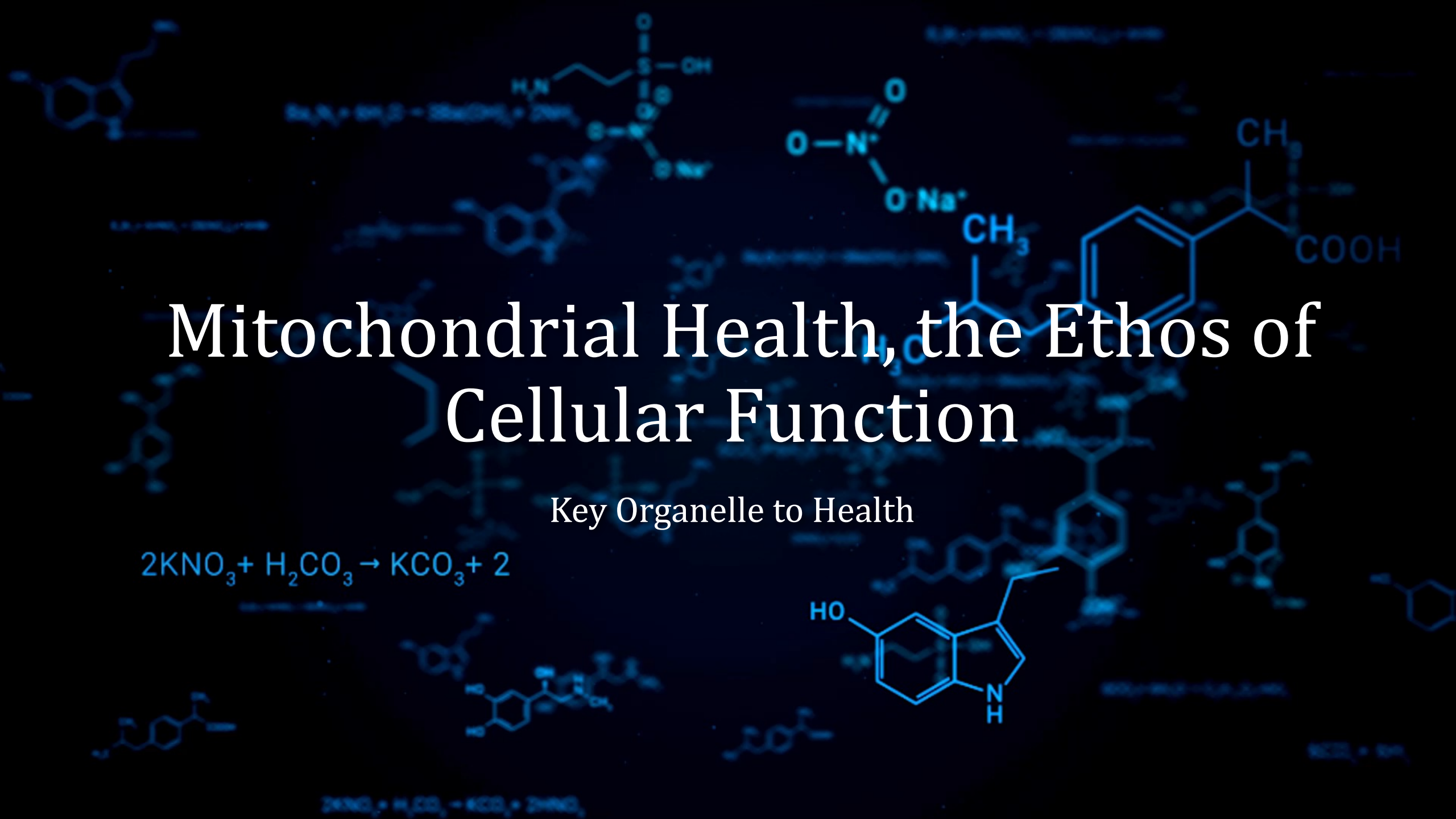
Mitochondrial Health, the Ethos of Cellular Function

Key Organelle to Health



The Mitochondria Symptomology

AGENDA

with Dr. Gaetano Morello

1. Mitochondrial structure and function within the organism
2. Molecular mechanisms underlying mitochondrial dysfunction.
3. The intricate interplay between mitochondrial metabolism and the gut microbiome
4. The nexus between mitochondrial dysfunction and fatigue
5. The critical role of mitochondrial redox in energy production
6. Strategies for upregulating mitochondrial function
7. Diagnostic approaches for identifying mitochondrial dysfunction

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University of British Columbia, BSc in Cell Biology,
Bastyr University 1991

- Complex Chronic Disease Program at BC Women's Hospital and Health Center in Vancouver
- ME/CFS, FM, Chronic Lyme, Long COVID
- Referral
- We do direct clinical care and involved in the facilitation of research
- We also have an ongoing educational resource for patients
- We've been seeing Post COVID-19 or Long COVID patients and the parallels with ME/CFS.
- My focus has been treating mitochondrial dysfunction
- gm@neoluminabio.com

Complex Chronic Disease (ME/CFS, FM, Chronic Lyme, Long Covid)

Symptoms reported in CCD patients:

- Fatigue
- Post Exertion Malaise (PEM)
- Cognitive Dysfunction (brain fog/memory)
- GI issues: bloating/gas, abdominal pain, constipation, diarrhea
- Sleep difficulties (a hallmark of most FM cases)
- Feels like the flu at times
- Pain; hurts all over, can change from one area to the other

Diagnosis dependent on:

- Exclusion of disease
- Symptoms rather than signs
- Thus far difficult to get reproducible laboratory findings
- Gold standard is “expert opinion

How do these diseases develop?
Important to spend time on Hx

Background

- Any age, but peak age 40-60
- 60-90% female in clinic, although less gender difference in population-based studies

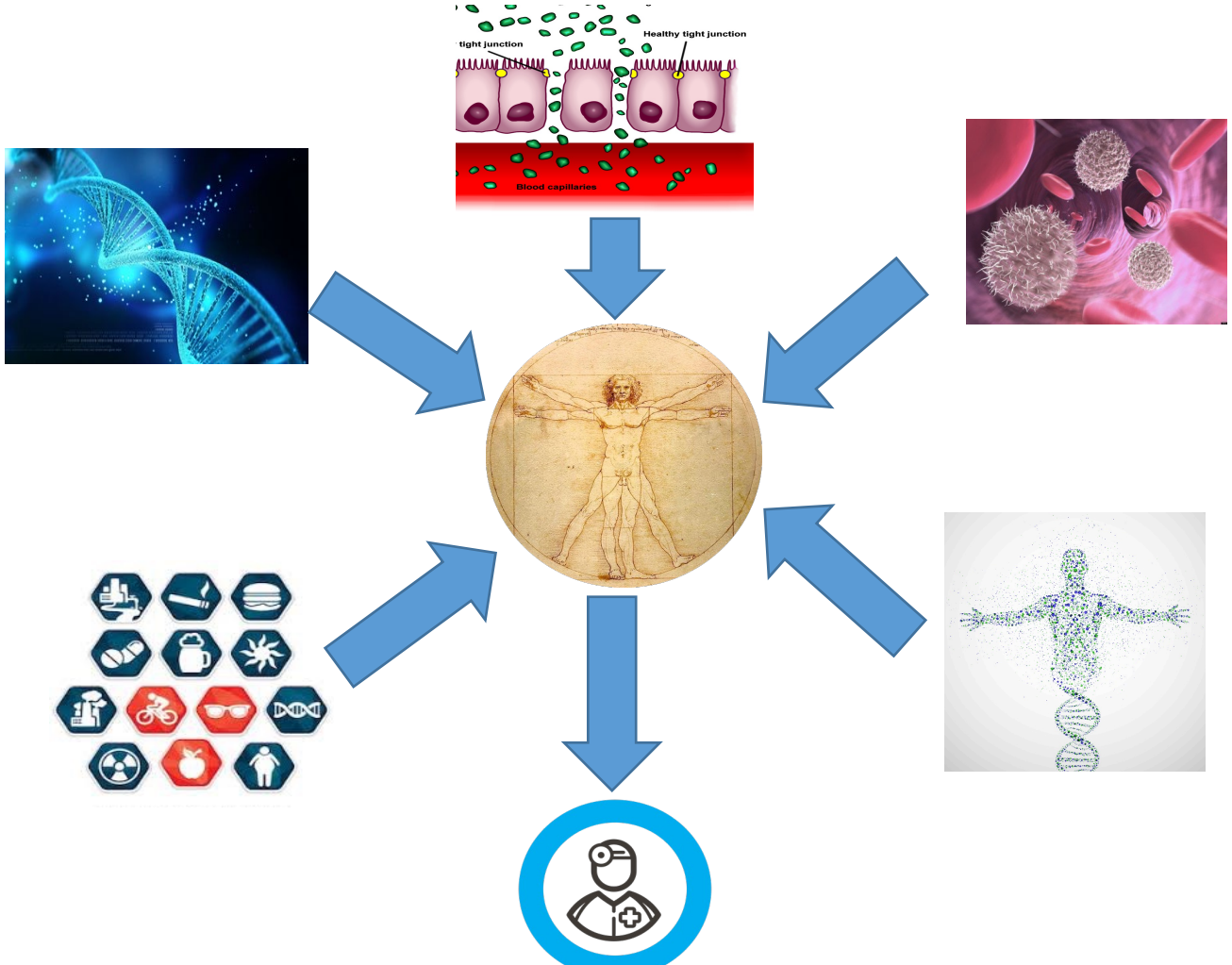
A “trigger” is often seen in the history:

- Mononucleosis or other viral infection (influenza),GI infection, Stress, MVA, frequent antibiotic use, etc.
- These conditions took a long time to resolve, developed symptoms; fatigue, cognitive dysfunction, pain, difficulty sleeping

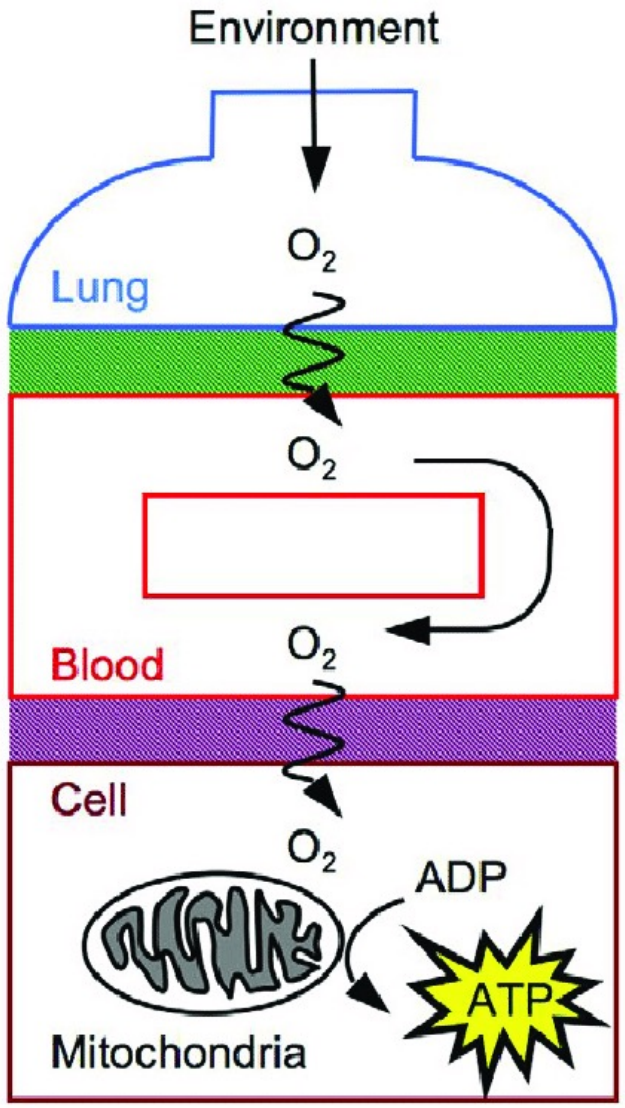
Many patients have been on numerous courses of antibiotics since early childhood

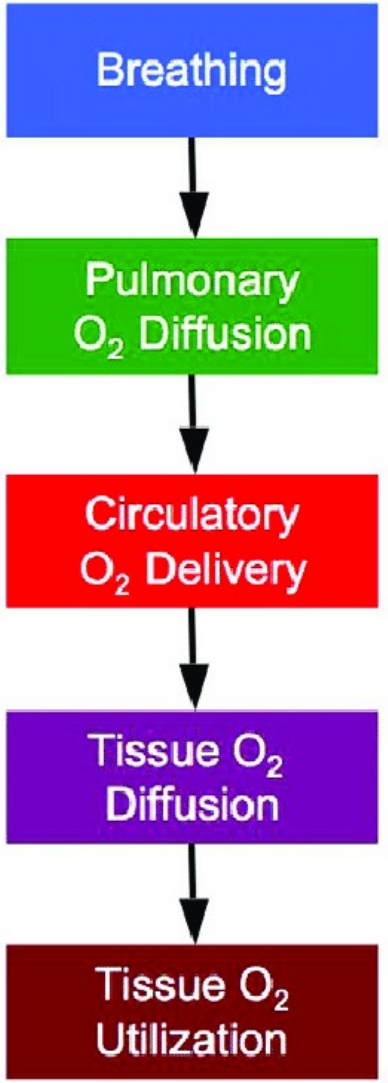
History of sympathetic up regulation

Systems creating our symptom experience



Life's Most Important Element



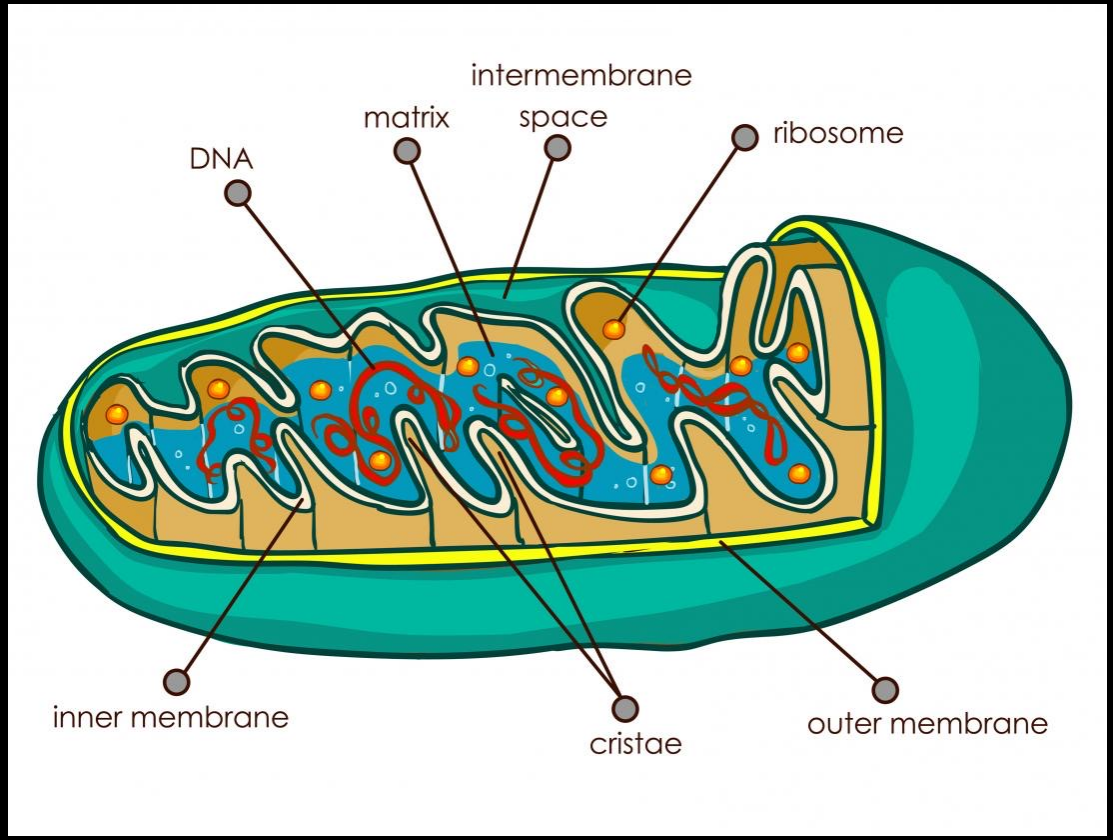


Mitochondria and their Structure

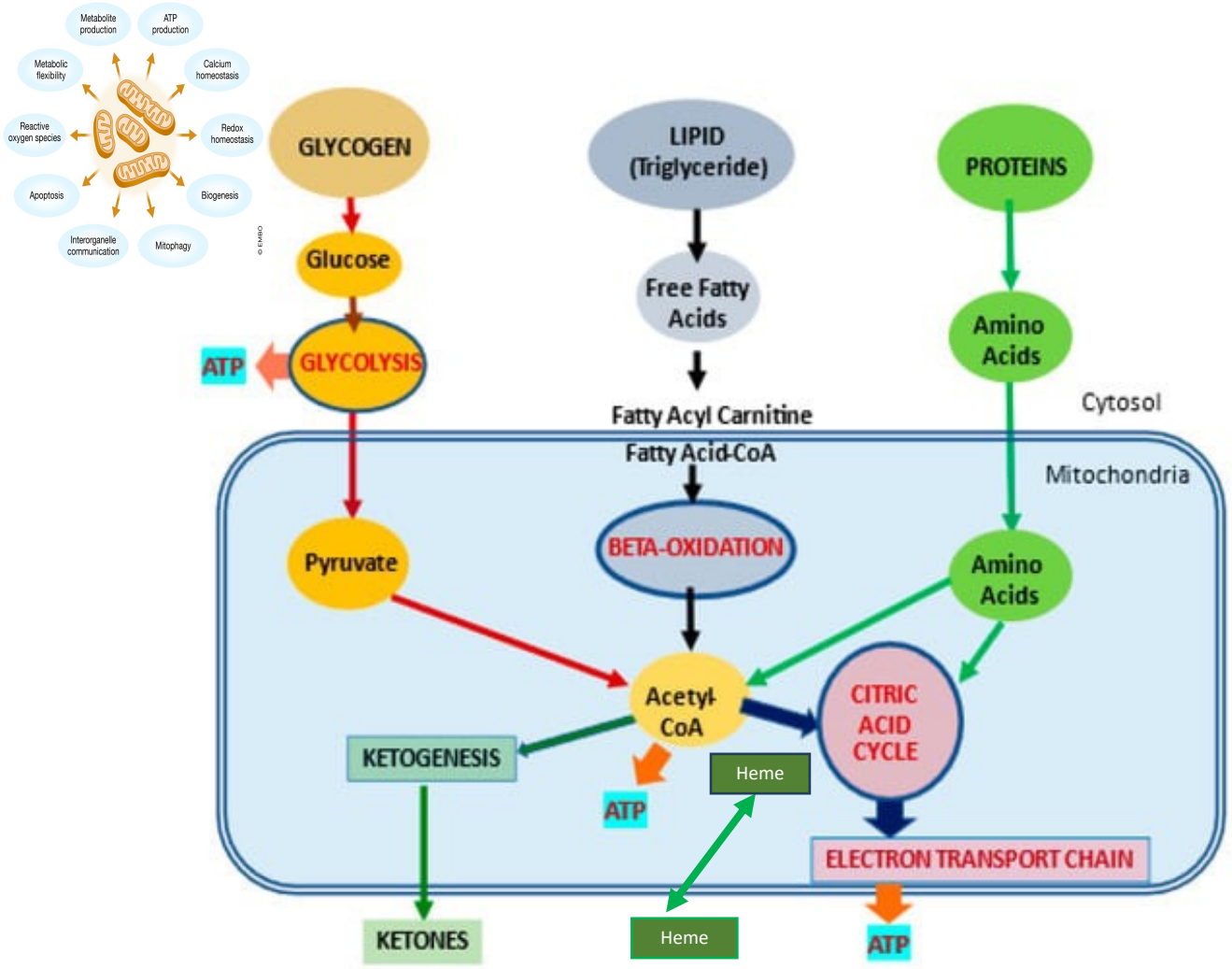
Unique Organelle:

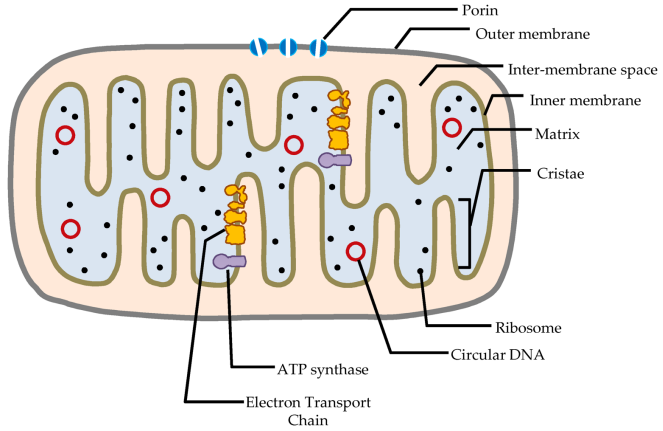
- Contains its own DNA
- Maternal Inheritance
- Makes 15% of its own proteins
- 1000-2000 mitochondria per cell
- 25% of cell volume
- Muscle cells uses about 10 million molecules of ATP every second
- Produce energy (ATP):
  5% anaerobic
  95% aerobic
  5% Krebs/citric acid cycle

- How many kg's of ATP does the body produce per day?



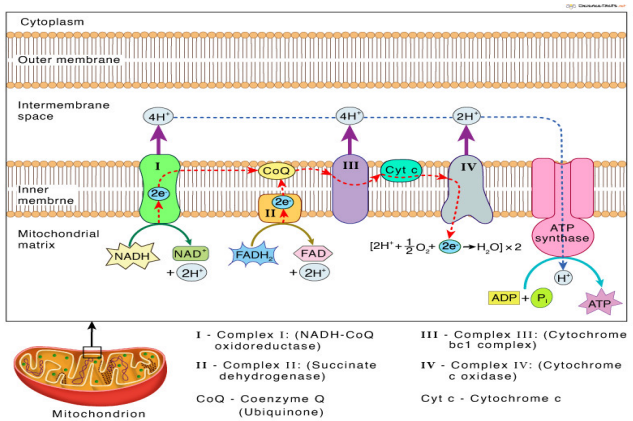
Mitochondrial Functions

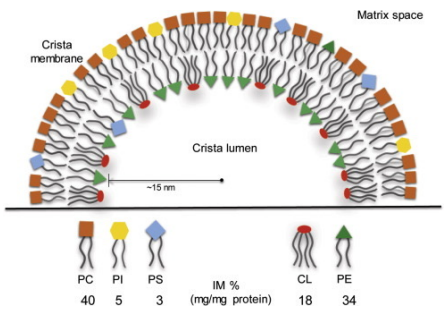


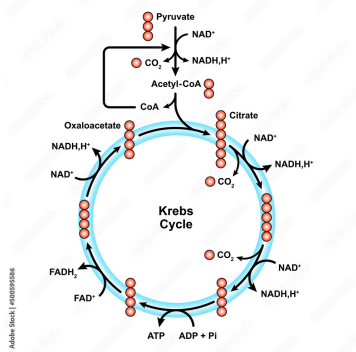


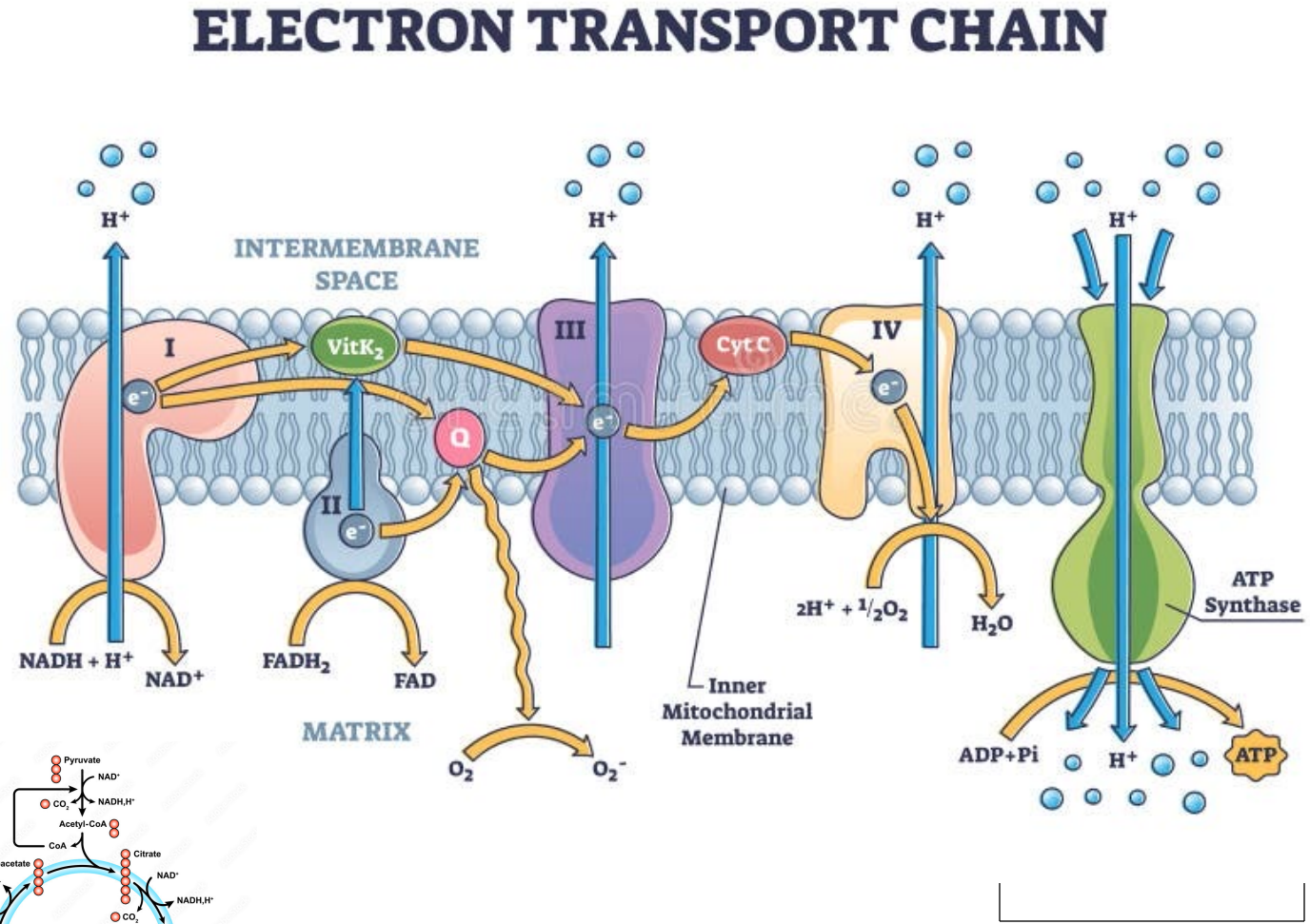
Many Functions;

1. Pyruvate going to Acetyl CoA (oxidative decarboxylation
2. Kreb Cycle
3. Beta Oxidation
4. Urea Cycle-aa giving up NH3, neutralized to urea
5. Gluconeogenesis-making glucose from aa's
6. Heme synthesis from Kreb cycle metabolites
7. Ketogenesis from Acetyl-CoA
8. Apoptosis-programmed cell death by release of cytc from Mito into cytoplasm releasing cataspaces
9. mtDNA replication and transcription, can get fission and the making of proteins



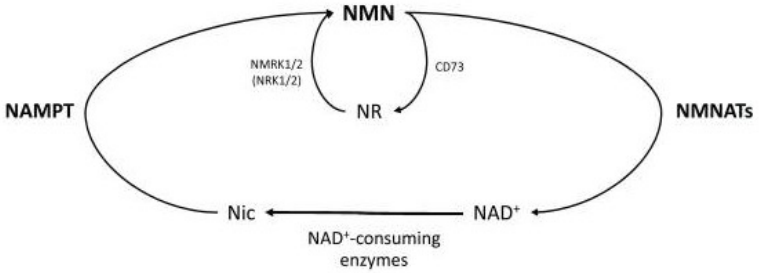






Chemiosmosis

nicotinamide mononucleotide



- Nicotinamide mononucleotide (NMN) is the direct precursor to NAD
- Supplementation with NMN is an effective way to replenish the body's declining NAD+ levels.
- In a placebo-controlled clinical study, healthy 20–60-year-old volunteers who supplemented with 250 mg of NMN per day were found to increase their NAD+ whole blood levels by 60% after four weeks without any adverse effects

Okabe, K., Yaku, K., Uchida, Y., et al. (2022). Oral administration of nicotinamide mononucleotide is safe and efficiently increases blood nicotinamide adenine dinucleotide levels in healthy subjects. Front Nutr, 9, 868640.

Health Conditions Linked to Impaired Mitochondrial Function

1. Autoimmune disorders
2. Chronic fatigue syndrome/ME
3. Generalized Fatigue
4. Fibromyalgia
5. Aging and degenerative disorders:
    - Neurodegenerative disease
    - Cancer
6. Adrenal dysfunction
7. Brain disorders
    - Anxiety
    - Attention deficit disorder
    - Autism
    - Depression

Mitochondrial Dysfunction & Chronic Disease

At the molecular level, a reduction in mitochondrial function occurs as a result of the following changes:

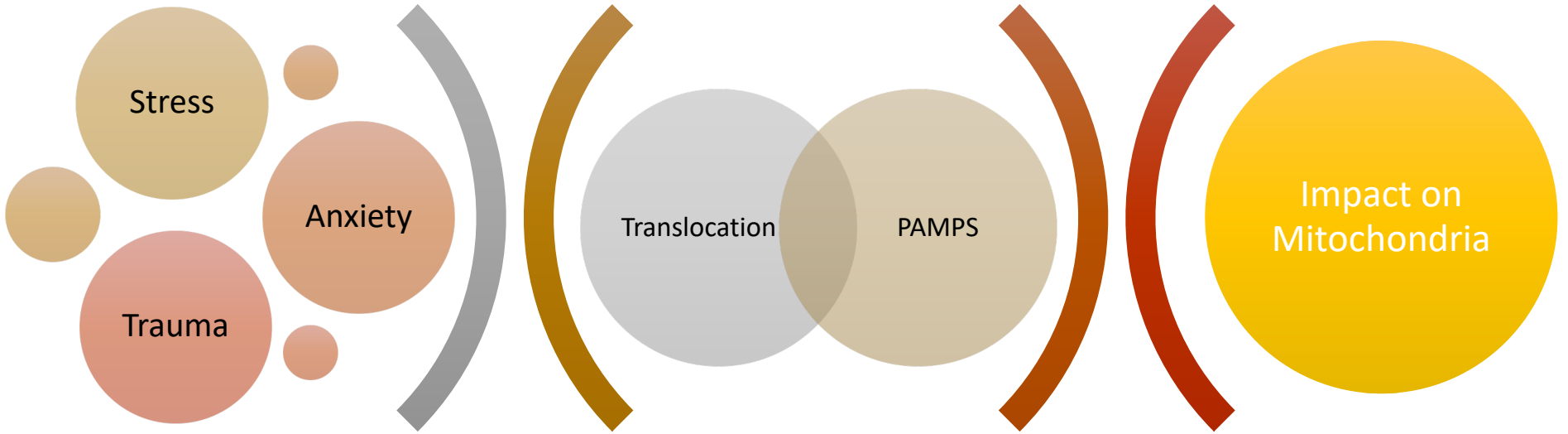
1. a loss of maintenance of the electrical and chemical transmembrane potential of the inner mitochondrial membrane,
2. alterations in the function of the electron transport chain
3. or a reduction in the transport of critical metabolites into mitochondria.

In turn, these changes result in a reduced efficiency of oxidative phosphorylation and a reduction in production of adenosine-5′-triphosphate (ATP).

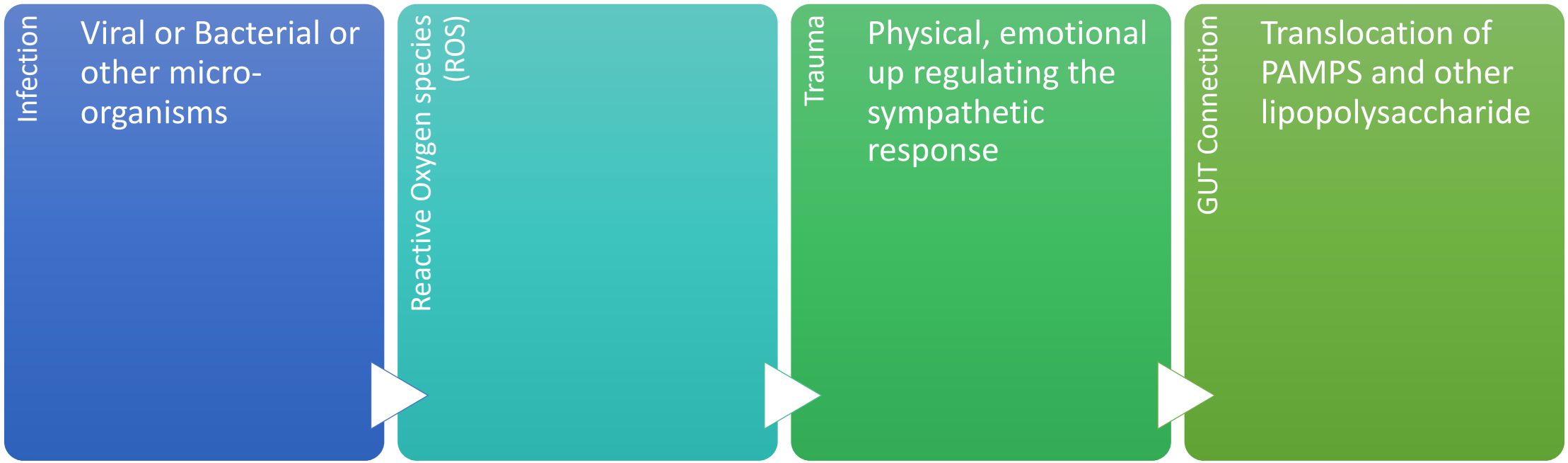
Nicolson GL. Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements. Integr Med (Encinitas). 2014; 13:35–43.

Factors in mitochondrial impairment

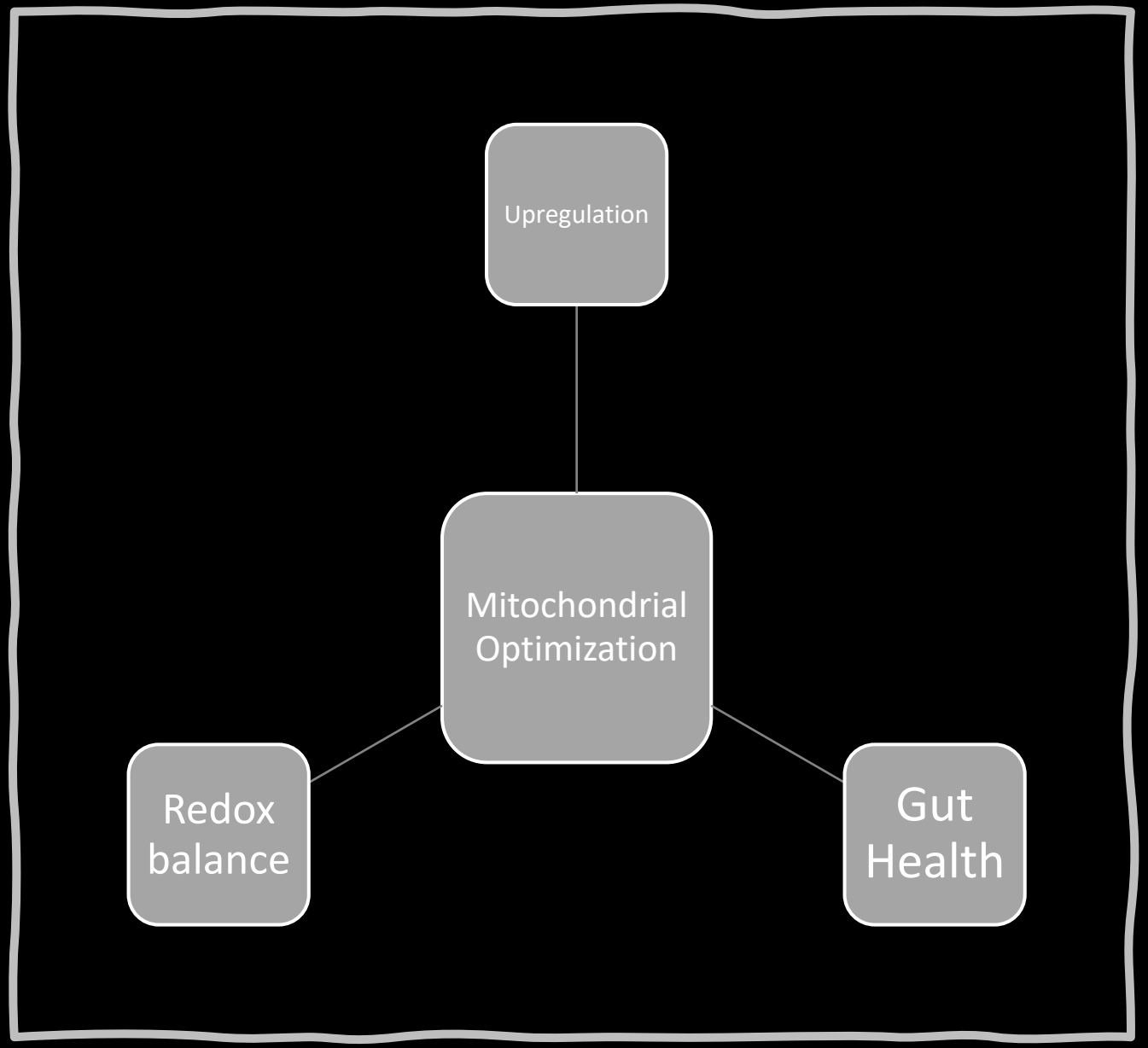
Trauma, Sympathetic Response



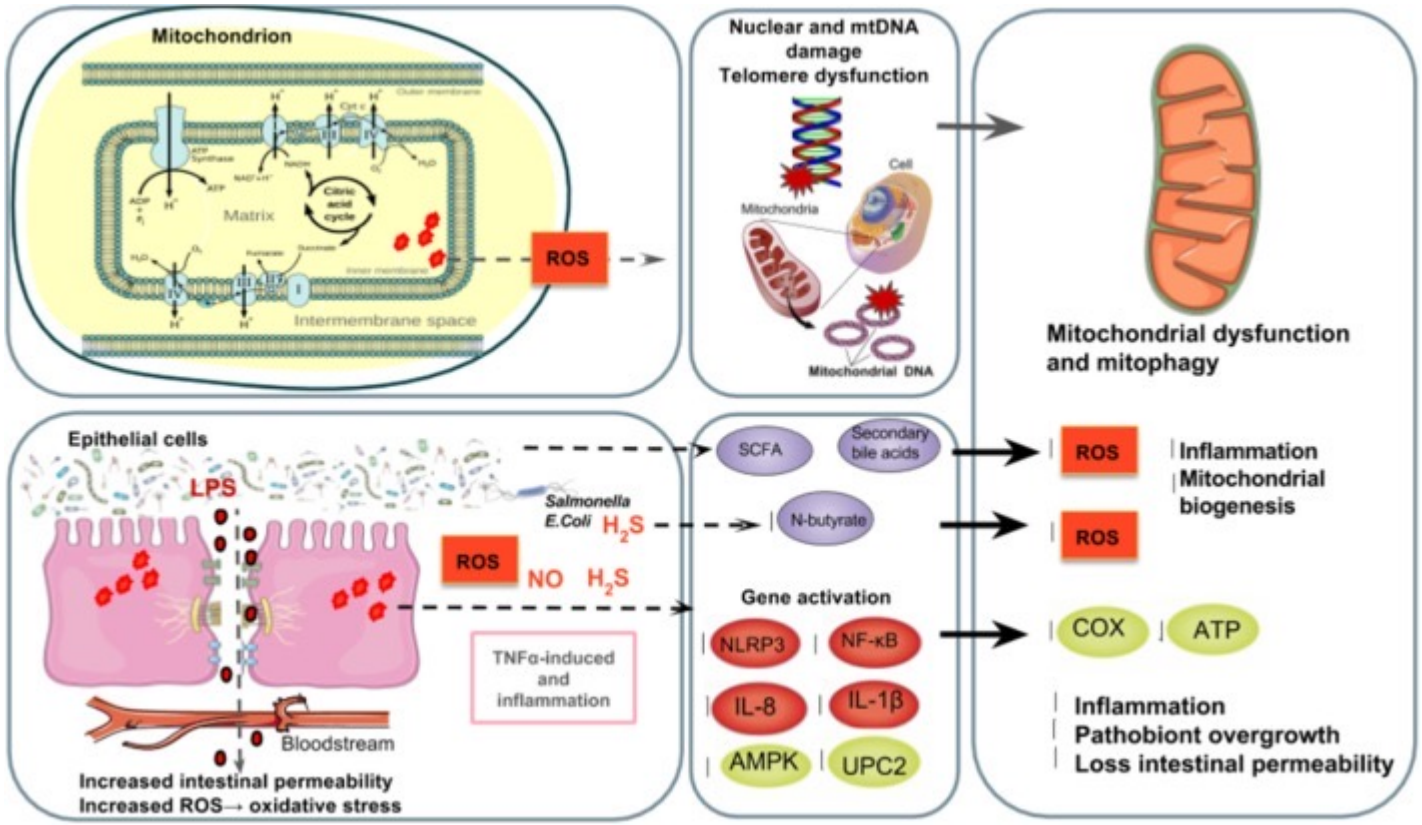
How does the Mitochondria become Impaired



Improving Mitochondrial Function



Gut and Mitochondria

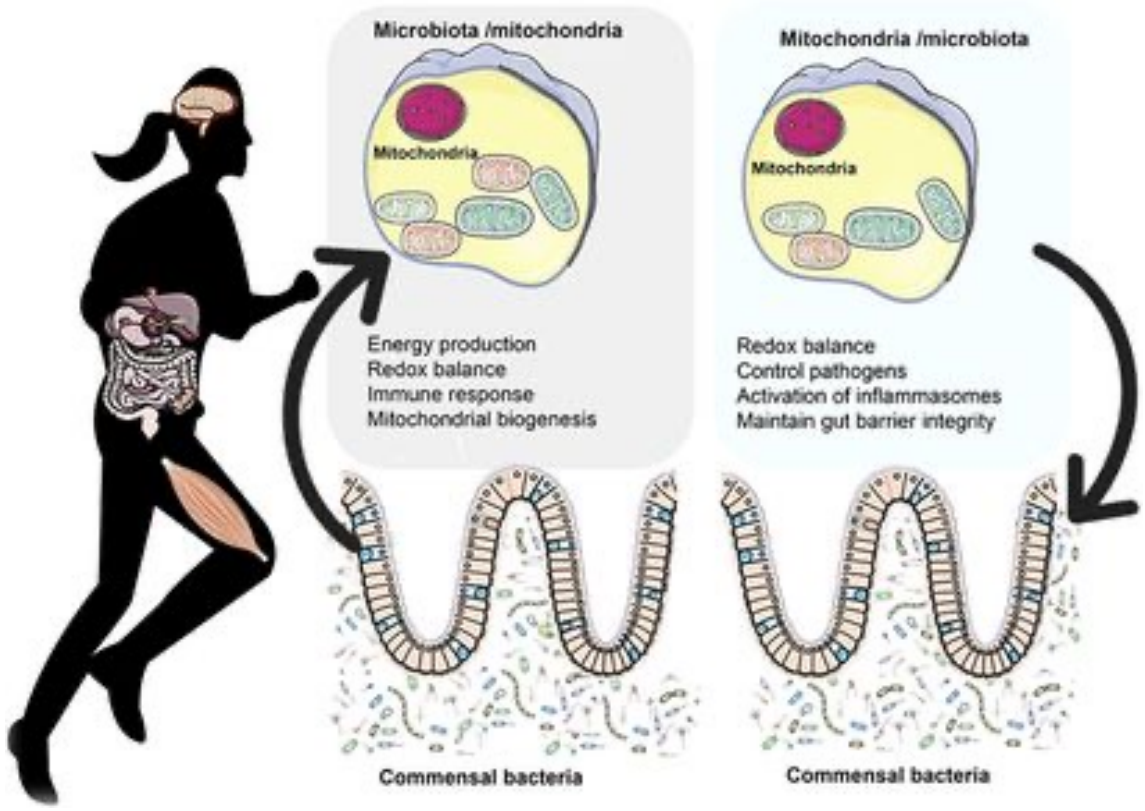


The gut microbiota's regulation of mitochondrial ROS production.

1. Athletes have two major sources of ROS and RONS: the mitochondrial electron transport chain and the intestinal epithelial cells and transmigrating neutrophils in the gut lumen in which free radicals such as NO and superoxide are produced. Poorly trained individuals and athletes who overtrain are at a higher risk of suffering from oxidative stress which increases mutations in DNA, shortens telomere length and alters mitochondrial biogenesis .

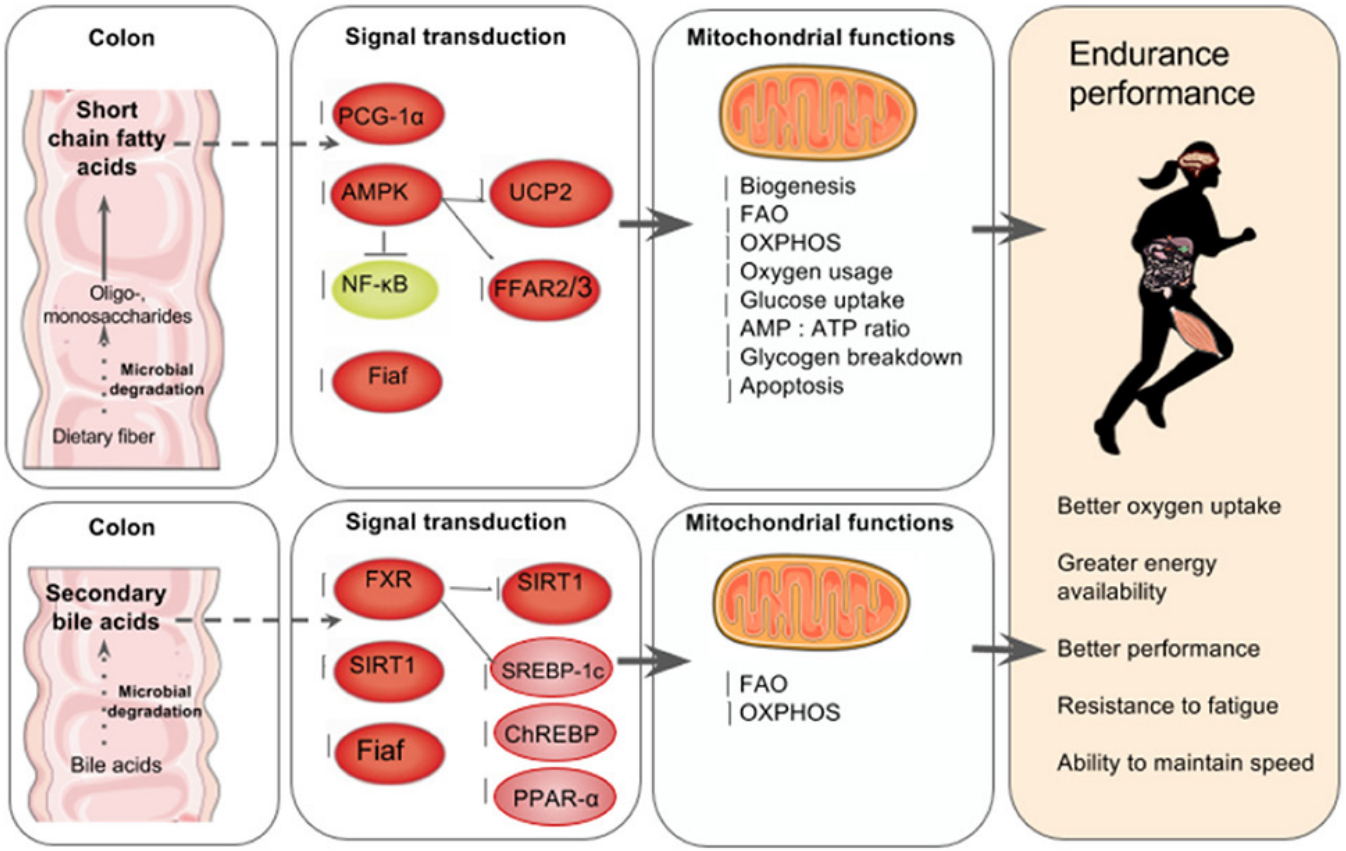
2:.The excessive release of stress hormones overtrained athletes experience as well as increased body oxygen uptake can generate ROS and RONS in the tissues that undergo ischemia and hypoperfusion. Ischemia-induced intestinal hyperpermeability can induce LPS translocation and an inflammatory cascade of TNFα , the ROS-triggering OXPHOS inhibitor and inflammasome NLRP3 which results in a mitochondria-mediated inflammatory responses and mitophagy, as well as NF-κB, IL-1β, IL- 6, and IL-8 expression . TNFα and IL-6 inhibit AMPK activation, which reduces glucose metabolism and FAO in mitochondria. Reduced expression of uncoupling protein 2 (UPC2) can lead to partial uncoupling of mitochondrial OXPHOS and elevated ROS production. Furthermore, pathobionts (i.e., *Fusobacterium, Veillonella*, and *Atopobium parvulum*) can produce hydrogen sulfide (H_2S) and nitrogen oxide (NO) which favors infectious proliferation and inflammation, inhibition of COX activity and butyrate β-oxidation in the colon which negatively affects mitochondrial function and energy production . On the other hand, SCFA such as N-butyrate and secondary bile acids, might influence mitochondrial functions related to energy production, mitochondrial biogenesis, redox balance and inflammatory cascades, making it a potential therapeutic target for endurance.

Crosstalk between Microbiota and Mitochondria



The bidirectional crosstalk between the gut microbiota and mitochondria. Gut microbiota to mitochondria crosstalk: Recent evidence shows there is a bidirectional crosstalk between the gut microbiota and mitochondria. Microbiota and their byproducts (SCFA and secondary bile acids) regulate redox balance and energy production. Secondary bile acid metabolism might also directly modify mitochondrial biogenesis, inflammation and intestinal barrier function in different types of cells (. In the mitchondria of colonocytes, butyrate undergoes FAO which produces acetyl-CoA that enters the TCA cycle resulting in ATP and CO_2). Among the SCFA, butyrate is a key regulator of energy production and mitochondrial function by inducing PGC-1α gene expression in skeletal muscles and brown adipose tissue (Gao et al., 2009) and improving respiratory capacity and FAO via AMPK-ACC pathway activation (Mollica et al., 2017). **Mitochondria to microbiota crosstalk:** Mitochondria regulate gut functions (Igarashi and Guarente, 2016; Wang et al., 2016), such as intestinal barrier protection (Peng et al., 2009) and mucosal immune response, which help maintain the mucus layer (Ma Y. et al., 2014) and intestinal microbiota (Shimada et al., 2012; Caron et al., 2014). *SIRT1* maintains intestinal barrier function through various mechanisms such as enhancing crypt proliferation and suppressing villous apoptosis (Wang et al., 2012), stimulating intestinal stem cell expansion in the gut (Igarashi and Guarente, 2016), regulating tight junction expression of zonulin ocludin-1, occludin and claudin-1 during hypoxia (Ma Y. et al., 2014). Mitochondrial genome variants may affect the gut microbiota composition. For example, polymorphisms in the *ND5*, and *CYTB* genes or D- Loop region of mitochondrial genome have been associated with specific gut microbiota compositions like *Eubacterium* and *Roseburia*, which are butyrate producers (Ma Y. et al., 2014). Additionally, the European haplotype HV has been associated with decreased odds of severe sepsis, higher OXPHOS capacity and ROS and RONS production (Jiménez-Sousa et al., 2015) as well as elevated VO_{2max} and aerobic ATP production in response to exercise

Microbiota Regulating energy production



The gut microbiota's regulation of mitochondrial energy production. Top left to right: In the colon, the gut microbiota ferment indigestible dietary fiber such as resistant starch and oligosaccharides to produce SCFA in the intestines that can account for up to 10% of human caloric requirements (den Besten et al., 2013). SCFA are key mediators of mitochondria energy metabolism and act as ligands for free fatty acid receptors 2 and 3 (*FFAR2, FFAR3*) that regulate glucose and fatty acid metabolism (den Besten et al., 2013; Kimura et al., 2014). SCFA regulate SIRT1 which plays a role in mitochondrial biogenesis via *PGC-1*α deacetylation, (Lakhan and Kirchgessner, 2010; Radak et al., 2013). In skeletal muscle cells, butyrate phosphorylates AMPK and p38 which then activates *PGC-1*α and thus FAO and ATP production. Butyrate also activates AMPK via UCP2-AMPK-ACC pathway (den Besten et al., 2015). Commensal bacteria such as *Lactobacillus rhamnosus* CNCMI–4317 has been associated with increased *Fiaf* expression (Jacouton et al., 2015). In lamina propia macrophages, SCFA also inhibit NF-κB activation that reducing inflammation associated with ulcerative colitis (Lührs et al., 2002). The result is increased mitochondrial biogenesis, FAO, OXPHOS, oxygen usage, glucose uptake, AMP, ATP ratio and glycogen breakdown and reduced apoptosis (Lantier et al., 2014; Canfora et al., 2015; den Besten et al., 2015). **Bottom left to right:** Anaerobic bacteria degrade 5–10% of bile acids (Gérard, 2013), and secondary bile acids regulate carbohydrate and lipid metabolism by modulating the transcription factor receptors farnesoid X receptor (*FXR*) and G-coupled membrane protein 5 (*TGR5*) resulting is increased FAO and OXPHOS (Nie et al., 2015). FXR mediates carbohydrate metabolism via regulating *SIRT1* and *Fiaf* expression as well as *SREBP-1c* and *ChREBP* activation (Kuipers et al., 2014; Joyce and Gahn, 2016) and fatty acid metabolism via PPAR-α activation (Joyce and Gahn, 2016). There is increasing evidence that secondary bile acid metabolism might also directly modify mitochondrial biogenesis, inflammation and intestinal barrier function in different types of cells (Gao et al., 2009; Korecka et al., 2013; Alex et al., 2014; Caron et al., 2014; Kazgan et al., 2014). The result of SCFA and secondary bile acid's role in mitochondrial biogenesis is better overall athletic performance due to better oxygen uptake, energy availability and fatigue resistance.

Fiaf(fat induced adipose factor),

Gut Improvement protocols

- Increases parasympathetic note reducing gut permeability.
- 200 mg evening

PharmaGABA

- Shown to reduce gut permeability in a doubleblind comparative study
- 1200 mg per day

PEA

- Shown to reduce pathogenic bacteria and increase beneficial bacteria

BB536

A RANDOMISED DOUBLE BLIND CONTROLLED TRIAL EXAMINING THE EFFECT OF PEA AND CBD ON THE PERMEABILITY OF THE HUMAN GUT IN VIVO

DG Couch, C Ortori, D Barrett, JN Lund and SE O'Sullivan
School of Medicine, Faculty of Science, University of Nottingham

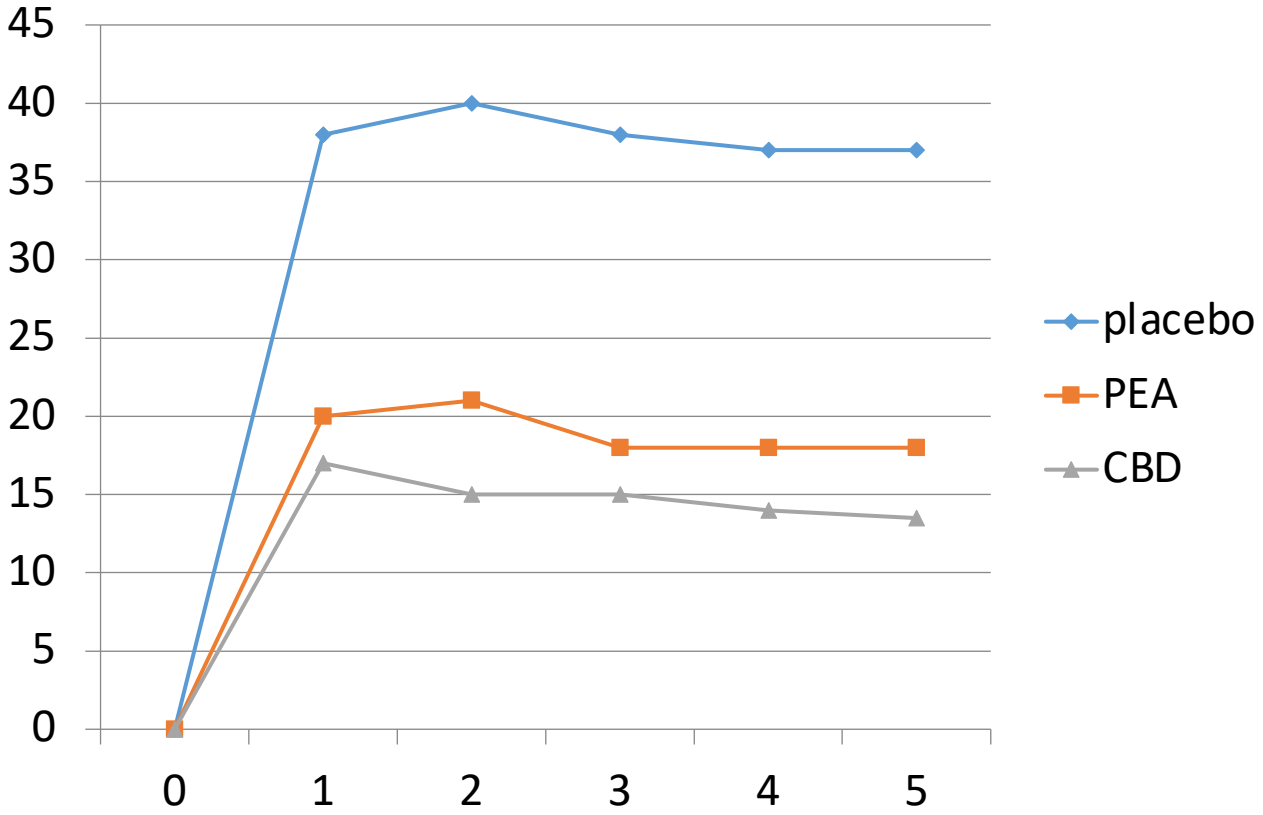
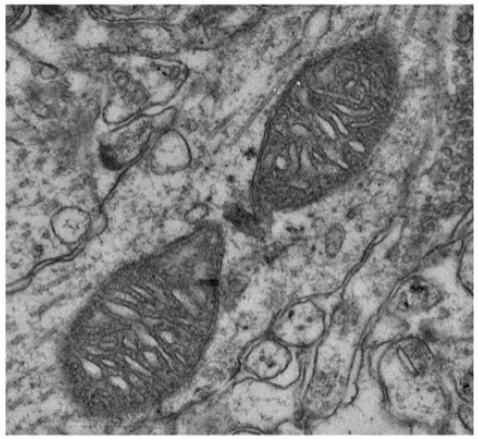


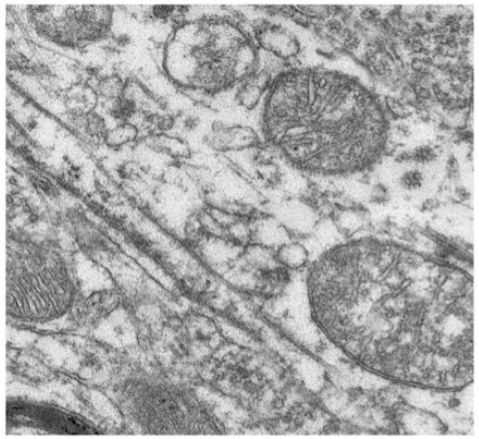
Figure 1 – The concentration ratios of urinary lactulose and mannitol over time in healthy participants treated with aspirin and either placebo, CBD or PEA, measured by LC MS. Results are expressed as mean ratios +/- SEM. Time points between groups were compared using two-way ANOVA using Dunnett's multiple comparisons test comparing to placebo at the same time point (*p

Mitochondrial Impairment

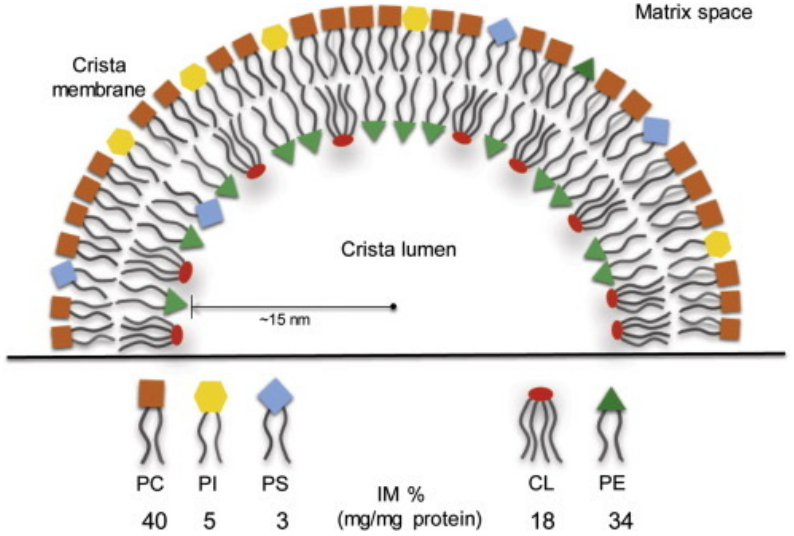
Decay



Young



Old

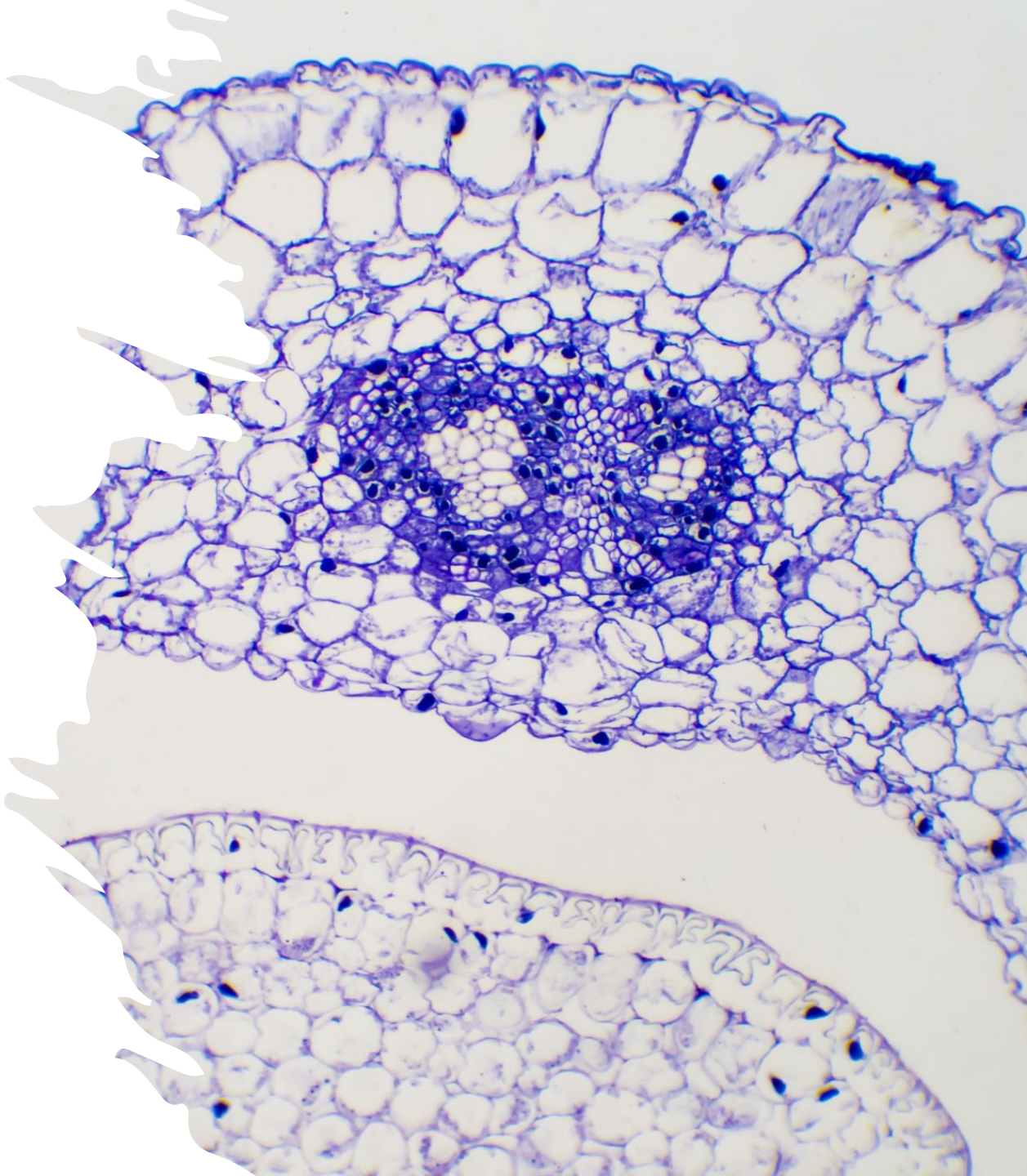


1. Decreased cardiolipin levels and structural deficit;
2. Decreased membrane potential (the driving force for ATP synthesis) and cellular oxygen consumption;
3. Increased oxidation and heterogeneity;
4. Prone to oxidative damage, leading to a vicious cycle.

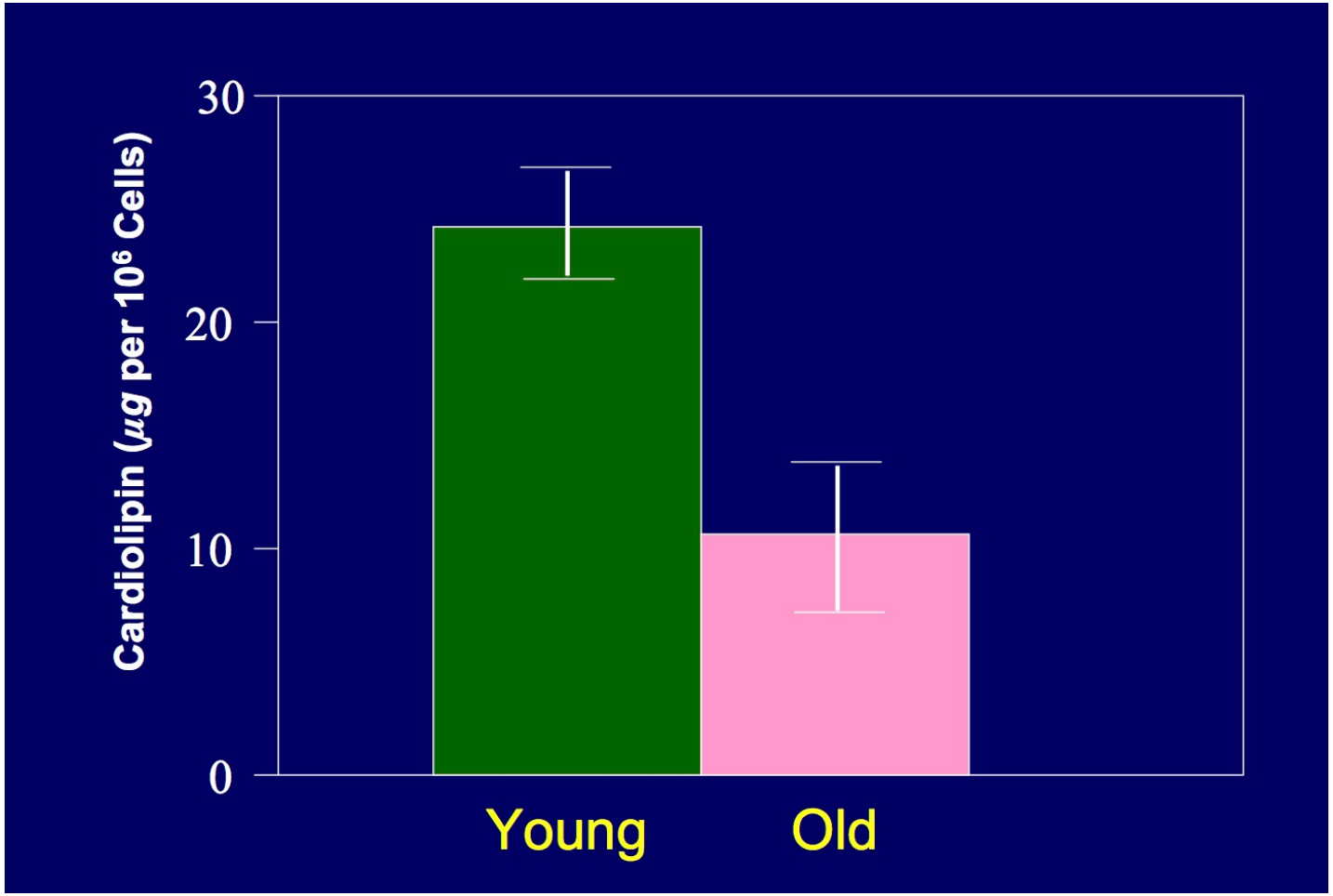
Mitochondria and cardiolipin

- Cardiolipin is a unique phospholipid located exclusively in the inner mitochondrial membrane where it is biosynthesized.

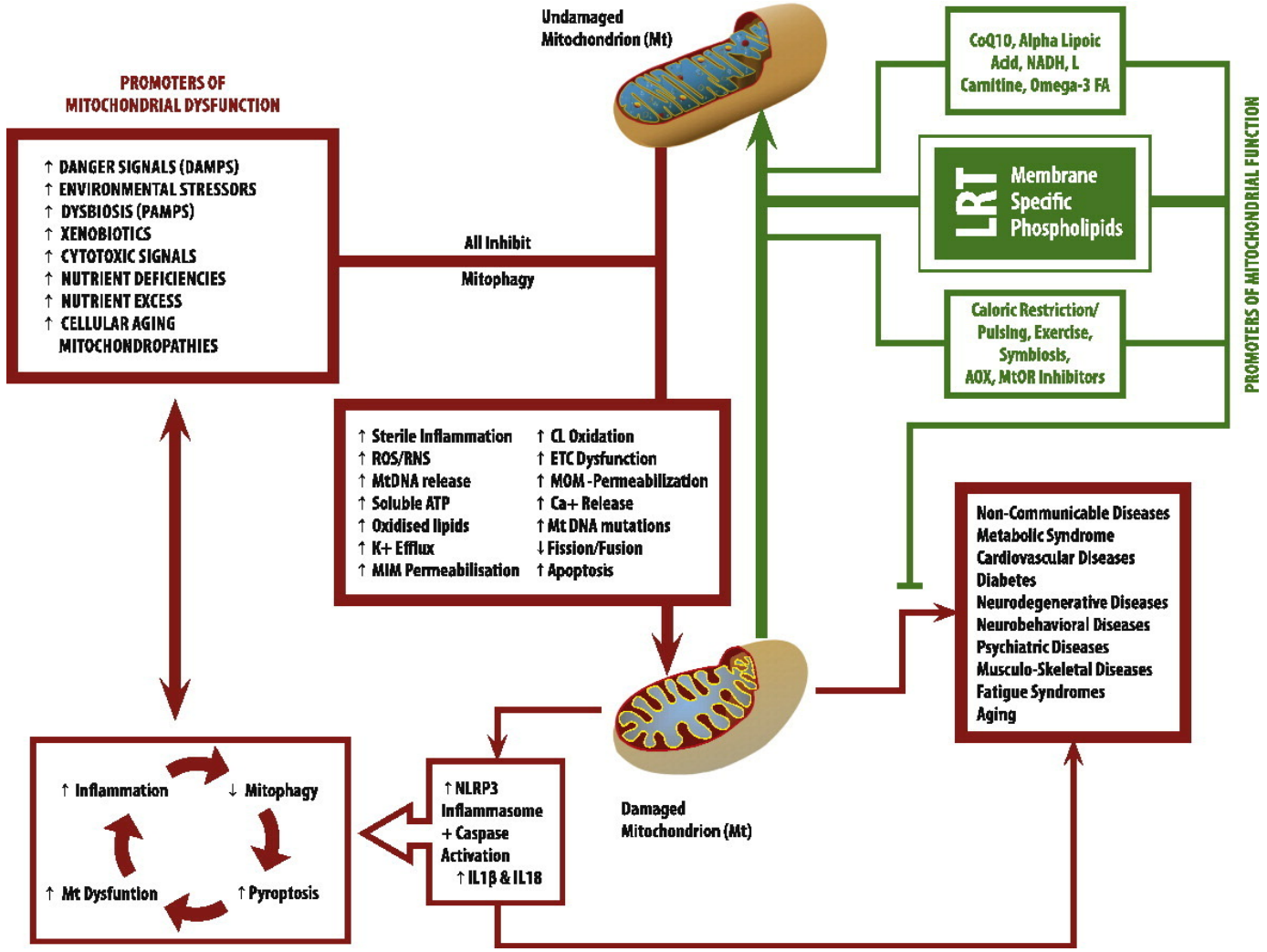
- This phospholipid is associated with membranes designed to generate an electrochemical gradient that is used to produce ATP.
- The ubiquitous and intimate association between cardiolipin and energy transducing membranes indicates an important role for cardiolipin in mitochondrial bioenergetic processes.
- Involved in mitochondrial membrane stability and dynamics.
- Interestingly, also found in bacterial cell walls



Mitochondrial Impairment *Cardiolipin Levels examined*



Lipid Replacement Therapy



Lipid Replacement Supplements

Review

Lipid Replacement Therapy: A natural medicine approach to replacing damaged lipids in cellular membranes and organelles and restoring function ☆☆

Membrane Lipid Replacement with Glycerolphospholipids Slowly Reduces Self-Reported Symptom Severities in Chemically Exposed Gulf War Veterans

by Garth L. Nicolson * and Paul C. Breeding

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Int. J. Transl. Med. **2022**, *2*(2), 164-173; **https://doi.org/10.3390/ijtm2020014**

Submission received: 14 March 2022 / Revised: 26 April 2022 / Accepted: 27 April 2022 / Published: 29 April 2022

Membranes (Basel). 2021 Dec; 11(12): 944. PMCID: PMC8707623
Published online 2021 Nov 29. doi: 10.3390/membranes11120944 PMID: 34940446

Fundamentals of Membrane Lipid Replacement: A Natural Medicine Approach to Repairing Cellular Membranes and Reducing Fatigue, Pain, and Other Symptoms While Restoring Function in Chronic Illnesses and Aging

Garth L. Nicolson,[1,*] Gonzalo Ferreira de Mattos,[2] Michael Ash,[3] Robert Settineri,[4] and Pablo V. Escribá[5]

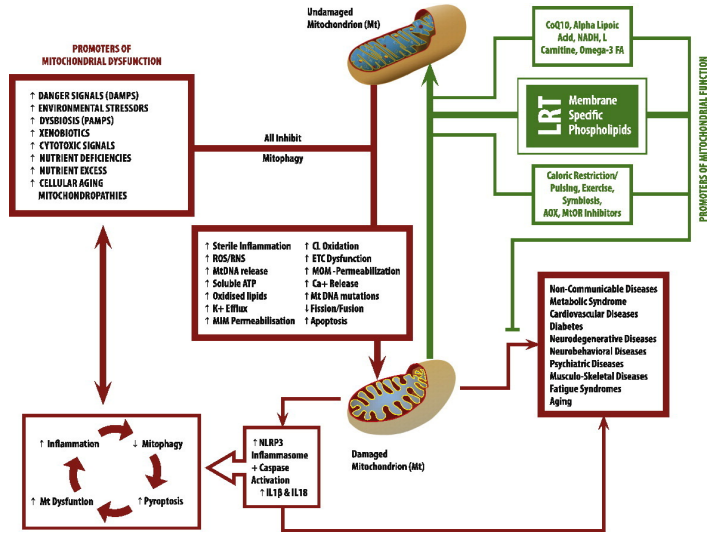
Supplement Facts

Serving Size: 4.5 grams per serving
Servings Per Container: 60

Amount Per Serving	%DV*
Phosphatidylcholine ..... 1,500 mg	.....*
Phosphatidylethanolamine ..... 600 mg	.....*
Phosphatidylinositol ..... 415 mg	.....*
Palmitoylethanolamide (PEA) ..... 150 mg	.....*
Glycerylphosphorycholine (alpha-GPC) ..... 75 mg	.....*
Phosphatidylserine ..... 55 mg	.....*
Vitamin E (Succinate) ..... 45 mg	.....*
FOS ..... 90 mg	.....*
Shilajit Extract Powder 20% Fulvic Acid ..... 90 mg	.....*

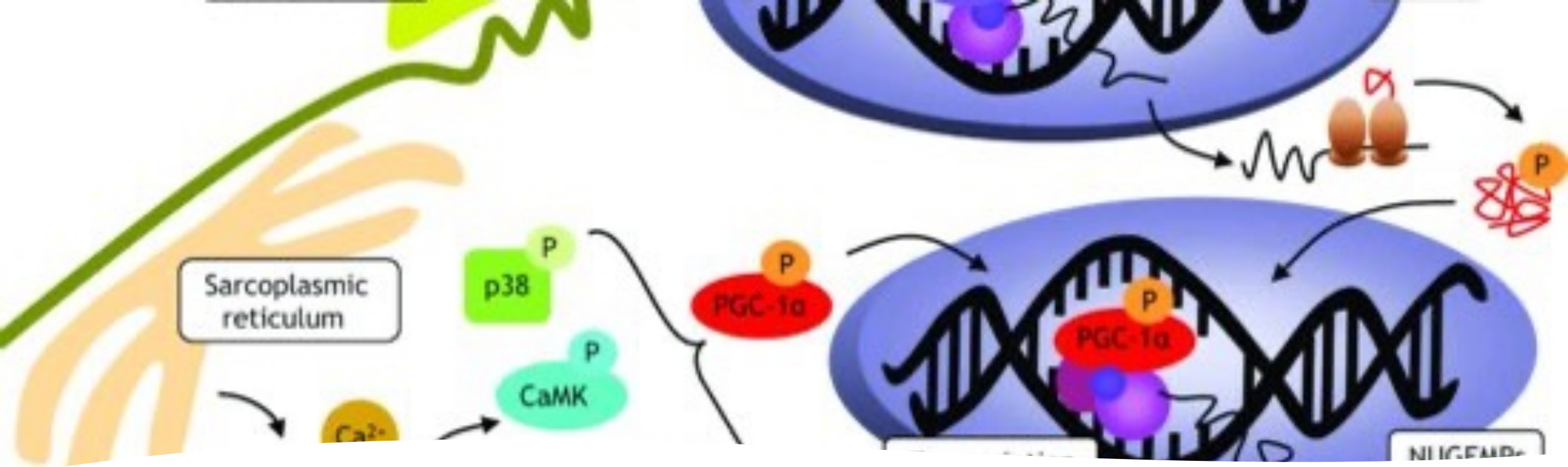
*** - Daily Value Not Established**

Other Ingredients: Soy Phospholipids, Maltodextrin.
Gluten Free, Dairy Free and Vegan



Improving Mitochondrial Function

1. Exercise
2. Balanced Macronutrient intake
3. Essential up regulation nutrients
4. Protection from oxidative damage
5. Improve GI epithelial Function
6. Detoxification from drugs, environmental toxins, glycation



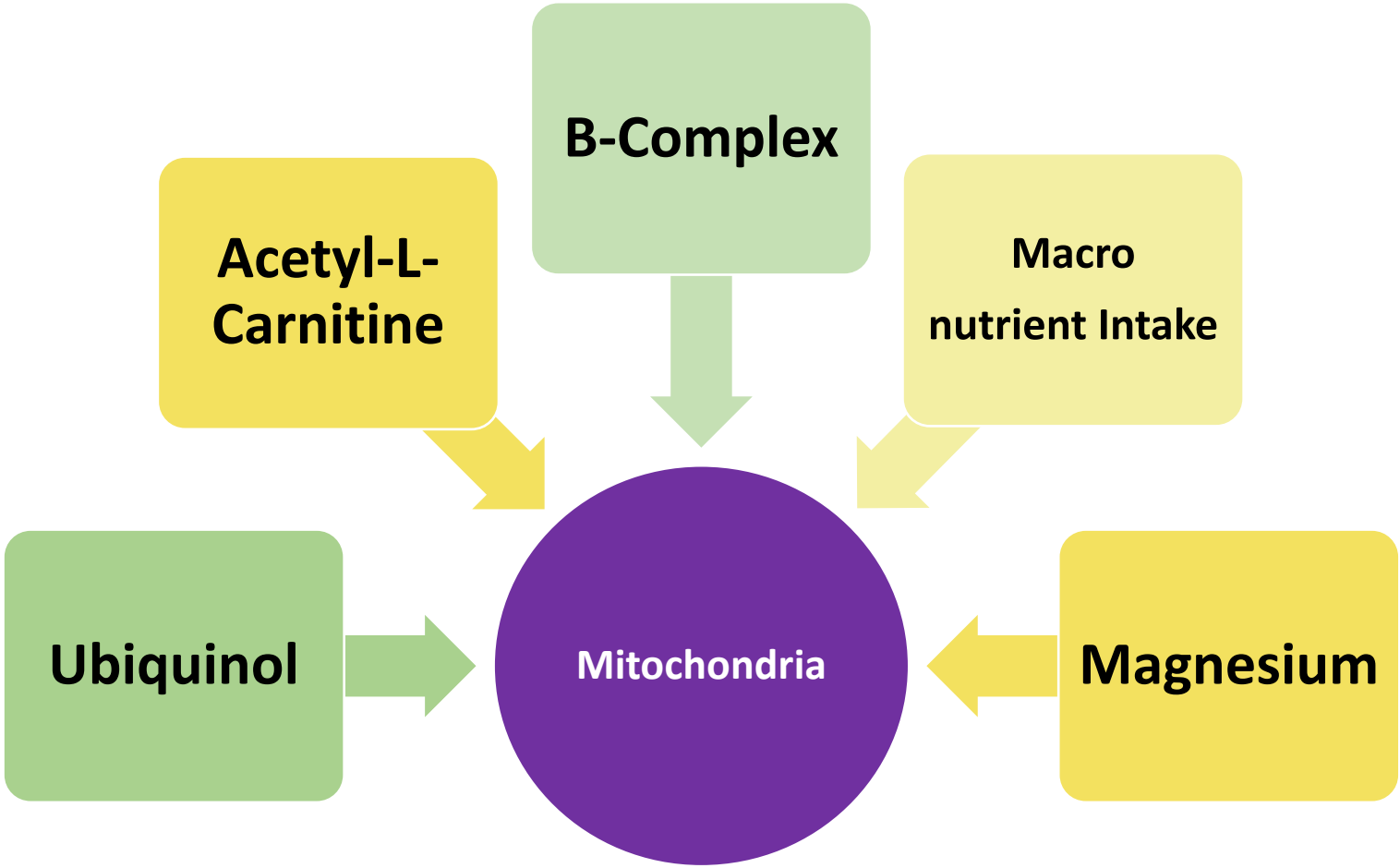
Improving Mitochondrial Function *Exercise*

- Mitochondrial biogenesis
  - synthesize more normal mitochondria by stimulating the cells
- Proven therapy
- Start slowly and build gradually

Effects of Exercise on Mitochondrial Content and Function in Aging Human Skeletal Muscle
Elizabeth V. Menshikova, Vladimir B. etc al.
J Gerontol A Biol Sci Med Sci.

Improving Mitochondrial Function

Macronutrient and Up-regulation

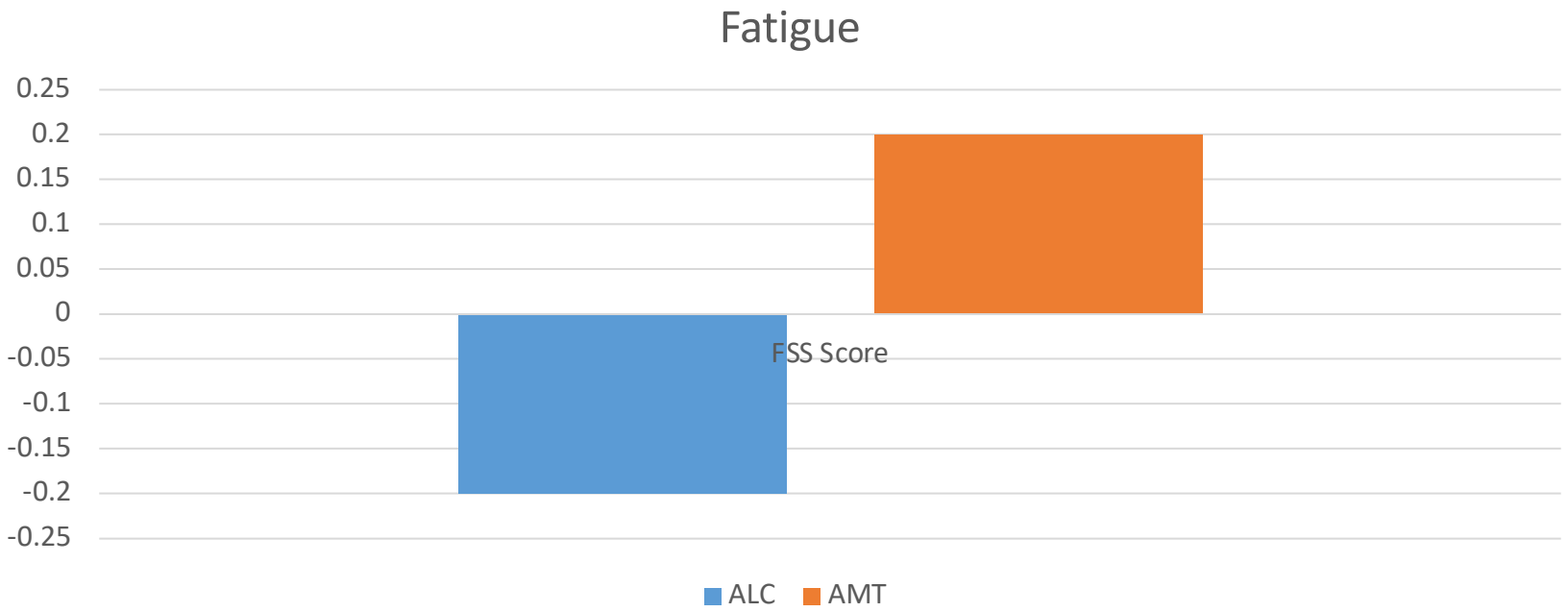


Acetyl-L-Carnitine (ACAR)

- Enriches mitochondrial fuel mixture through increased fatty acid transport and beta oxidation of fats
- Acetyl group can be donated to choline to form acetylcholine. Benefits include restored nerve function in peripheral neuropathy and cognitive disorders.
- Acetyl group can also be used to for methylation in the liver and to help produce increased energy in Kreb's cycle
- ACAR supplementation shown to promote nerve regeneration and reduce peripheral neuropathy symptoms

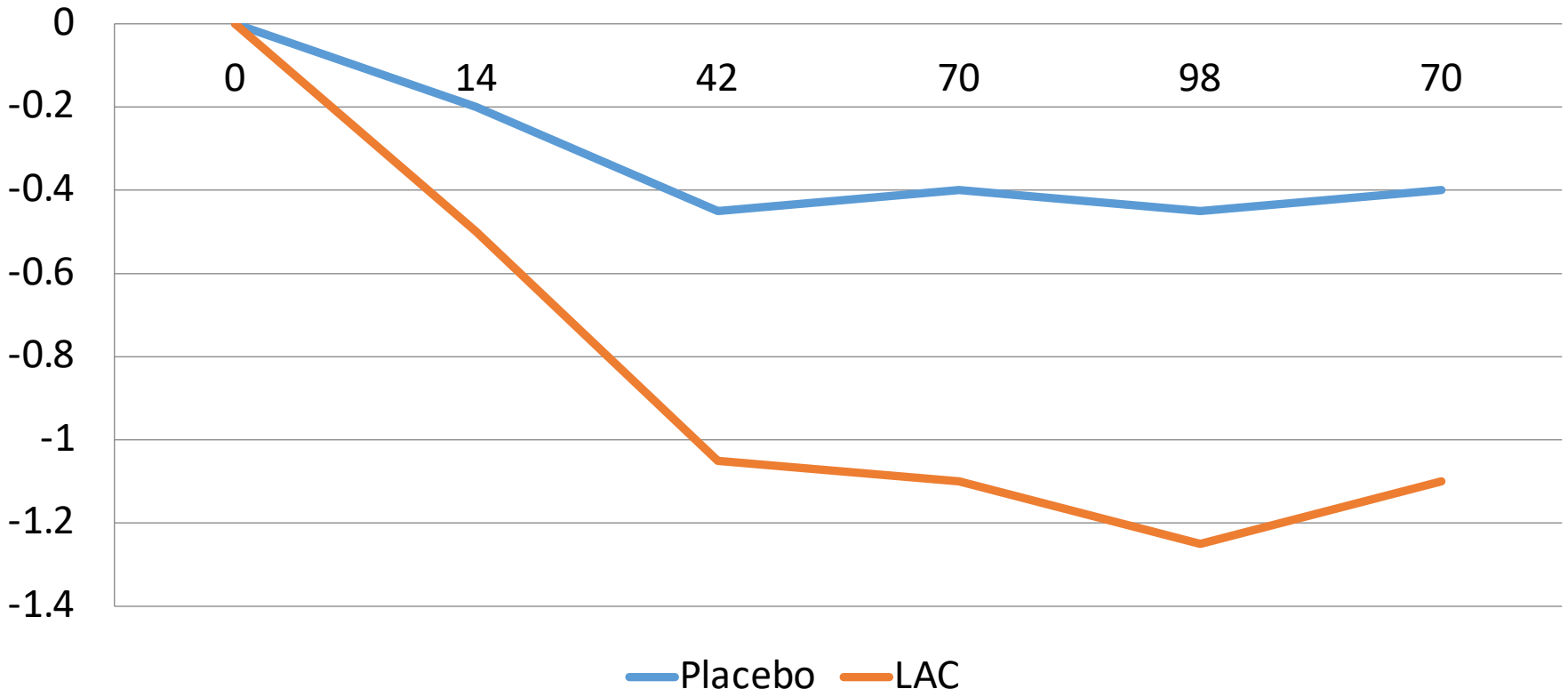
{Hart AM, et al. *AIDS* 2004,18:1549-87}

ALC in MS



Tommasinni E et al. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot,randomised, double-blind, crossover trial. Journal of the Neurological Sciences. 2004; 218:103– 108

ALC and FM Pain



Rossini M et al. Clinical and Experimental Rheumatology 2007; 25: 182-188.

ALC and Fatigue in the Elderly

- Malaguarnera M et al. Archives of Gerontology and Geriatrics.2008;46:181–190

	Active	Placebo
Muscle Pain	-27%	-3%
Fatigue Severity Score	-22.5%	+1.2%
Sleep Disorders	-28%	-4%
Functional Status	+17.10	+0.6

Improving Mitochondrial Function
Ubiquinol

Made in human cells

Important for a host of functions
- Shuttling electrons in the respiratory chain
- Shuttling electrons when fat is broken down
- Signaling in cell

Falls as we age (70 yr old has 50% levels of a 20 yr old)

Diabetics appear to have difficulty converting ubiquinone to ubiquinol

Insoluble in water (powder formulations have poor absorption)

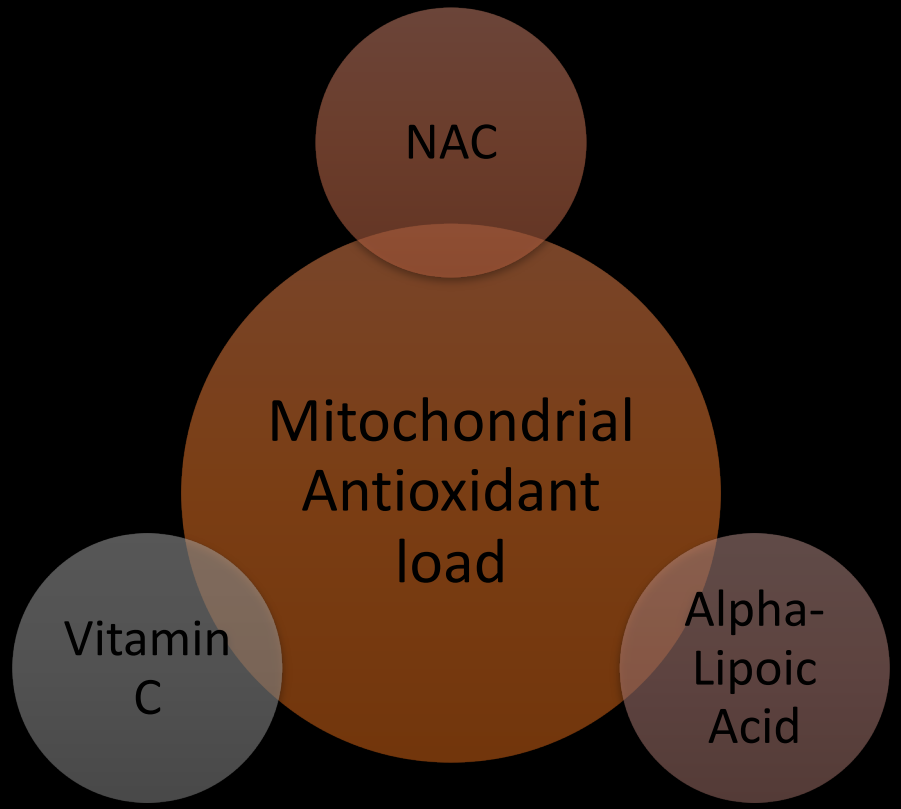
Ubiquinol has better bioavailability and clinical outcomes at lower doses

Dosing:
- CoQ10 as Ubiquinol: (preferred)
  - Adult: 50-600 mg once daily
- Co Q 10 as Ubiquinone:
  - Adult: 300-2400 mg in 2-3 divided doses

Contraindications: none

Side Effects: sleep disruption, wakefulness

Improving Mitochondrial Function
Antioxidant Plan



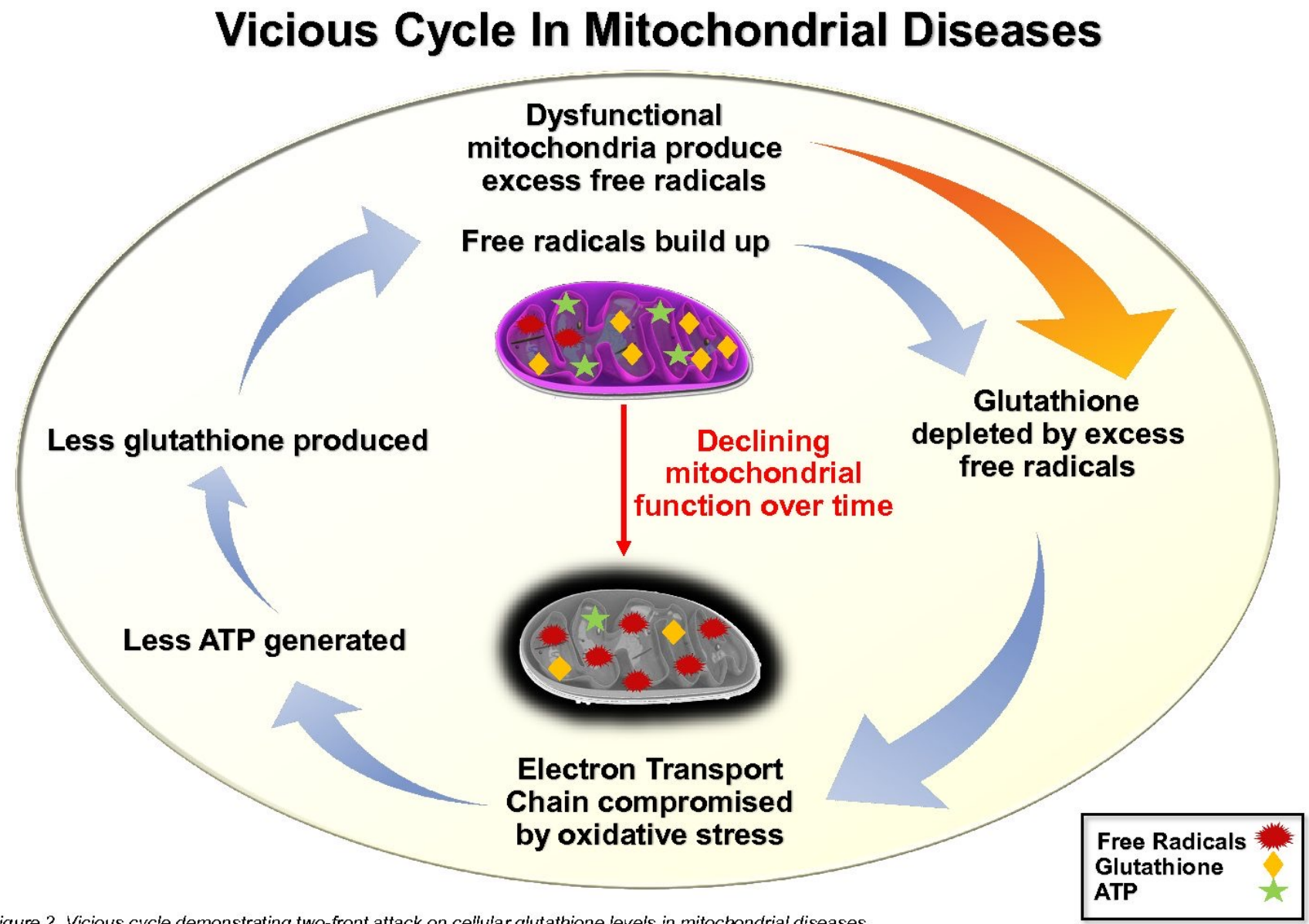
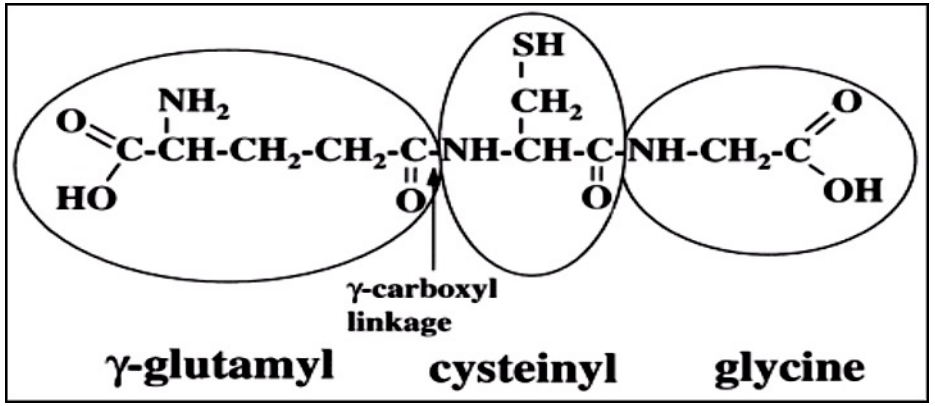


Figure 2. Vicious cycle demonstrating two-front attack on cellular glutathione levels in mitochondrial diseases.

Reduced L Glutathione

Supplement Form

- Tri-peptide of Glutamic acid, Cysteine and Glycine.
- Fermented from Torula yeast
- Reduced form



In Mitochondria

- Among the arsenal of antioxidants and detoxifying enzymes existing in mitochondria, mitochondrial glutathione (mGSH) emerges as the main line of defense for the maintenance of the appropriate mitochondrial redox environment to avoid or repair oxidative modifications leading to mitochondrial dysfunction and cell death.

Glutathione Functions

- Direct chemical neutralization of singlet oxygen, hydroxyl radicals, and superoxide radicals
- Cofactor for several antioxidant enzymes
- Regeneration of vitamins C and E
- Detoxification:
  - Neutralization of free radicals produced by Phase I liver metabolism of chemical toxins
  - One of approximately 7 liver Phase II reactions, which conjugate the activated intermediates produced by Phase I to make them water soluble for excretion by the kidneys
  - Transportation of mercury out of cells and the brain
- Regulation of cellular proliferation and apoptosis
- Vital to mitochondrial function and maintenance of mitochondrial DNA (mtDNA)

Pizzorno J et al. Glutathione. Integr Med (Encinitas). 2014 Feb; 13(1): 8–12

Protein (25 grams in morning daily)

VERY EFFECTIVE IN IMPROVING PATIENTS OVER ALL WELL BEING

IMPROVES ENERGY LEVELS AND FUNCTIONALITY

INCREASES LEVELS OF GLUTATHIONE

REGULATES BLOOD SUGAR

PROVIDES KEY COMPONENTS FOR IMMUNOGLOBULIN

Improving Mitochondrial Function
R-Alpha Lipoic Acid

Clinical Uses for R-Alpha Lipoic Acid	•Anti-oxidant •Anti-glycation agent •Blood sugar normalizer •Mitochondria support •Glutathione up-regulation
Dose:	•50-100 mg QD •Therapeutically 100-300 mg QD
SE:	•Minor side effects include skin reactions and gastrointestinal effects, such as nausea and vomiting.

Alpha-Lipoic acid

Research paper

α-Lipoic acid improves mitochondrial biogenesis and dynamics by enhancing antioxidant and inhibiting Wnt/Ca^{2+} pathway to relieve fluoride-induced hepatotoxic injury

Yanghuan Yu, Jipeng Xu, Hao Li, Jia Lv, Yaqin Zhang, Ruiyan Niu, Jundong Wang, Yangfei Zhao, Zilong Sun

(+)-Lipoic acid reduces mitochondrial unfolded protein response and attenuates oxidative stress and aging in an in vitro model of non-alcoholic fatty liver disease

Lucia Longhitano, Alfio Distefano, Nicolò Musso, Paolo Bonacci, Laura Orlando, Sebastiano Giallongo, Daniele Tibullo, Simona Denaro, Giuseppe Lazzarino, Jessica Ferrigno, Anna Nicolosi, Amer M. Alanazi, Federico Salomone, Emanuela Tropea, Ignazio Alberto Barbagallo, Vincenzo Bramanti, Giovanni Li Volti, Giacomo Lazzarino, Daniele Torella & Angela Maria Amorini

Journal of Translational Medicine **22**, Article number: 82 (2024) | Cite this article

DOI: 10.1007/s11064-007-9403-0 • Corpus ID: 26113912

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Jiankang Liu • Published in Neurochemical Research 20

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TLDR Administating mitochondrial nutrients, such as α-lipoic acid and its derivatives in combination with other mitochondrial nutrients to aged people and patients suffering from neurodegenerative diseases, may be an effective strategy for improving mitochondrial and cognitive dysfunction.

Expand

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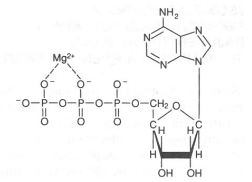
Expand

Improving Mitochondrial Function

Magnesium

- Nearly 99% of the total body magnesium is located in bone or the intracellular space.
- Second plentiful cation of the extracellular fluids.
- Mg^{2+} is a cofactor of all enzymes involved in phosphate transfer reactions utilizing ATP and other nucleotide triphosphates as substrate.
- Required for the structural integrity of numerous intracellular proteins and nucleic acids.
- A substrate or cofactor for important enzymes such as adenosine triphosphatase, guanosine triphosphatase, phospholipase C, adenylate cyclase, and guanylate cyclase.
- A required cofactor for the activity of over 300 other enzymes.
- A regulator of ion channels; an important intracellular signaling molecule.
- A modulator of oxidative phosphorylation.



Mg^{2+} is chelated between the beta and gamma phosphates, diminishes the dense anionic character of ATP