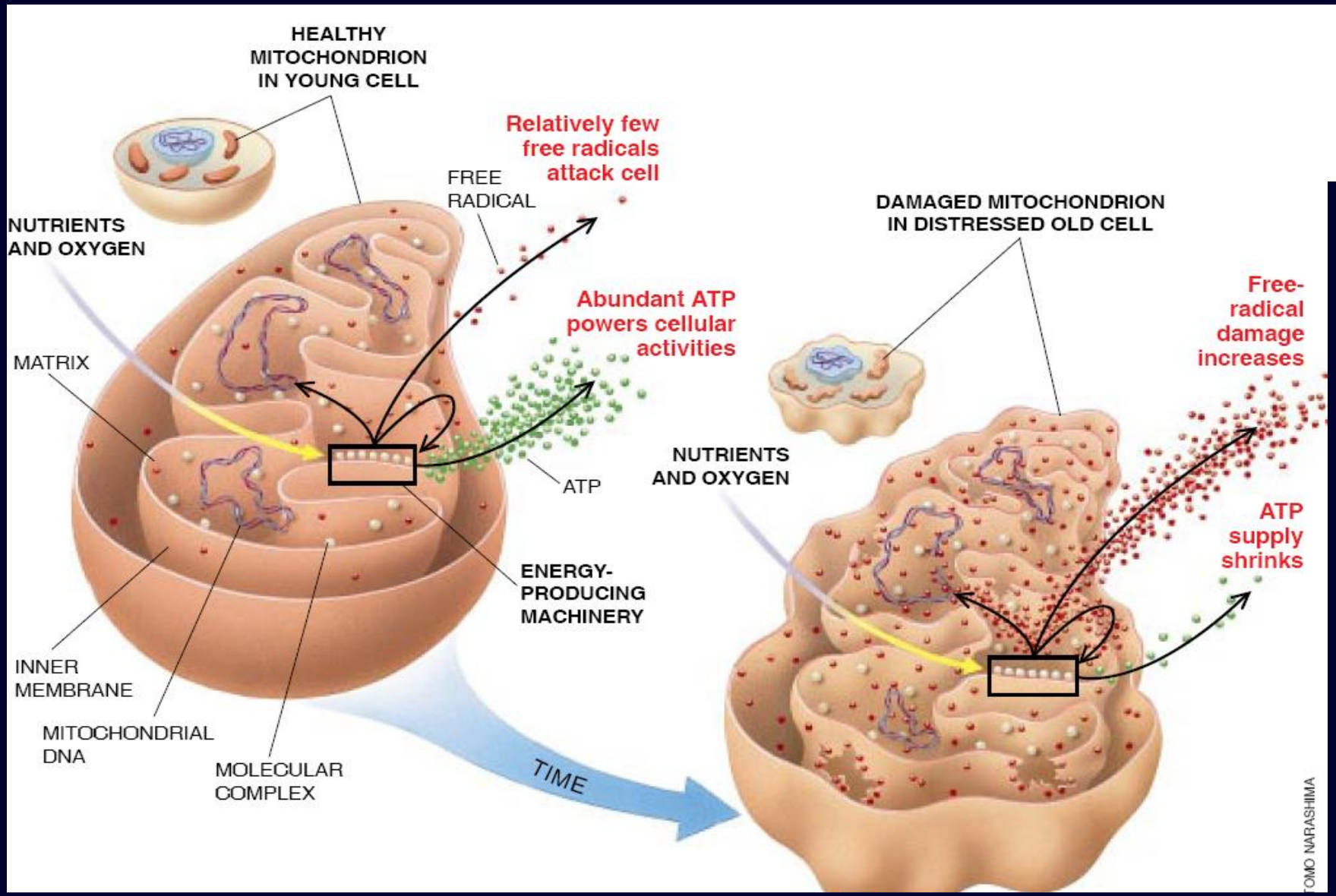


Figure 1. Activation of Nrf2-Keap1 signaling by xenohormetic phytochemicals with cancer chemopreventive potential.

Surh YJ. Ann NY Acad Sci. 2011;1229:1-6.


HEALTHY MITOCHONDRION IN YOUNG CELL
Relatively few free radicals attack cell
FREE RADICAL
NUTRIENTS AND OXYGEN
Abundant ATP powers cellular activities
MATRIX
ATP
ENERGY-PRODUCING MACHINERY
INNER MEMBRANE
MITOCHONDRIAL DNA
MOLECULAR COMPLEX
TIME
DAMAGED MITOCHONDRION IN DISTRESSED OLD CELL
Free-radical damage increases
NUTRIENTS AND OXYGEN
ATP supply shrinks
TOMO NARASHIMA

Ketogenic diet

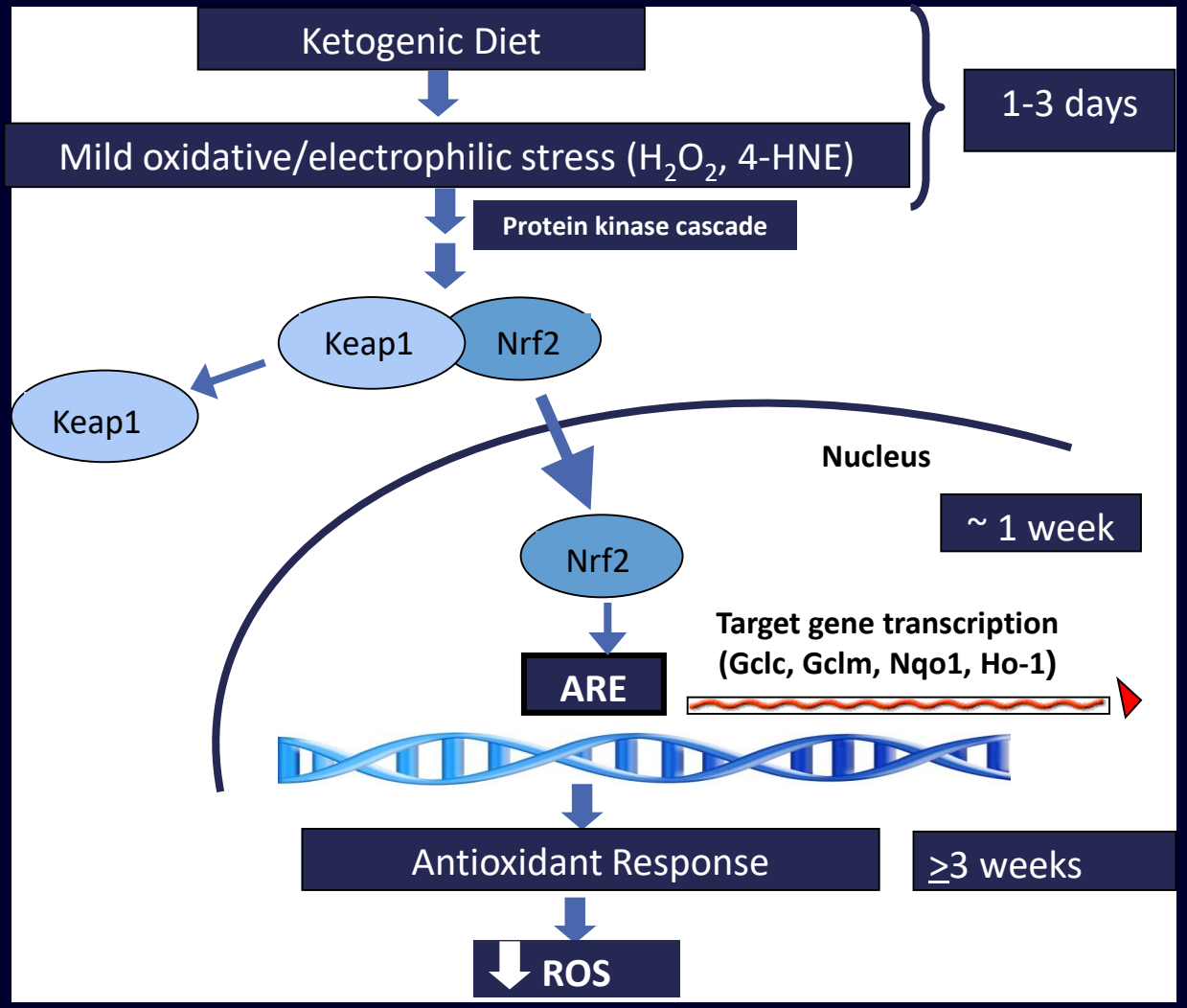
- Reduces inflammation (NF*k*B)
- Enhances mitochondrial biogenesis
- Enhances ATP production
- Reduces ROS production
- Reduces apoptosis
- Increases insulin sensitivity
- Increases leptin sensitivity

IFM™

The ketogenic diet (KD)

- Mimics fasting state – switches metabolism of glucose to metabolism of ketones
- Clinically-used treatment for intractable seizures in children and adolescents
- High fat – low carbohydrate (4:1, fat:non-fat)
- Efficacy appears to be independent of seizure type
- Mechanism of action unknown but attributed to ketone bodies, glycolysis, and mitochondrial metabolism
- Research direction: clinic to bench

Activation of the Nrf-2 adaptive response in the ketogenic diet

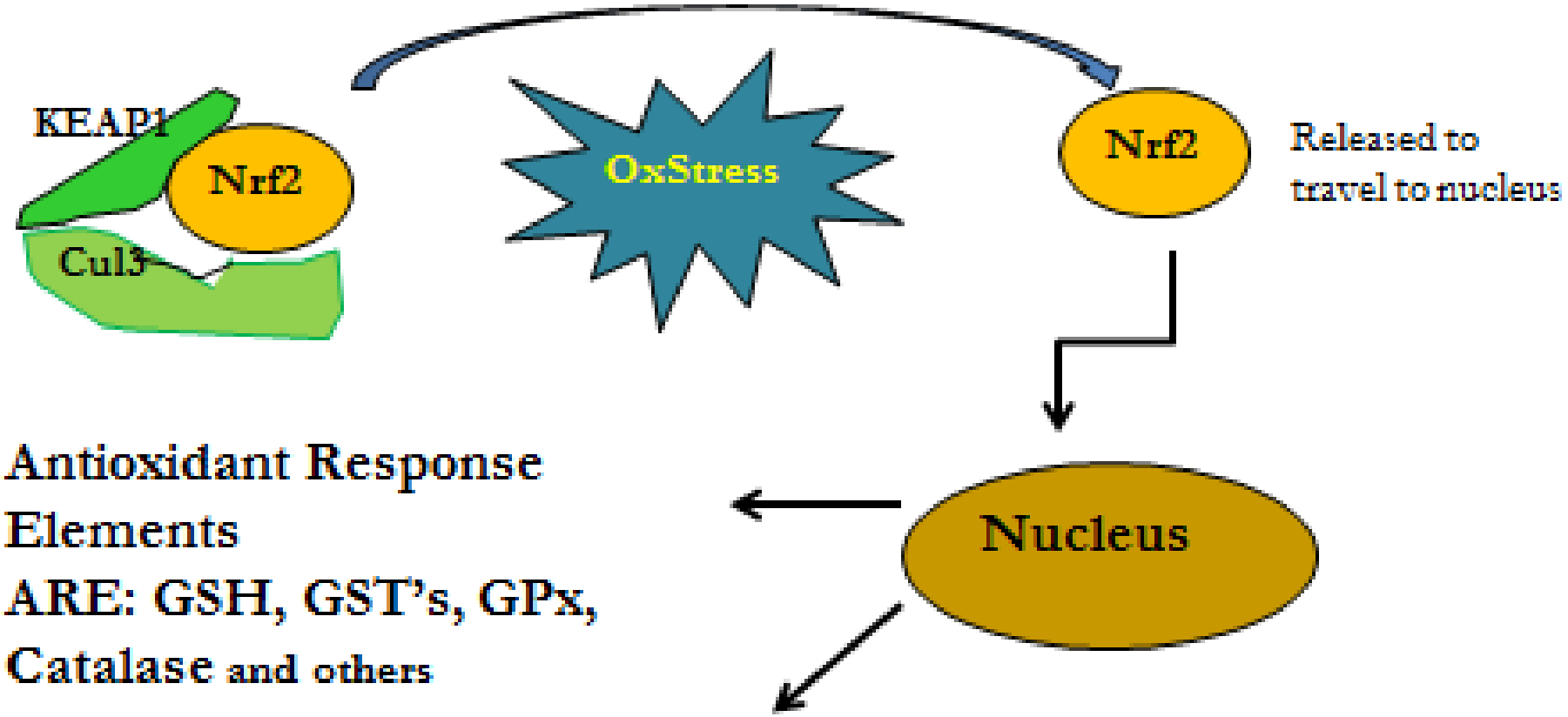


Milder and Patel, Epilepsy Res. 2011

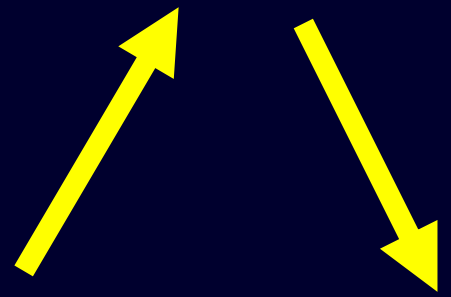
The perfect storm (insulin resistance)

- Glucose unable to enter cell
- β oxidation is inhibited leading to lipid accumulation in skeletal muscle, liver, & heart
- Gluconeogenesis is inhibited
- Krebs cycle intermediates are depleted
- Only one option remains: break down muscle and replace it with fat
- All these conditions are intracellular energy deficits (obesity, CHF, cachexia, diabetes, fatty liver)

Nrf2, the Oxidant 'Thermostat' of the Cell: The 'Oxidant-stat'



Nrf2 activation



- Oxidative stress
- Caloric restriction
- Curcumin
- Green tea extract
- Pterostilbene
- Sulforaphane
- Garlic (allicin)
- DHA

- Catalase
- Glutathione
- SOD
- GST (Phase II detox)
- Inhibits NF-kB
- Inhibits microglial activation

- Oxidative stress
- Caloric restriction
- Curcumin
- Green tea extract
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- Sulforaphane
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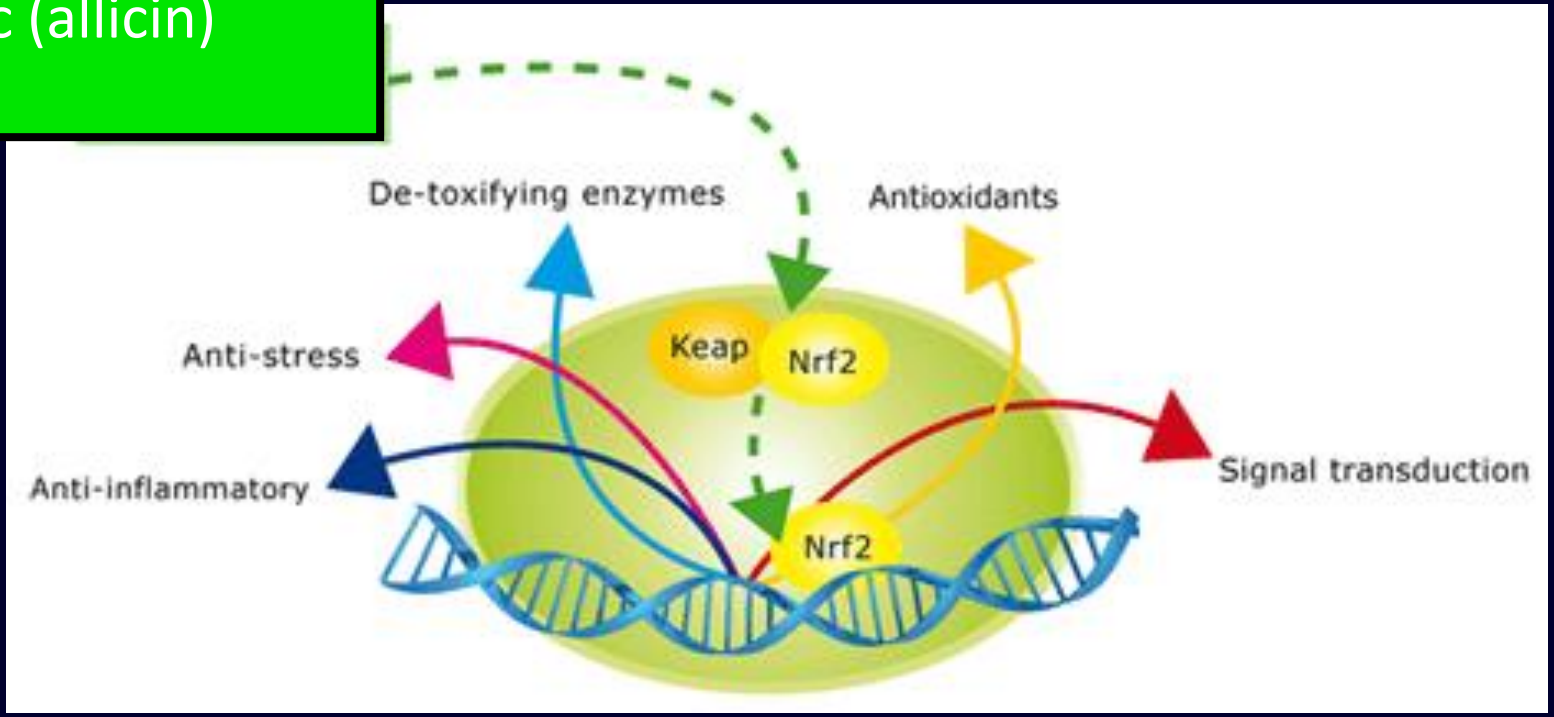
- DHA



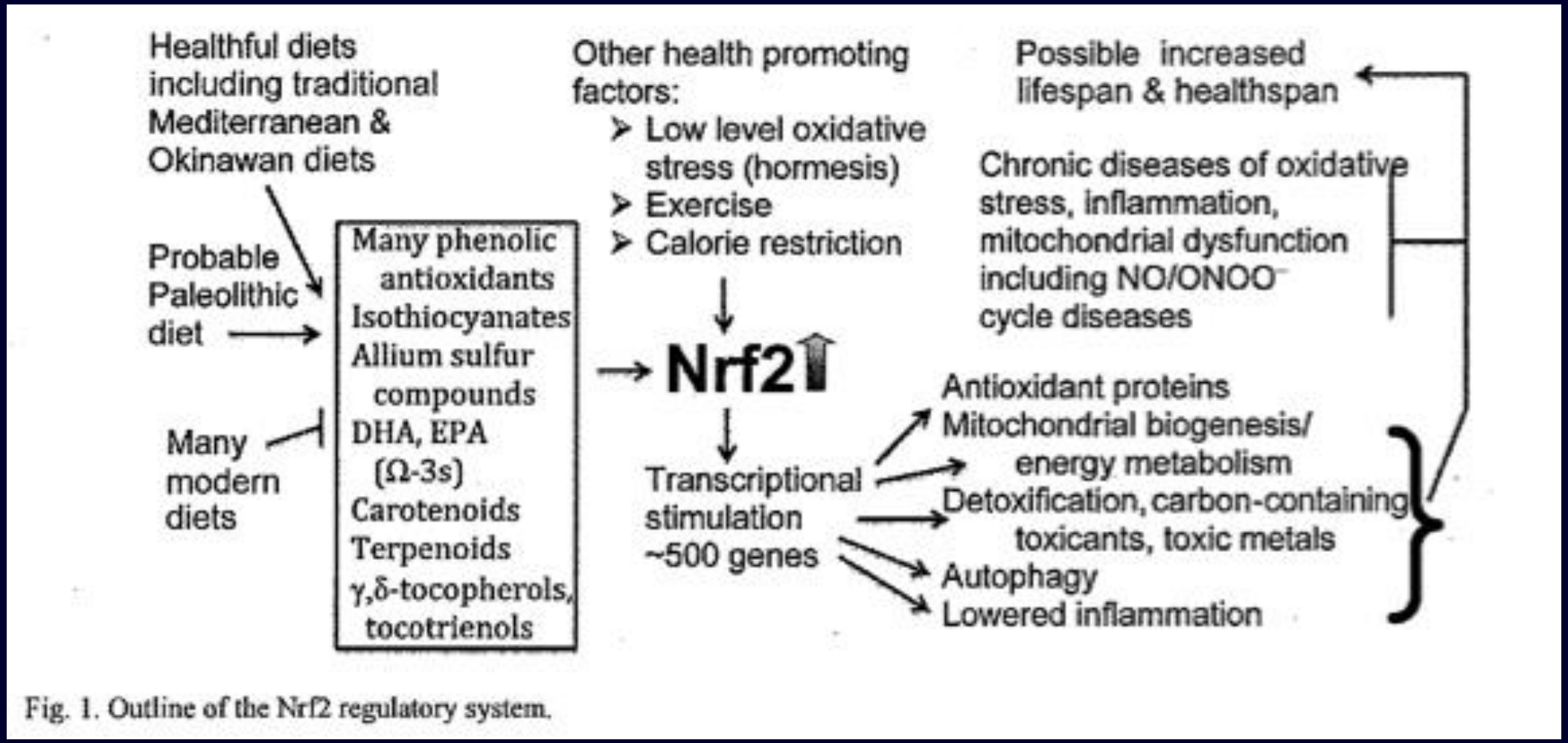
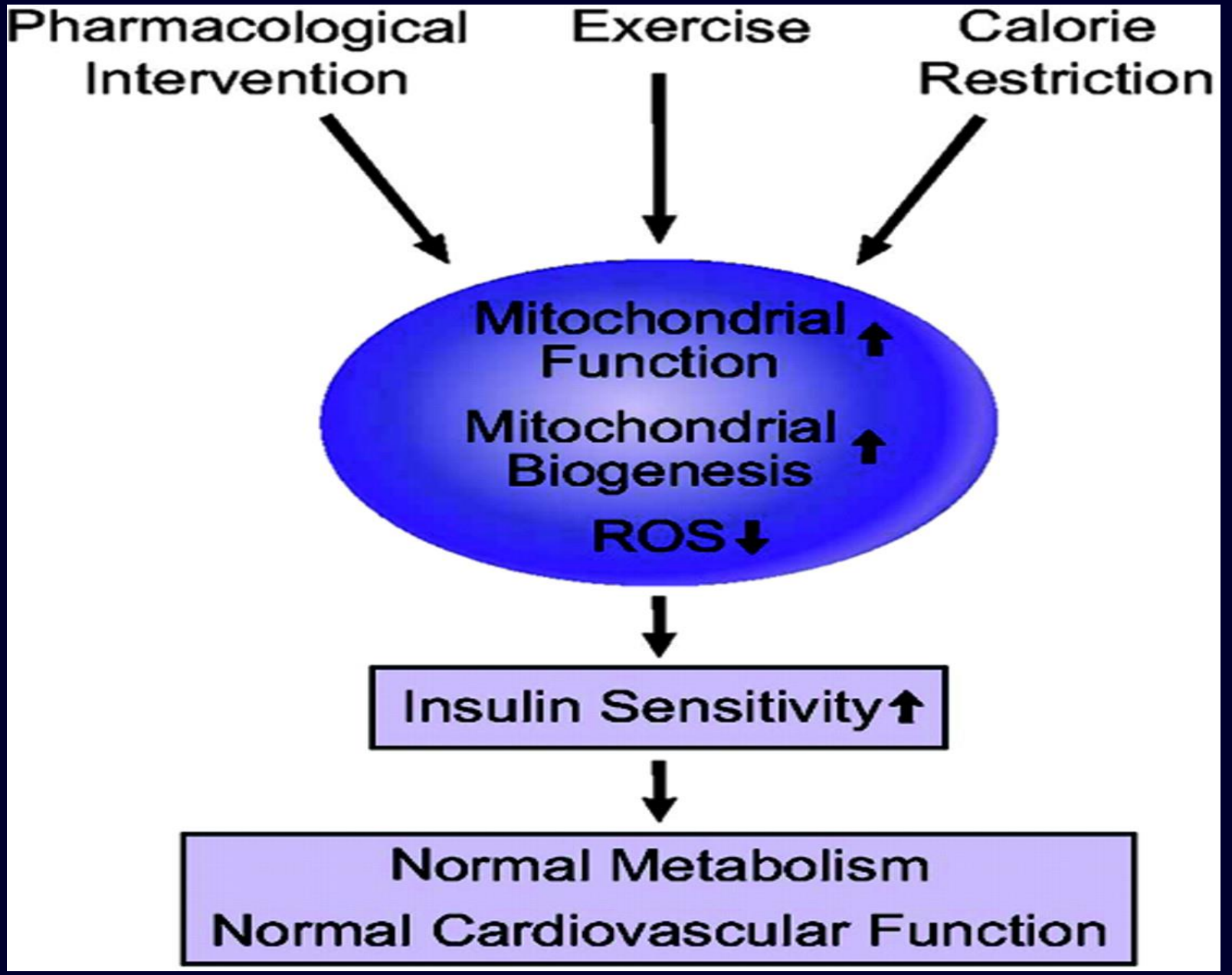


Fig. 1. Outline of the Nrf2 regulatory system.

Pall ML, Levine S. Nrf2, Master Cytoprotection & Detoxification Regulator, is Raised by Many Health Promoting Factors . . . Acta Physiologica Sinica. 2015 67(1):1-18.

Objectives

- Review mitochondrial structure, function and metabolism
- Discuss the pathophysiology of mitochondrial damage, including dietary factors, ROS, and toxins
- **Review ways to support mitochondria with diet, nutrients, phytochemicals, and lifestyle**



Kim J et al. Circulation Research 2008;102:401-414

Exercise increases mitochondrial numbers

Moderate intensity exercise 4 months:

- 67% increase in mitochondrial density
- 55% increase in cardiolipin content
- Increase in mitochondrial oxidation enzymes
- All linked to improvement in hemoglobin A1c and fasting plasma glucose

Toledo, GS, et al. Diabetes 2007; 56:2142–2147

Phytochemicals that support mitochondrial function

- Curcumin (turmeric)
- Sulforaphane (broccoli)
- Berberine
- Quercetin
- Resveratrol (red wine)
- Pterostilbene (purple berries)
- Green tea polyphenols

Nutrients that support mitochondrial function

- Acetyl-L-carnitine: 1500-3000 mg
- Alpha lipoic acid: 300-900 mg
- Coenzyme Q10 (ubiquinone): 50-200 mg
- Magnesium: 100-500 mg

Neurobiol Aging. 2013, pii: S0197-4580(13)00525-3
Mech Ageing Dev. 2010 Jul-Aug;131(7-8):473-9

Nutrients that support mitochondrial function

- N-acetylcysteine: 500-3000 mg
- Creatine: 5-15 grams
- Melatonin: 3-20 mg
- Ketogenic & branched chain amino acids
- Nicotinamide riboside: 250-1000 mg

Aging, 2011, Vol 3(5): 464-478
Neurobiol Aging. 2013, pii: S0197-4580(13)00525-3
Mech Ageing Dev. 2010 Jul-Aug;131(7-8):473-9

Benefits of enhanced mitochondrial function

- ↓ ROS / Oxidative Stress
- ↑ Metabolic Function
- ↑ Energy Level
- ↑ Exercise Performance
- ↓ Body Fat / ↑Lean Muscle Mass
- ↓ Age-Related Deterioration
- ↑ Increased Lifespan (?)
- Cancer suppression

Treatment: a TO DO list to support mitochondrial function

- ❑ Get adequate nutrition
- ❑ Stay cool and hydrate
- ❑ Prevent infections
- ❑ Exercise (physical & mental)
- ❑ Avoid toxins
- ❑ Intermittent fasting
- ❑ Avoid simple and processed carbs

Treatment: a TO DO list to support mitochondrial function

Supplements:

- ❑ CoQ-10
- ❑ Omega-3 Fatty Acids
- ❑ B-Vitamins (particularly B2 & B3)
- ❑ Alpha-Lipoic Acid
- ❑ Nrf2 Activators
- ❑ Rhodiola

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