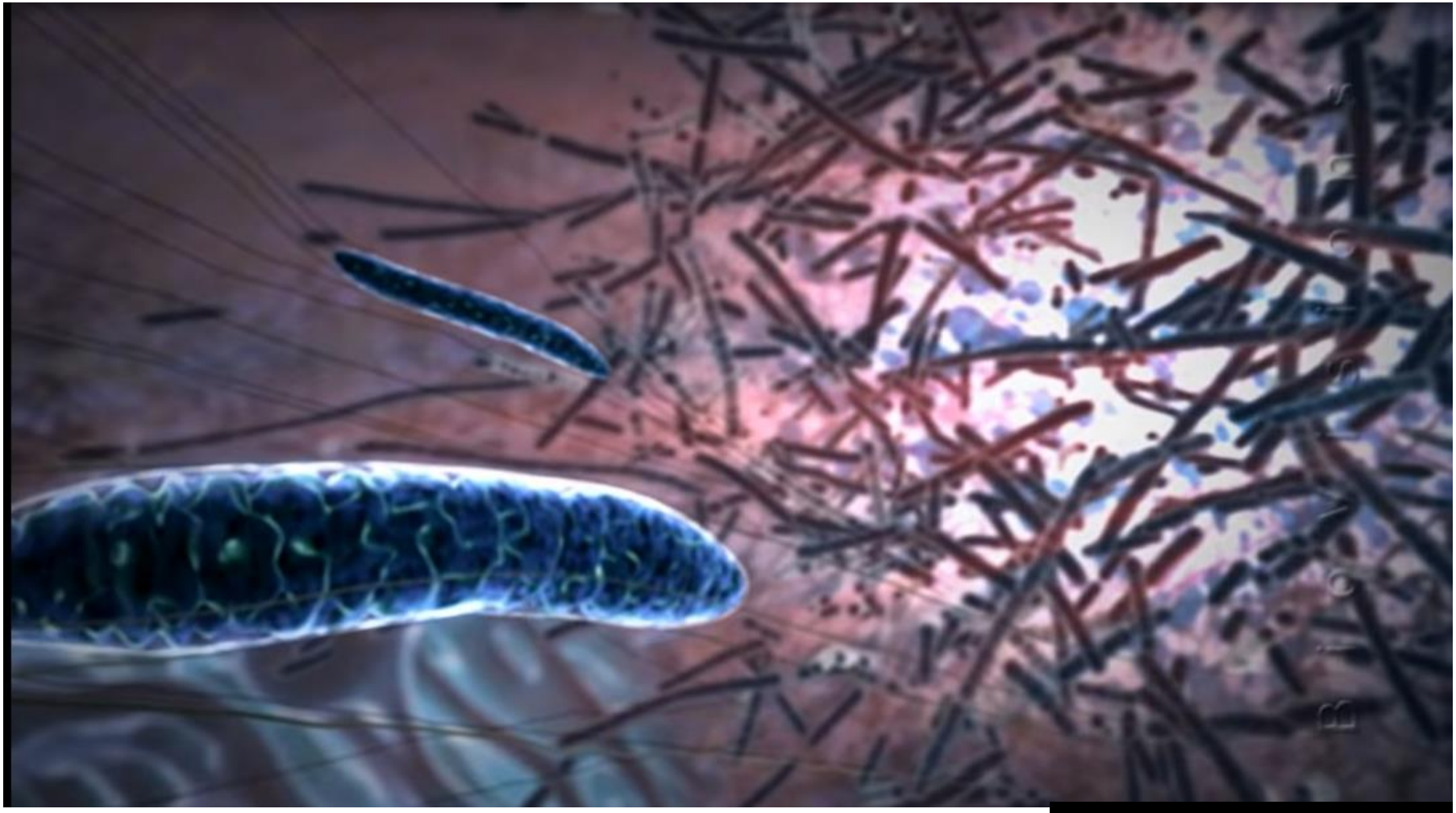
The Mitochondria and Chronic Health Conditions, Part 1

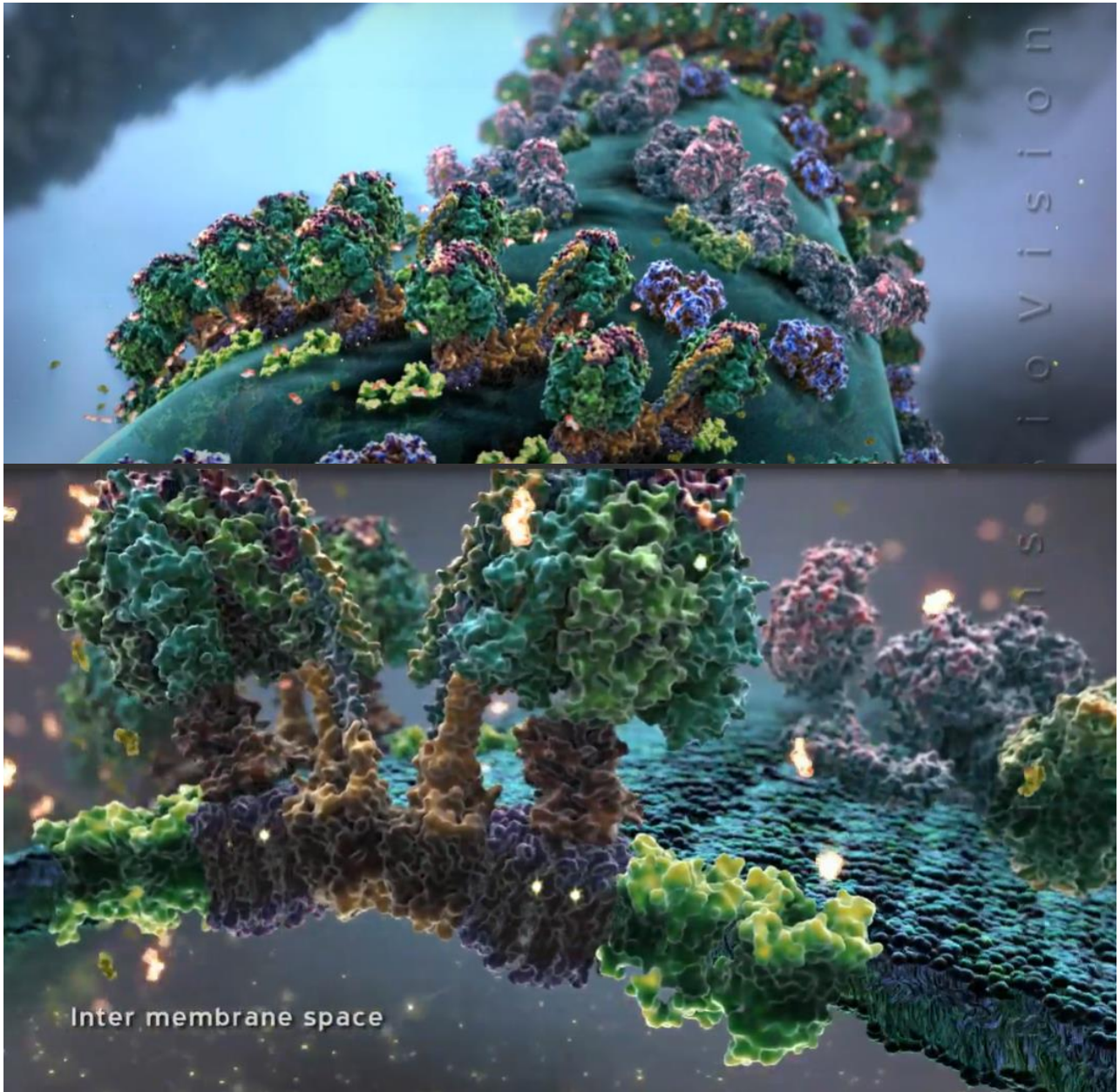
Professor Brigitte Koenig, Magdeburg Molecular Detections
Gilian Crowther MA (Oxon), Dip NT/ND
www.aonm.org

Our mitochondria power our cells, and a lot more ...

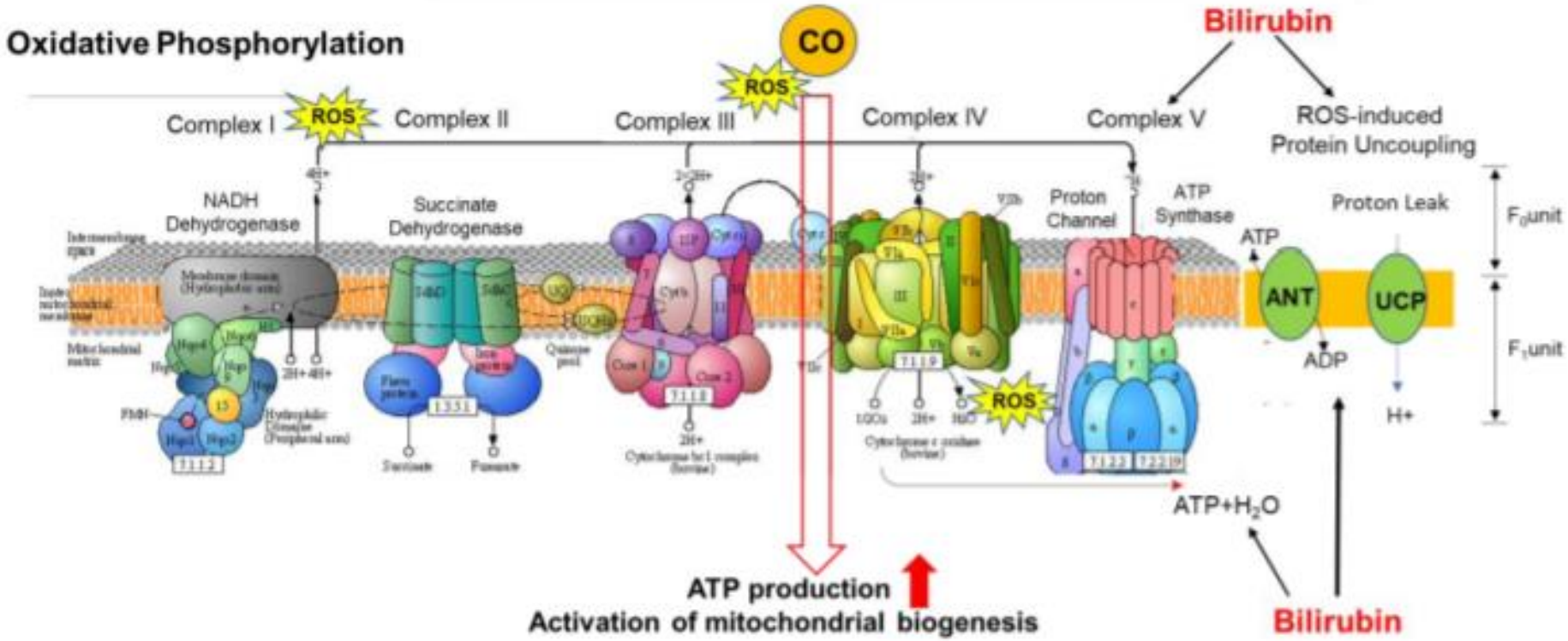


Biovisions Powering the Cell, Mitochondria, biovisions.mcb.harvard.edu
https://www.youtube.com/watch?v=RrS2uROUjK4

The electron transport chain (ETC) – 5 complexes



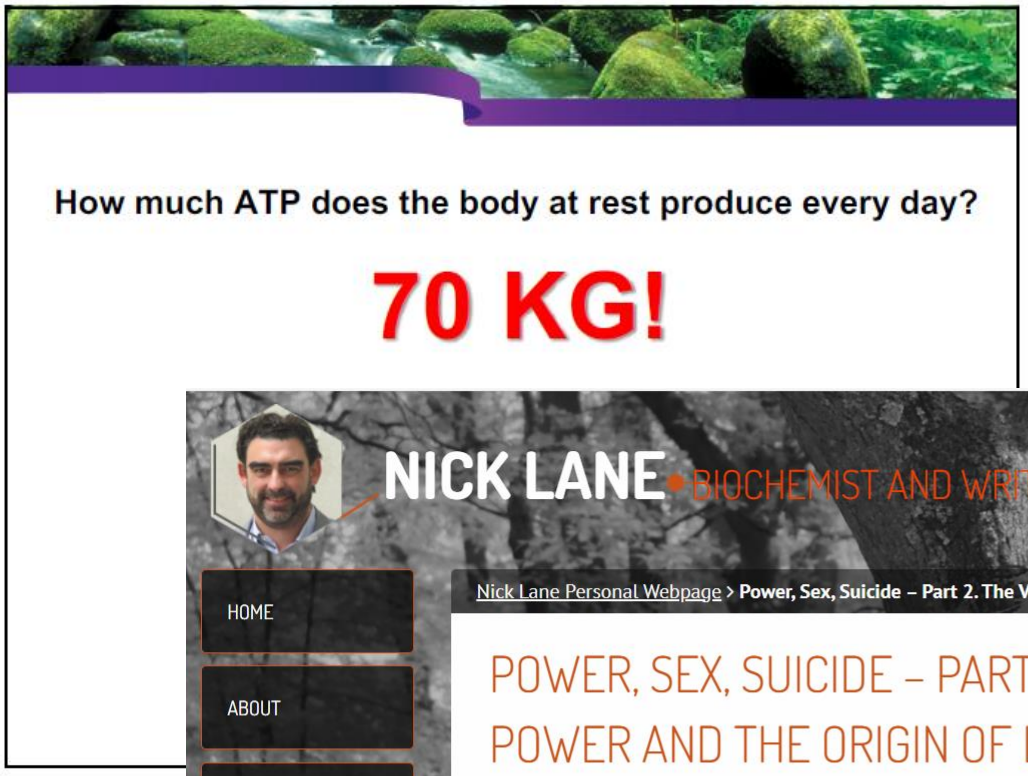
36 ATP are generated along the electron transport chain from glucose; 146 (oleic acid) and more from fats



… but an incredibly complex process, so many inputs required …

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7402116/pdf/antioxidants-09-00636.pdf

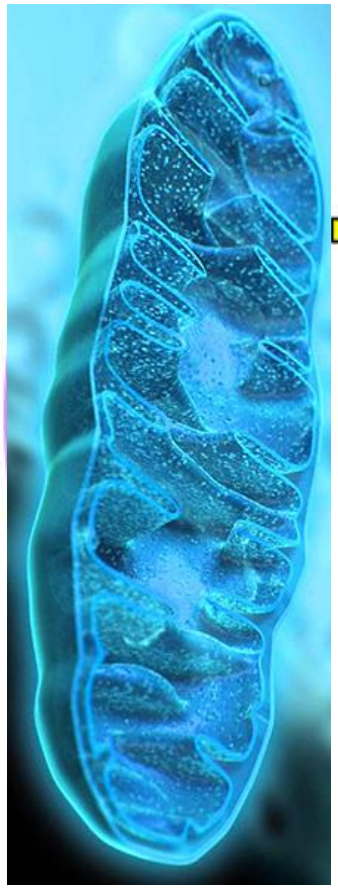
We (should) produce our body weight in ATP each day, and convert 10,000 x more energy than the sun every second



"Gram per gram, … you are converting 10,000 times more energy than the sun every second." Professor Nick Lane, UCL

https://nick-lane.net/chapters/power-sex-suicide-part-2-vital-force-proton-power-origin-life/

What do we lose if our mitochondria go down?



Bioenergetics

Biosynthesis

Signaling

Examples

High-intensity energy metabolism and nutrient sensing

Heme
Ureagenesis
Cholesterol
Much of the acetyl-CoA & SAM needed for protein acetylation & methylation

Calcium-dependent signalling

T cell function

Neutrophil activation

O_2 sensor for vasoconstriction

Apoptosis (release of Cytochrome C)

… and much more …

Source: Chandel NS. Mitochondria as signaling organelles. BMC Biology 2014 12:34; Chandel NS et al. Mitochondrial reactive oxygen species trigger hypoxia-induced transcription. Proc Natl Acad Sci U S A. 1998; Ledderose C et al. Mitochondria are gate-keepers of T cell function by producing the ATP that drives purinergic signaling. J Biol Chem. 2014); Quintana A et al. T cell activation requires mitochondrial translocation to the immunological synapse. Proc Natl Acad Sci U S A. 2007; Bao Y. Mitochondria regulate neutrophil activation by generating ATP for autocrine purinergic signaling. J Biol Chem. 2014

Acquired conditions in which mitochondrial dysfunction has been implicated

Table 2
Acquired conditions in which mitochondrial dysfunction has been implicated

Diabetes (Wallace, 2005; Fosslien, 2001; West, 2000)
Huntington's disease (Stavrovskaya and Kristal, 2005)
Cancer (Wallace, 2005), including hepatitis-C virus-associated hepatocarcinogenesis (Koike, 2005)
Alzheimer's disease (Stavrovskaya and Kristal, 2005)
Parkinson's disease (Stavrovskaya and Kristal, 2005)
Bipolar disorder (Stork and Renshaw, 2005; Fattal et al., 2006)
Schizophrenia (Fattal et al., 2006)
Aging and senescence (Wallace, 2005; Savitha et al., 2005; Skulachev and Longo, 2005; Corral-Debrinski et al., 1992; Ames et al., 1993)
Anxiety disorders (Einat et al., 2005)
Nonalcoholic steatohepatitis (Lieber et al., 2004)
Cardiovascular disease (Fosslien, 2001), including atherosclerosis (Puddu et al., 2005)
Sarcopenia (Bua et al., 2002)
Exercise intolerance (Conley et al., 2000)
Fatigue, including chronic fatigue syndrome (Fulle et al., 2000; Buist, 1989), fibromyalgia (Park et al., 2000; Yunus et al., 1988), and myofascial pain (Yunus et al., 1988)

Sources: Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol. 2007 Aug;83(1):84-92.

Agenda

- **What pathways may have become compromised?**
- ATP Profile
- Mitochondrial Health Index
- Lactate/Pyruvate Index

Some of the energy-generation pathways that may have become compromised

Macronutrients

Are macronutrient fuels accessing the cell sufficiently?
Are the fuels the most efficient for generating mitochondrial energy?

Membranes

Are the cellular membranes of the right composition/sufficiently intact?
Any blockages in the membranes?

Micronutrients/cofactors

Correct substrates for the Krebs cycle?
Are the mitochondria able to metabolise the substrates? If not, why not?
Do the complexes of the electron transport chain have the right substrates?

Oxidative stress

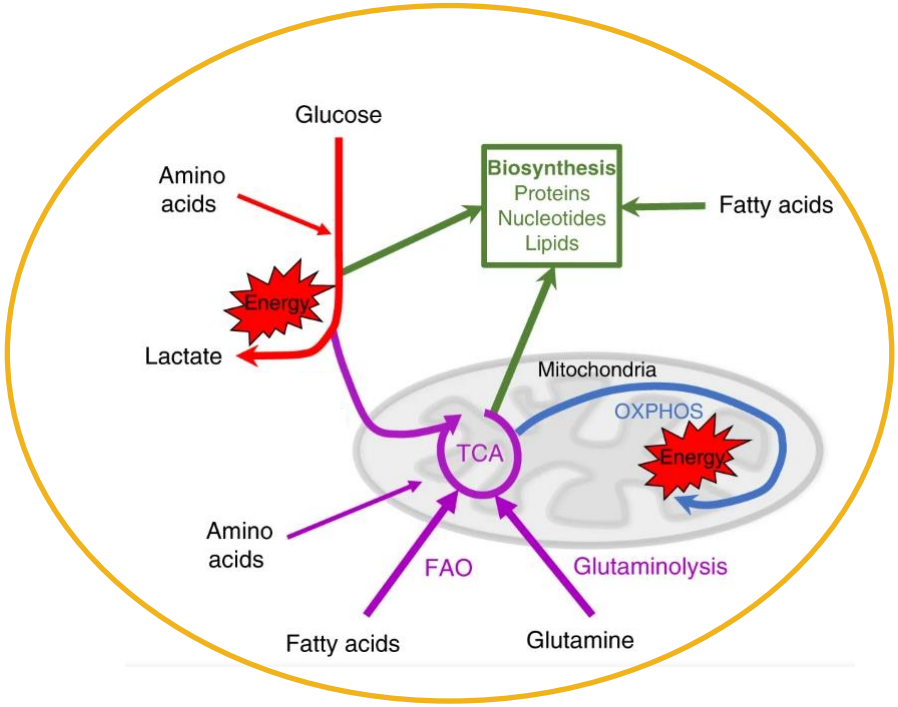
High ROS within the cell?
High ROS within the mitochondria?

Mitochondrial mass/composition

Insufficient numbers of mitochondria, or non-intact?

Obstacles along the electron transport chain

Blocks?
Proton leak?



Source: *MMD, O&M und Ernaehrung,* Mitochondrien – texts from 2016/No. 156 through to 2020/No. 171 Prof. Dr. rer. nat. Brigitte König; *mitochondrial research by Martin D. Brand and others (e.g. https://pubmed.ncbi.nlm.nih.gov/28270511/); https://www.nature.com/articles/s41467-019-10015-4; other references available on request*

Agenda

- What pathways may have become compromised?
- **ATP Profile**
- Mitochondrial Health Index
- Lactate/Pyruvate Index

ATP Profile – the mitochondria at rest

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MMD

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Patient	AW	Date of birth	01.01.1990
		Entry on	23.07.2021
Order No.:			
Date of sample	22.07.2021	Validated by	Prof. Dr. Brigitte König
Sample type	CPDA vacutainer	Cell type	PBMC
Results status	**Final report**	Results status on	23.07.2021

ATP profile

Test	Result	Unit	Reference range	Result [%]
Total ATP	0.8	fmol/cell		
Mitochondrial ATP capacity	0.4	fmol/cell		50
Glycolytic ATP capacity	0.5	fmol/cell		63
Reserve ATP capacity	0.10	fmol/cell		13

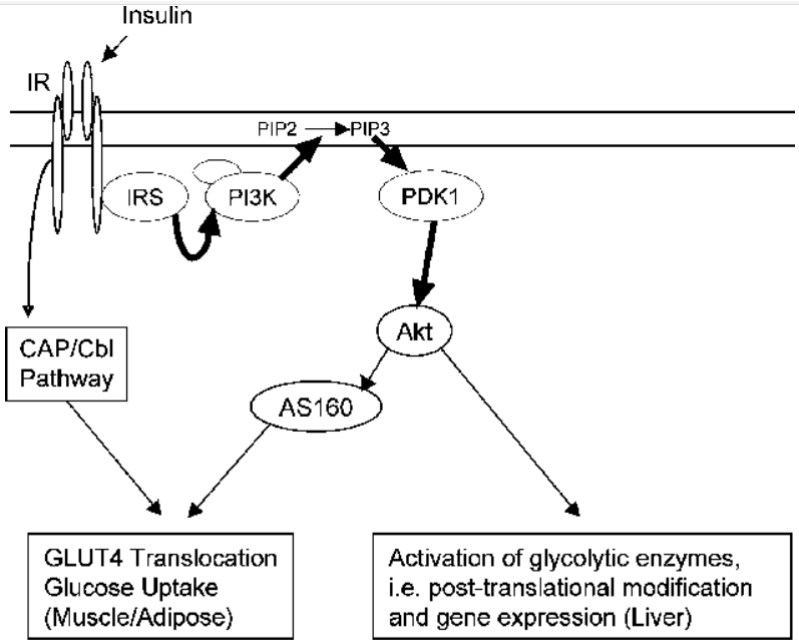
Reference range total ATP									
fmol/cell	<0.8	0.8 - 1.0	1.0 - 1.2	1.2 - 1.4	1.4 - 1.6	1.6 - 2.0	2.0 - 2.5	2.5 - 3.0	3.0 - 5.0
Reference range mitochondrial ATP capacity									
fmol/cell	<0.8	0.8 - 1.0	1.0 - 1.2	1.2 - 1.4	>1.4				
Reference range glycolytic ATP capacity									
fmol/cell	<0.8	0.8 - 1.0	1.0 - 1.2	1.2 - 1.4	>1.4				
Reference range reserve ATP capacity									
fmol/cell	<0.2	0.2 - 0.3	0.3 - 0.4	0.4 - 0.6	0.6 - 0.9	0.9 - 1.0	1.0 - 1.2	1.2 - 1.5	>1.5

Impaired glycolytic ATP capacity: Could insulin resistance be an issue? In 95% of the US population, Dr. Pizzorno said last w/e*

Insulin plays a significant role in this array of glycolysis regulation. In the short term, insulin, through insulin signaling pathways controls glucose entry and regulates the levels of F-2,6-P_2, a key regulator of glycolysis.

ScienceDirect.com
https://www.sciencedirect.com › article › abs › pii

Regulation of glycolysis—role of insulin - ScienceDirect.com



Scheme outlining insulin signaling and the regulation of glycolysis. In various tissues, insulin controls distinct components of glycolysis. IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphotidylinositol-3-kinase; PIP2, phosphotidylinositol-,4,5-phosphate; PIP3, phosphotidylinositol-3,4,5-phosphate; GLUT4, glucose transport 4; and PDK, phosphotidylinositol-dependant kinase.

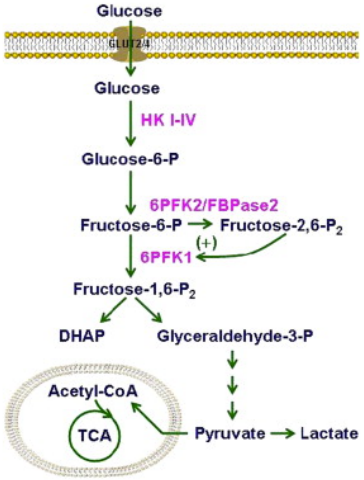


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Figure 1. Major steps of glycolysis. Glycolysis is the pathway for the generation of pyruvate/lactate from glucose. Depending on cell types in which glycolysis occurs, glucose uptake is mediated mainly by glucose transporter 2 (GLUT2) or GLUT4. Following glucose uptake, rates of glycolysis are determined at steps of glucose phosphorylation, which is catalyzed by hexokinase II or hexokinase IV (glucokinase, GK), and the generation of fructose-1,6-bisphosphate, which is catalyzed by 6-phosphofructo-1-kinase (6PFK1). The latter is activated by fructose-2,6-bisphosphate (F2,6P_2), whose production is controlled by 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (6PFK2/FBPase2). DHAP, dihydroxyacetone phosphate; TCA, tricarboxylic acid cycle.

Source: 1. Wu C, Khan SA, Lange AJ. Regulation of glycolysis-role of insulin. Exp Gerontol. 2005 Nov;40(11):894-9;
2. Hers HG. Mechanisms of blood glucose homeostasis. J Inherit Metab Dis. 1990;13(4):395-410; Nutrition Medicine Institute (NMI) Summit, London, "Mitochondrial Nutrition for Energy, the Brain, and Healthy Ageing"< Oct. 11/12, 2024

Lots can be done to manage & resolve insulin resistance/ MetSyn

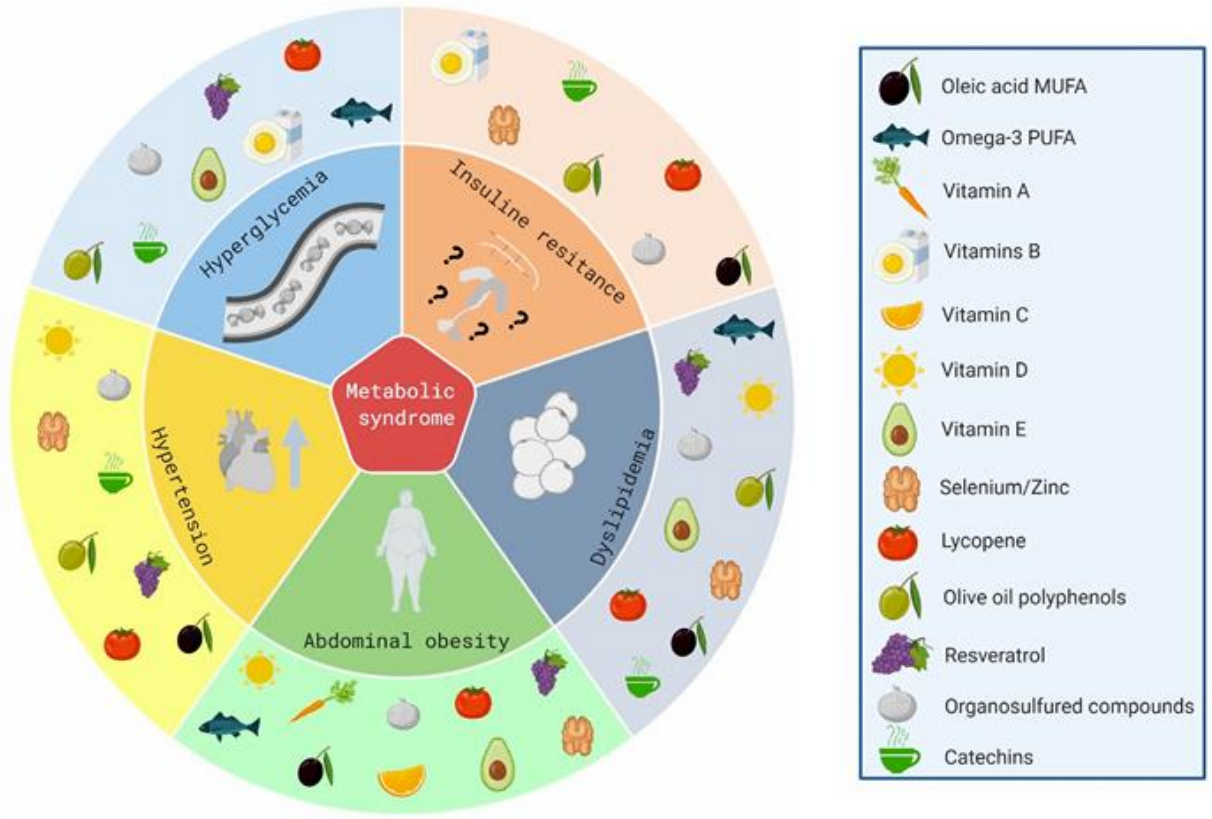
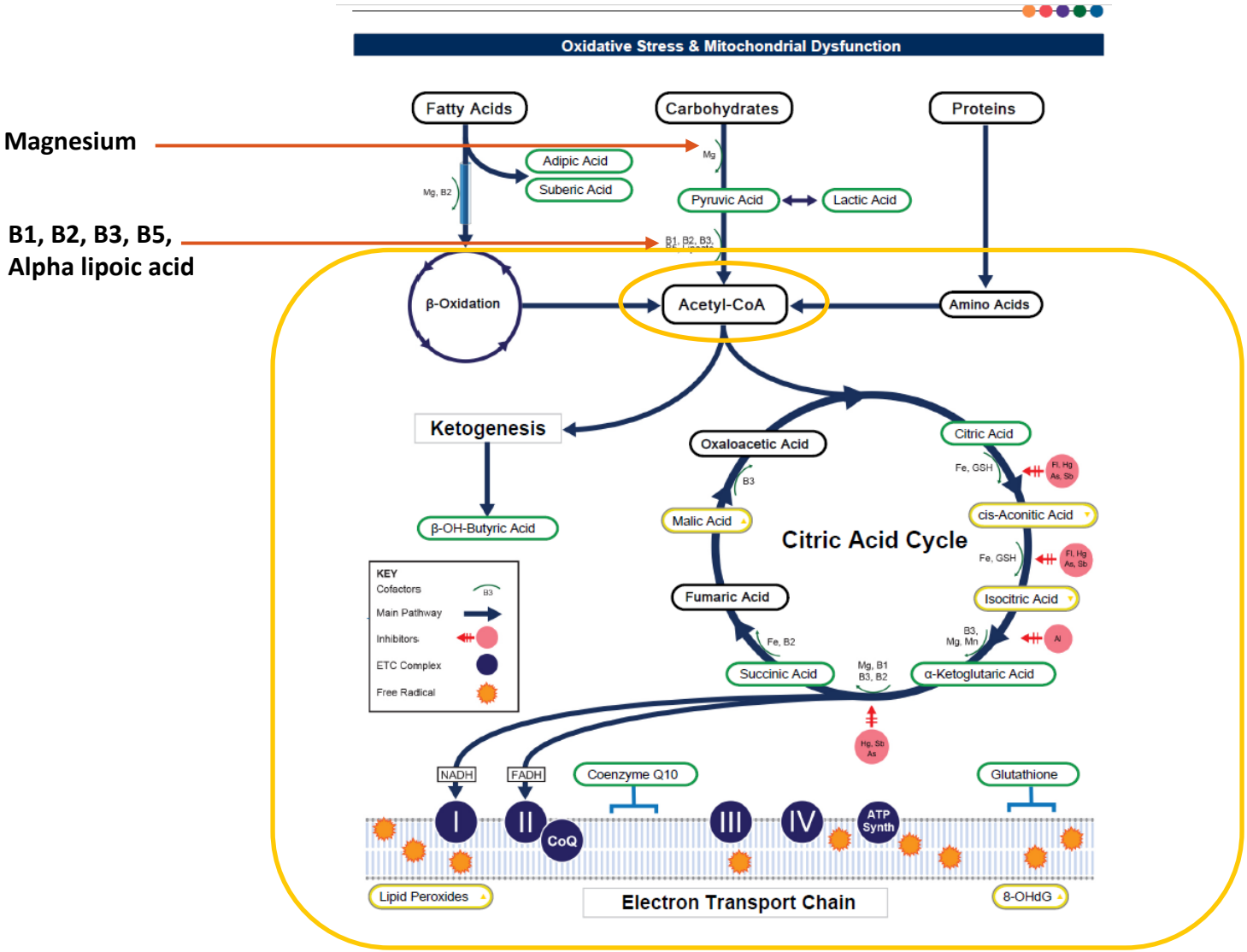


Figure 4. Main nutrient impact on metabolic syndrome (MetS) components. The MetS is a constellation of pathologic conditions which includes hyperglycemia, insulin resistance, dyslipidemia (hypertriglyceridemia and low high density lipoprotein (HDL)-cholesterol levels), central obesity, and hypertension. Several studies have demonstrated that nutrients such as oleic acid monounsaturated fatty acid (MUFA), omega-3 polyunsaturated fatty acids (PUFAs), vitamins A, B, C, D, and E, selenium and zinc elements, lycopene, olive oil polyphenols, resveratrol, organosulfured compounds, and catechins have a positive impact on MEtS components, improving the onset and development of the disease.

Source: García-García FJ, Monistrol-Mula A, Cardellach F, Garrabou G. Nutrition, Bioenergetics, and Metabolic Syndrome. Nutrients. 2020 Sep 11;12(9):2785..

Impaired glycolytic ATP capacity: Cofactors may be lacking to get pyruvic acid into the mitochondria



Source: ©Genova Diagnostics ▪ A.L. Peace-Brewer, PhD, D(ABMLI), Lab Director ▪ CLIA Lic. #34D0655571 ▪ Medicare Lic #34-8475 (with permission)

Natural sources of B vitamins

B1 - Asparagus; Beef; Brewer's yeast; Lamb; Legumes; Liver; Nuts; Pork; Rye; Spirulina; Wheat germ; Whole grains. Synergistic Nutrients - Vitamins B2, B3, B5, B6, B12, Cu, Choline, Mn, Mg, Mo, Phosphate, Zn

B2 - Almonds; Asparagus; Avocados; Beans; Currants; Eggs; Milk and dairy products; Organ meats; Sprouts; Wholegrain cereals; Yeast; Broccoli. Synergistic Nutrients - Vitamin A, B1, B3, B5, B6, B12, Biotin, Cr, Cu, Cysteine, B9, Glutathione, Insulin, Fe, Mg, Mo, Phosphate, K, Thyroxine, Zn

B3 - Almonds; Beef; Chicken; Eggs; Fish; Halibut; Legumes; Mackerel; Meat; Peanuts; Salmon; Sardines; Sunflower seeds; Yeast. Synergistic Nutrients - Vitamin B1, b2, B6, B12, C, Cr, Zn, K, Mn, P, Cu, B9, Fe, Mg, Methionine, SAMe, Mo, Se, Tryptophan

B5 - Avocado; Baker's yeast; Beans; Brains; Blue vein cheese; Egg yolk; GLV; Heart; Kidney; Lentils; Liver; Lobster; Milk; Mushrooms; Oranges; peanut butter; Peas; Royal jelly; Sweet potato; Wholegrain cereal. Synergistic Nutrients - Vitamins B1, B2, B3, B12, C, Biotin, Cr, Cysteine, B9, Glycine, Methionine, Phosphate, Na, K, Zn

B6 - Avocado; Bananas; Brewer's yeast; Carrot; Cereal; Chicken; Egg yolk; Ham; Legumes; Lentils; Mackerel; Oatmeal; Offal; Peanuts; Salmon; Tuna; Sunflower seeds; Walnuts. Synergistic Nutrients - Vitamin B1, B2, B3, B5, B12, C, E, Biotin, Cr, Cu, B9, Leucine, Mg, K, Phosphate, Se, Na, Zn

B7 - Biotin - Bacterial synthesis in gut; Bean sprouts; Butter; Bulgar wheat; Cashews; Egg yolk; Kidney; Liver; Milk; Oats; Peanuts; Soy beans; Wholegrain cereal; Yeast. Synergistic Nutrients - Bifidobacterium, Cr, Vitamin B2, B3, B5, B6, B12, B9, Mg, Mn

B9 - Folic Acid - Barley; Beans; Eggs; Endive; GLV; Lentils; Liver; Organ meats; Sprouts; Soybeans; Yeast. Synergistic Nutrients - Vitamin B2, B3, B5, B6, B12, C, Biopterin, Biotin, Cu, Fe, Mg, Methionine, Serine, Zn.

B12 - Bacterial synthesis occurs in the gut. Brain; Clams; Egg yolk; Herring; Kidney; Liver wurst; Meat; Milk; Oysters; Salmon; Sardines; Swiss cheese. Synergistic Nutrients - Vitamin A, B1, B2, B5, B6, C, E, Biotin, Ca, Cobalt, Cu, B9, Fe, Methionine, N-Acetyl cysteine, Omega-3, Phosphate, Se.

GLV = green leafy vegetables

Source: Osiecki H (2014) The Nutrient Bible 9th Edition Bio Concepts Publishing Australia; http://www.alfiestrust.com/wp-content/uploads/2017/09/NutrientSourcesVitsMinsAGT.pdf

Thiamine a critical and rate-limiting cofactor to multiple enzymes involved in this process, including those at the entry points

cells

MDPI

Review

Hiding in Plain Sight: Modern Thiamine Deficiency

Chandler Marrs [1,*] **and Derrick Lonsdale** [2]

[1] Independent Researcher, Henderson, NV 89074, USA
[2] Emeritus, Cleveland Clinic, Cleveland, OH 44195, USA; derricklonsdale@hotmail.com
* Correspondence: drchandlermarrs@gmail.com

Abstract: Thiamine or vitamin B1 is an essential, water-soluble vitamin required for mitochondrial energetics—the production of adenosine triphosphate (ATP). It is a critical and rate-limiting cofactor to multiple enzymes involved in this process, including those at the entry points and at critical junctures for the glucose, fatty acid, and amino acid pathways. It has a very short half-life, limited storage capacity, and is susceptible to degradation and depletion by a number of products that epitomize modern life, including environmental and pharmaceutical chemicals. The RDA for thiamine is 1.1–1.2 mg for adult females and males, respectively. With an average diet, even a poor one, it is not difficult to meet that daily requirement, and yet, measurable thiamine deficiency has been observed across multiple patient populations with incidence rates ranging from 20% to over 90% depending upon the study. This suggests that the RDA requirement may be insufficient to meet the demands of modern living. Inasmuch as thiamine deficiency syndromes pose great risk of chronic morbidity, and if left untreated, mortality, a more comprehensive understanding thiamine chemistry, relative to energy production, modern living, and disease, may prove useful.

Keywords: thiamine deficiency; thiamine deficiency metabolic disease; thiamine deficiency hyperglycemia; thiamine deficiency critical illness

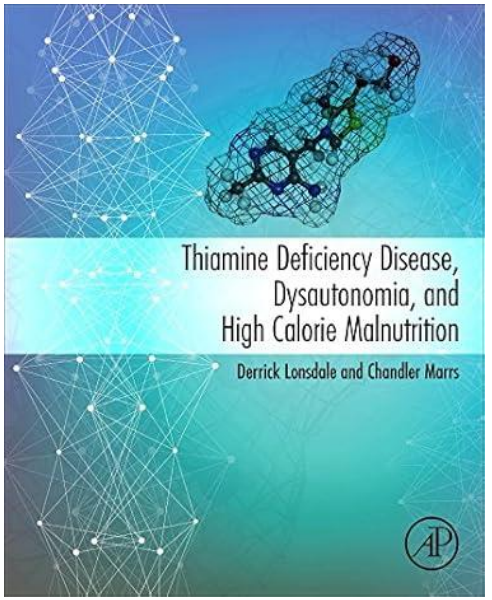
Citation: Marrs, C.; Lonsdale, D. Hiding in Plain Sight: Modern Thiamine Deficiency. *Cells* **2021**, *10*, 2595. https://doi.org/10.3390/cells10102595

Academic Editor: David Sebastián

1. Introduction

"There is often something sinister about familiar concepts. The more familiar or 'natural' they appear, the less we wonder what they mean; but because they are widespread and well-known, we tend to act as if we know what we mean when we use them [1]."

"Thiamine or vitamin B1 is an essential, water-soluble vitamin required for mitochondrial energetics—the production of adenosine triphosphate (ATP). It is a critical and rate-limiting cofactor to multiple enzymes involved in this process, including those at the entry points and at critical junctures for the glucose, fatty acid, and amino acid pathways."



Source: Marrs C, Lonsdale D. Hiding in Plain Sight: Modern Thiamine Deficiency. Cells. 2021 Sep 29;10(10):2595, with thanks to Elliot Overton.

Natural sources of magnesium

Magnesium - Almonds; Barley; Brewer's yeast; Cashews; Cocoa; Cod; Eggs; Figs; Kelp; GLV; Legumes; Lima beans; Mineral water; Molasses; Parsnips; Seeds; Soy beans; Wholegrain cereals. Synergistic Nutrients - Vitamins B1, B6, C, D, Glucose polymer, K, B, Ca. Heavy metal antagonists - Pb, Cd.

Source: 1. : Osiecki H (2014) The Nutrient Bible 9th Edition Bio Concepts Publishing Australia; http://www.alfiestrust.com/wp-content/uploads/2017/09/NutrientSourcesVitsMinsAGT.pdf; 2. *https://www.hsph.harvard.edu/nutritionsource/magnesium/*

Right balance of electrolytes vital in the “metallome” (1/2)

ELSEVIER

Free Radical Biology and Medicine
Volume 182, March 2022, Pages 182-191

Invited Review Article

Mineral requirements for mitochondrial function: A connection to redox balance and cellular differentiation ☆

David W. Killilea [a], Alison N. Killilea [b]

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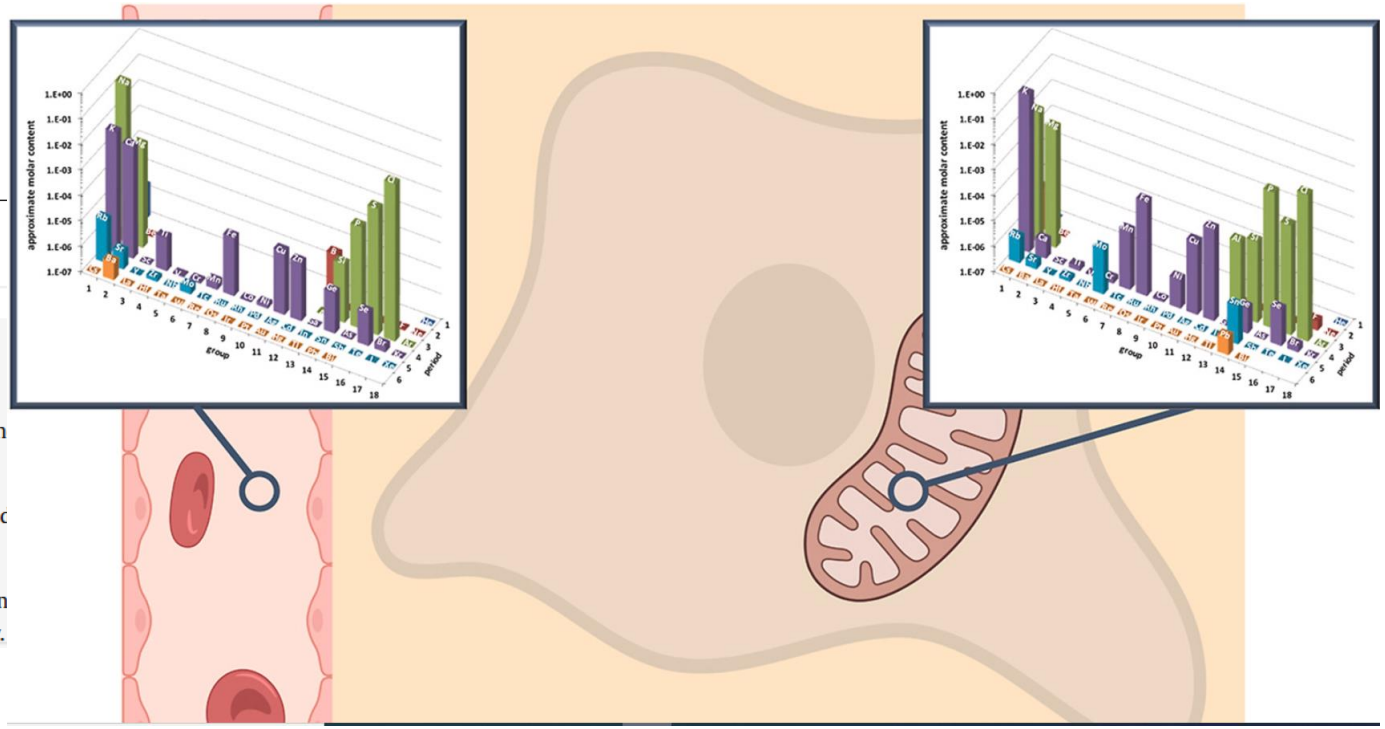
https://doi.org/10.1016/j.freeradbiomed.2022.02.022

Highlights

- Eleven of the 12 minerals essential for human h roles within mitochondrial metabolism.
- Increased oxidative stress within the mitochonc consequence of aberrant mineral homeostasis.
- Low oxidative stress is key for long-lived cell lin mineral levels is important for cellular potency.



Source: https://www.sciencedirect.com/science/article/pii/S0891584922000752

Right balance of electrolytes vital in the “metallome” (2/2)

Table 1. Metals and metalloids known in the mammalian mitochondria.

Element	Serum/plasma concentration	Entry into in mitochondria	Mitochondrial concentration	Sequestration	Metabolic role(s)
Confirmed essential:					
Ca	2.1–2.6 mM	yes	0.1–20 μM	yes	yes
Co	2–8 nM	yes	50–90 nM	yes	yes
Cr	1–31 nM	–	–	–	–
Cu	11–30 μM	yes	71–115 μM	yes	yes
Fe	9–31 μM	yes	0.5–1.1 mM	yes	yes
K	3.5–5.1 mM	yes	150–180 mM	yes	yes
Mg	0.7–1.1 mM	yes	0.4–0.7 mM	yes	yes
Mn	8–18 nM	yes	3–16 μM	yes	yes
Mo	1–31 nM	yes	1–6 μM	yes	yes
Na	136–145 mM	yes	5–50 mM	yes	yes
Se	0.6–1.8 μM	yes	–	–	yes
Zn	11–18 μM	yes	167–300 μM	yes	yes

Source: https://www.sciencedirect.com/science/article/pii/S0891584922000752

Thyroid hormone, T3, stimulates mitochondrial metabolism

Important to do a thyroid panel

cells

MDPI

Review

Bioenergetic Aspects of Mitochondrial Actions of Thyroid Hormones

Federica Cioffi †, Antonia Giacco †, Fernando Goglia and Elena Silvestri *

Department of Science and Technology, University of Sannio, federica.cioffi@unisannio.it (F.C.); antonia.giacco@unisannio.i
* Correspondence: silvestri@unisannio.it; Tel.: +39-082-430-5
† These authors contributed equally to the work.

Abstract: Much is known, but there is also much mor hormones (TH) exert on metabolism. Indeed, despite tl as one of the most important regulators of metabolic mechanisms control/regulate these actions. Given th mitochondria are the main cellular site where metaboli have been the subject of extensive investigations. In cerning both thyroid hormones (such as the mechani active TH derivatives) and the mechanisms of energy ics, respiratory chain organization in supercomplexes pathways of investigation in the field of the control of of action of TH at cellular level. In this review, we high the complex relationship between TH, including some respiratory chain.

Keywords: iodothyronines; bioenergetics; mitochondri

Citation: Cioffi, F.; Giacco, A.; Goglia, F.; Silvestri, E. Bioenergetic Aspects of Mitochondrial Actions of Thyroid Hormones. *Cells* **2022**, *11*, 997. https://doi.org/10.3390/cells11060997

1. Introduction

1.1. Respiratory Chain, Oxidative Phosphorylation

The oxidative phosphorylation system (OXPH

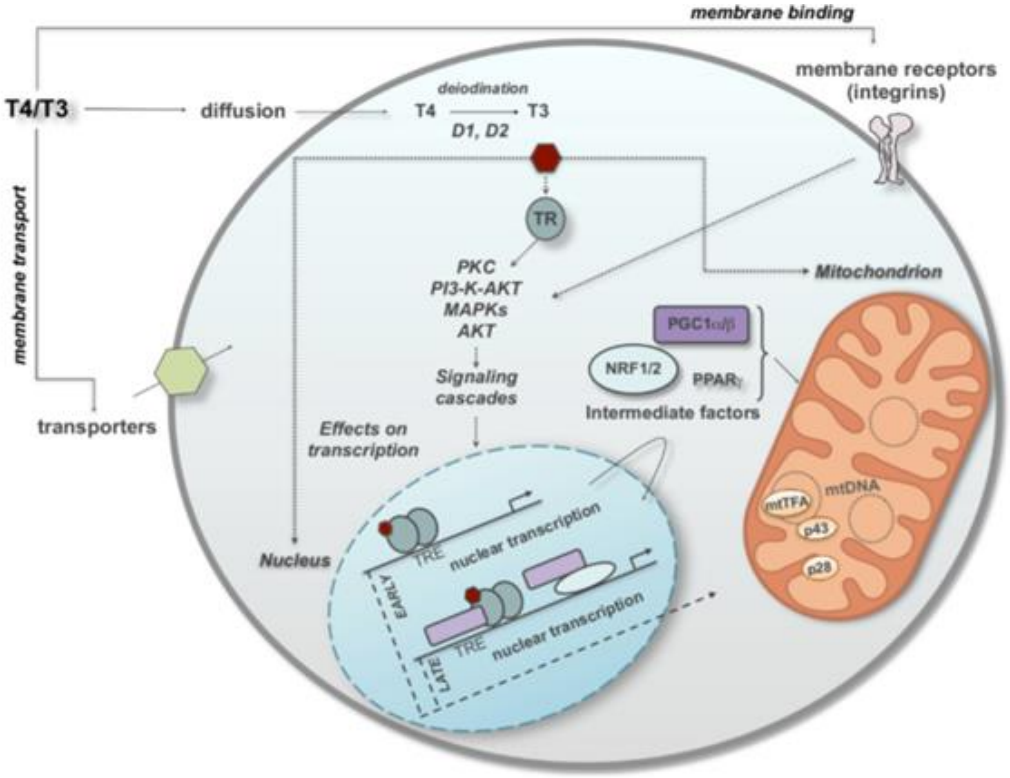


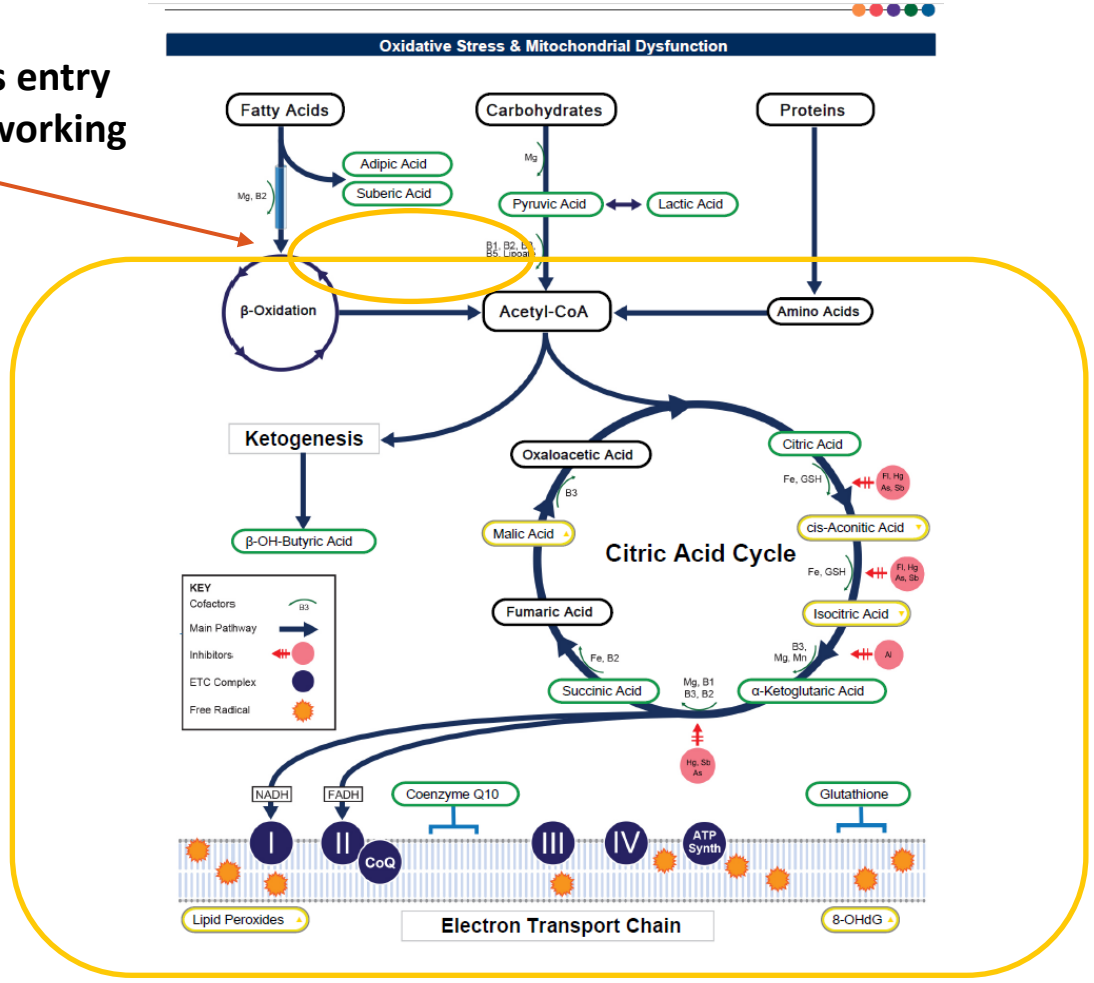
Figure 1. Schematic summary of the main cellular pathways through which TH regulate mitochondrial functions. TH (T4/T3) move from outside the plasma membrane into the cytoplasm (trough passive diffusion or active transport) or bind to surface receptor such as integrin αvb3. In the cytoplasm, deiodination allows the conversion of T4 into T3 by DIO1 or DIO2 action, and T3 can bind

Source: Chocron ES et al. The trifunctional protein mediates thyroid hormone receptor-dependent stimulation of mitochondria metabolism. Mol Endocrinol. 2012 Jul;26(7):1117-28; Cioffi F, Giacco A et al. Bioenergetic Aspects of Mitochondrial Actions of Thyroid Hormones. Cells. 2022 Mar 15;11(6):997.

If mitochondrial ATP capacity on the ATP profile is stronger: fatty acids are getting in

Mitochondrial ATP capacity	1.33	fmol/cell	84
Glycolytic ATP capacity	1.12	fmol/cell	70

Then this entry point is working better



There are however mitochondrial fatty acid oxidation disorders (FAODs) (inherited metabolic diseases) that affect the transport of fatty acids into mitochondria:

- **Carnitine transporter defect**
- **Carnitine-acylcarnitine translocase (CACT) deficiency**
- **LCHAD deficiency**
- **Etc.**

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Agenda

- What pathways may have become compromised?
- ATP Profile
- **Mitochondrial Health Index**
- Lactate/Pyruvate Index

Mitochondrial Health Index: mitochondrial performance under pressure; top page

Requisition:Mitochondrial Health Index / PBMCs

Sample type: Blood in CPDA vials

Summary

	Patient´s value	Target value (optimal)
Mitochondrial Health Index (MHI)	0.00	>2.5
Mitochondrial Bioenergetics		
Coupling efficiency, %	86	90-95
Reserve respiration capacity, %	0	>400
Cellular oxygen consumption profile		
Non-mitochondrial respiration as a share of total respiration, %	32	<10
Proton leak as a share of total respiration, %	10	5-10
Share of respiration used for mitochondrial ATP generation, %	58	>90
ATP turnover rate (mitochondrial oxygen utilisation)		
ATP base turnover, %	100	<20
ATP reserve, %	0	>80
Basal oxygen consumption rate in pmol oxygen/min	28.75	
Potential maximum oxygen consumption rate in pmol oxygen/min	22	>500
Cellular energy phenotype		
At rest	Resting	Resting
On energy demand	Resting	Energetic/Aerobic
Metabolic potential, mitochondrial percentage	84	>350
Metabolic potential, glycolysis percentage	151	>350
Oxygen consumption/glycolysis on energy demand	Strong preference for anaerobic glycolysis	

Optimal	Slightly high / low	Moderately high/low	Very high/low	Extremely high/low

Second page of the MHI, with a summary derived from the markers

	None	Slight	Moderate	Considerable	Extreme
Mitochondrial dysfunction					√
Cellular imbalance				√	

Indications of					
Increased formation of oxygen radicals in the cell	√	No Yes	Insufficient ATP formation on energy demand	√	No Yes
Increased formation of oxygen radicals in the mitochondria	✓	No Yes	Limited glucose utilisation		No Yes
Restricted function of the electron transport chain in the mitochondria	√	No Yes	Limited fatty acid oxidation		No Yes
Limited number of functionally intact mitochondria	√	No Yes	Acute inflammation, active chronic inflammation/ autoimmune disease	✓	No Yes

Further diagnostic opportunities for personalised therapy

Investigate minerals and further mitochondrial cofactors
Investigate mitochondrial mass (mtDNA:nDNA/number of mitochondria) and analyse mitochondrial mutations that influence ATP generation (e.g., the common deletion mt4977bp).

- **Upregulated ROS in the cells**
- **Compromised function of the electron transport chain**
- **Limited no. of functionally intact mitochondria**
- **Insufficient ATP on demand**

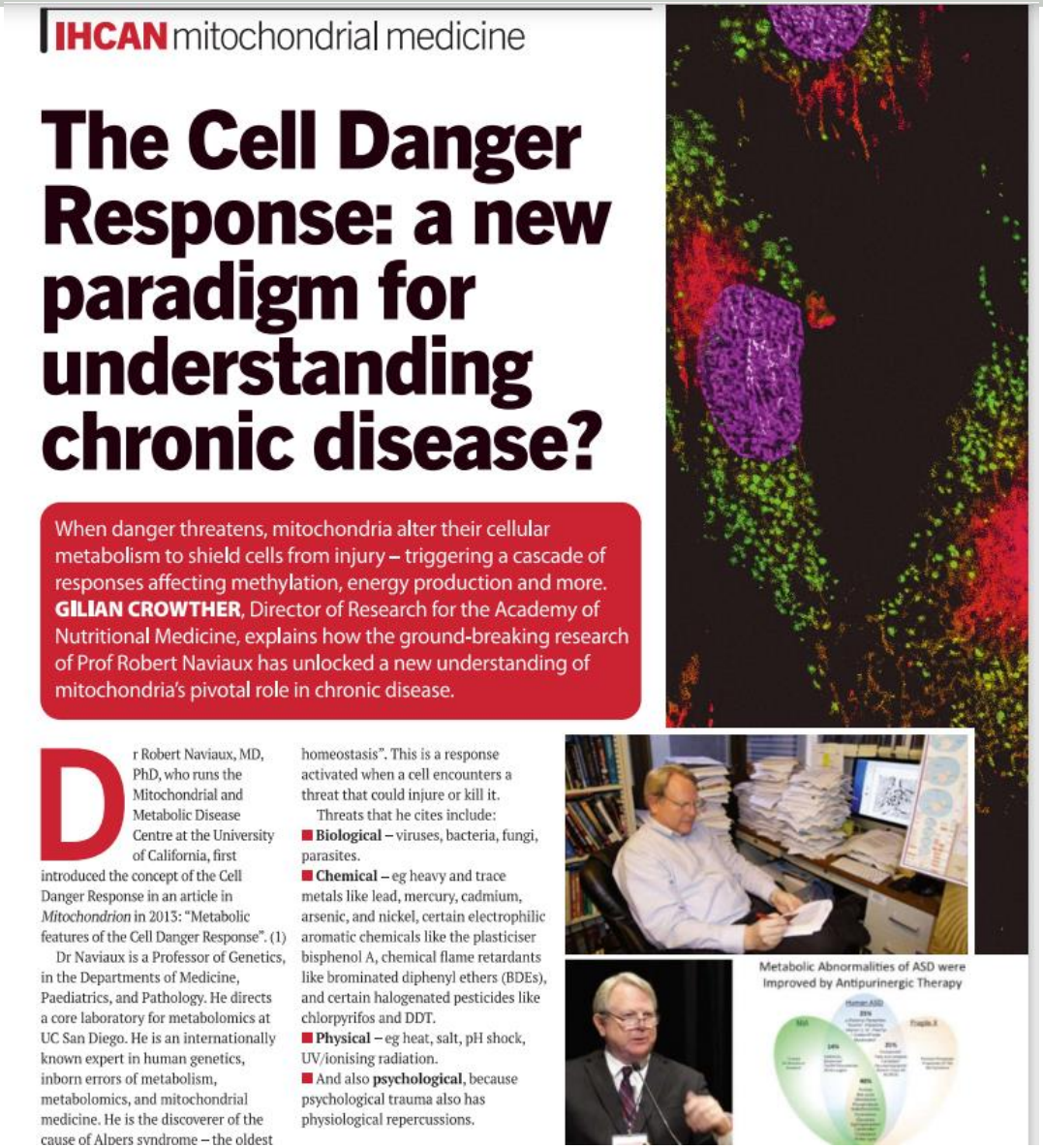
Downregulation of the mitochondria always worth considering: the CDR – a protective mechanism

Dr. Robert Naviaux, who runs The Mitochondrial and Metabolic Disease Center at the University of California, introduced the concept of the Cell Danger Response in an article in Mitochondrion in 2013: "The cell danger response (CDR) is the evolutionarily conserved metabolic response that protects cells and hosts from harm. It is triggered by encounters with chemical, physical, or biological threats that exceed the cellular capacity for homeostasis."

Threats are for example:

- **Biological** – viruses, bacteria, fungi, parasites
- **Chemical** – e.g. heavy and trace metals like lead, mercury, cadmium, arsenic, and nickel, certain electrophilic aromatic chemicals like the plasticizer bisphenol A, chemical flame retardants like brominated diphenyl ethers (BDEs), and certain halogenated pesticides like chlorpyrifos and DDT.
- Physical – e.g. heat, salt, pH shock, UV/ionising radiation
- And also psychological, because psychological trauma also has phyiological repercussions

When danger is detected, mitochondria alter their cellular metabolism to shield the cell from further injury. They downregulate as a protective mechanism.



IHCAN mitochondrial medicine

The Cell Danger Response: a new paradigm for understanding chronic disease?

When danger threatens, mitochondria alter their cellular metabolism to shield cells from injury – triggering a cascade of responses affecting methylation, energy production and more. **GILIAN CROWTHER**, Director of Research for the Academy of Nutritional Medicine, explains how the ground-breaking research of Prof Robert Naviaux has unlocked a new understanding of mitochondria's pivotal role in chronic disease.

Dr Robert Naviaux, MD, PhD, who runs the Mitochondrial and Metabolic Disease Centre at the University of California, first introduced the concept of the Cell Danger Response in an article in *Mitochondrion* in 2013: "Metabolic features of the Cell Danger Response". (1)

Dr Naviaux is a Professor of Genetics, in the Departments of Medicine, Paediatrics, and Pathology. He directs a core laboratory for metabolomics at UC San Diego. He is an internationally known expert in human genetics, inborn errors of metabolism, metabolomics, and mitochondrial medicine. He is the discoverer of the cause of Alpers syndrome – the oldest

homeostasis". This is a response activated when a cell encounters a threat that could injure or kill it.

Threats that he cites include:

- **Biological** – viruses, bacteria, fungi, parasites.
- **Chemical** – eg heavy and trace metals like lead, mercury, cadmium, arsenic, and nickel, certain electrophilic aromatic chemicals like the plasticiser bisphenol A, chemical flame retardants like brominated diphenyl ethers (BDEs), and certain halogenated pesticides like chlorpyrifos and DDT.
- **Physical** – eg heat, salt, pH shock, UV/ionising radiation.
- And also **psychological**, because psychological trauma also has physiological repercussions.

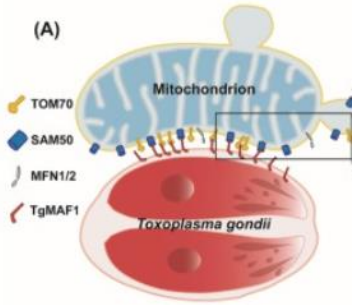
Source: *Naviaux RK. Metabolic features of the Cell Danger Response. Mitochondrion. 2014 May;16:7-17*
https://www.ihcan-mag.com/imag/aonm.pdf

Many pathogens/contaminants can prevent mitochondria from using their oxidative phosphorylation

Address, or at least log as key influencing factors:

Address the "Removes"

- Viral/bacterial infections: These increase non-mitochondrial respiration because the cell uses oxygen to try to kill the pathogens rather than for energy[1]; deplete the host's mitochondrial anti-viral defences to keep themselves alive[2]; Borrelia also steal ATP from their host to fuel their flagellum, etc.[3]
- Biotoxins/mycotoxins: Ochratoxin A uncouples the mitochondria and inhibits Complex 2[4]
- Some parasites: E.g. Toxoplasma, which can tether and disable mitochondria[5]



- Heavy metals: Al induces permeability (MPT)[6], Hg induces mito dysfunction[7], Arsenic increases mitochondrial ROS formation, lipid peroxidation and mitochondrial membrane potential collapse[8]
- Pesticides, herbicides: e.g. glyphosate: blocks Shikimate pathway: bacterial energy generation,[9] it also chelates minerals, including copper …
- Chemical contaminants: e.g. Lindane[10]
- Household chemicals
- EMFs
- Medications: Block various ETC complexes
- Microbiome
- Spike protein

Source: 1. Naviaux RK. Metabolic features of the Cell Danger Response. Mitochondrion. 2014 May;16:7-17; 2. https://www.nature.com/ articles/s12276-021-00602-1; 3. https://pubmed.ncbi.nlm.nih.gov/22710875/; 4. https://pubmed.ncbi.nlm.nih.gov/5441684/; 5. https://www.sciencedirect.com/science/article/ pii/S1471492222000320; 6. https://link.springer.com/article/10.1007/s007750000144; 7. https://link.springer.com/chapter/10.1007/978-3-319-03777-6_1; 8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3813354/; 9. https://roundupprisks.com/2016/04/09/glyphosate-and-mitochondrial-dysfunction/; 10. https://europepmc.org/article/MED/6205709

Viral remnants from SARS-CoV-2 as well as the spike protein have been shown to downregulate the mitochondria

Source: SARS-CoV-2-Research Aug 02, 2021 1 year ago

BREAKING! German Researchers Discover That SARS-CoV-2 Virus Proteins Manipulate Autophagy In Human Host Cells

NEWS / CORONAVIRUS

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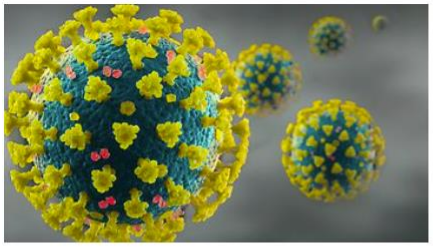
BREAKING! German Researchers Discover That SARS-CoV-2 Virus Proteins Manipulate Autophagy In Human Host Cells

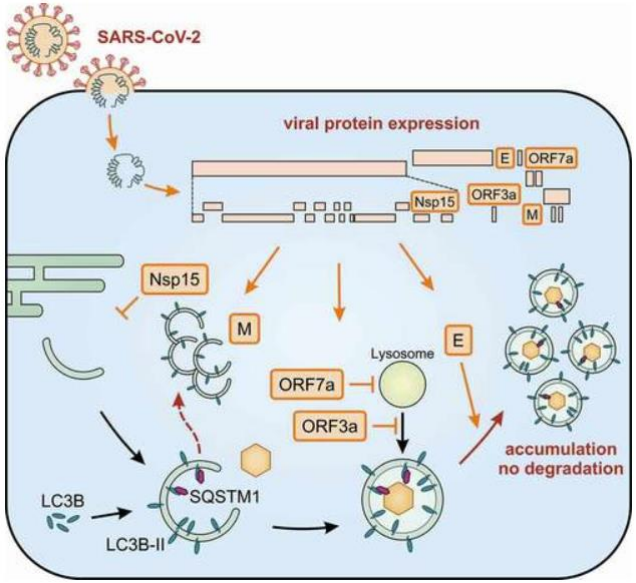
Source: SARS-CoV-2-Research Aug 02, 2021 1 year ago



In a new study by researchers from the Institute of Molecular Virology, Ulm University Medical Center-Germany, it was found that the SARS-CoV-2 coronavirus was able to manipulate autophagy in the human host.

A key and critical component of the innate immune defenses, macroautophagy/autophagy targets viruses and viral components for lysosomal degradation and exposes pathogen-associated molecular patterns to facilitate recognition.

However, it has been found that certain viruses evolved sophisticated strategies to antagonize **autophagy** and even exploit it to promote their replication.



Source: Koepke L, Hirschenberger M, Hayn M, Kirchhoff F, Sparrer KM. Manipulation of autophagy by SARS-CoV-2 proteins. Autophagy. 2021 Sep;17(9):2659-2661, https://www.tandfonline.com/doi/full/10.1080/15548627.2021.1953847, https://www.thailandmedical.news/news/breaking-german-researchers-discover-that-sars-cov-2-virus-proteins-manipulate-autophagy-in-human-host-cells

B vitamins vital throughout the entire cycle ...

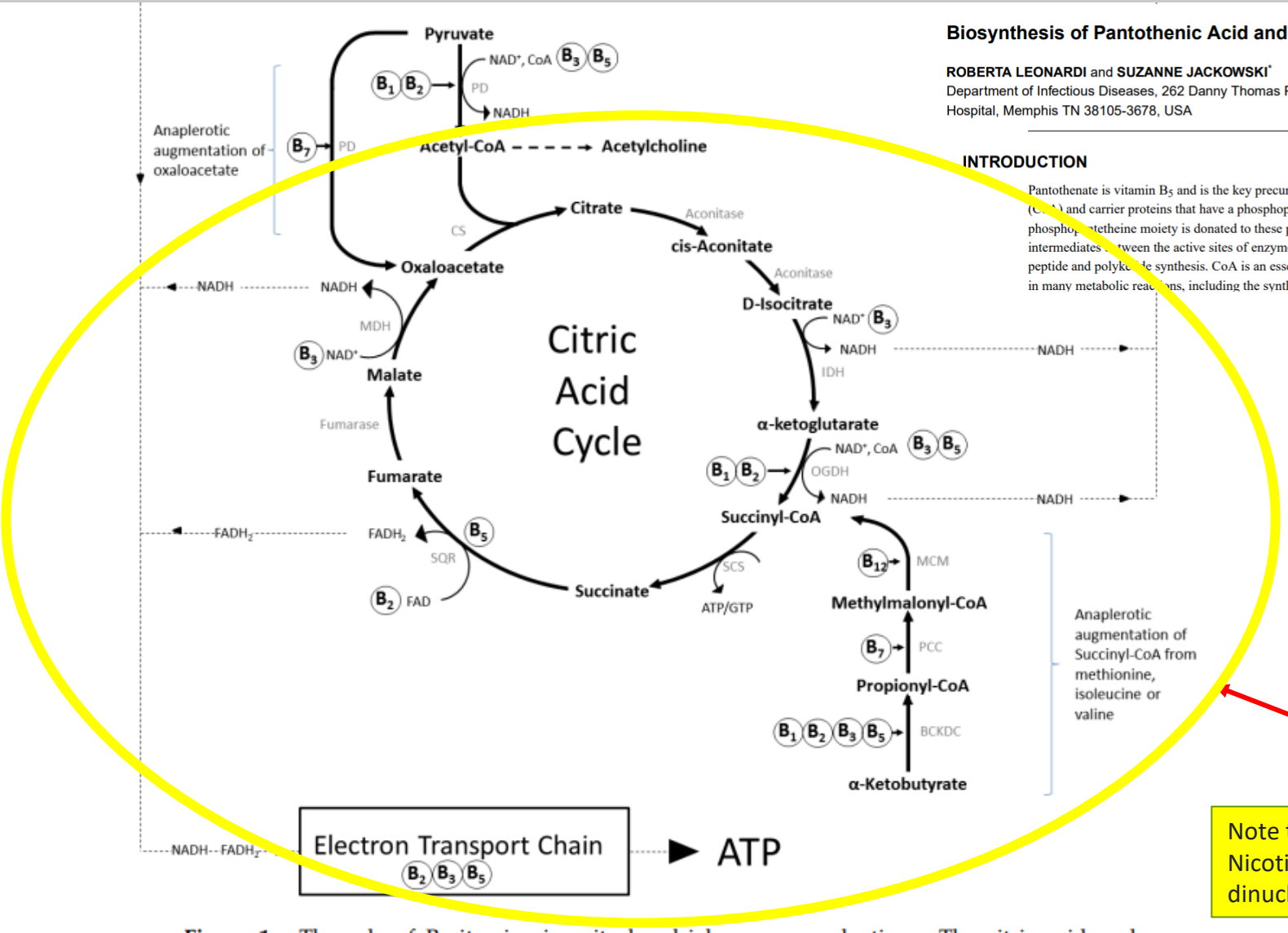


Figure 1. The role of B-vitamins in mitochondrial energy production. The citric acid cycle

Biosynthesis of Pantothenic Acid and Coenzyme A

ROBERTA LEONARDI and **SUZANNE JACKOWSKI***
Department of Infectious Diseases, 262 Danny Thomas Place, St. Jude Children's Research Hospital, Memphis TN 38105-3678, USA

INTRODUCTION

Pantothenate is vitamin B_5 and is the key precursor for the biosynthesis of coenzyme A (CoA) and carrier proteins that have a phosphopantetheine prosthetic group. The phosphopantetheine moiety is donated to these proteins by CoA and is used to shuttle intermediates between the active sites of enzymes involved in fatty acid, non-ribosomal peptide and polyketide synthesis. CoA is an essential cofactor for cell growth and is involved in many metabolic reactions, including the synthesis of phospholipids, synthesis and

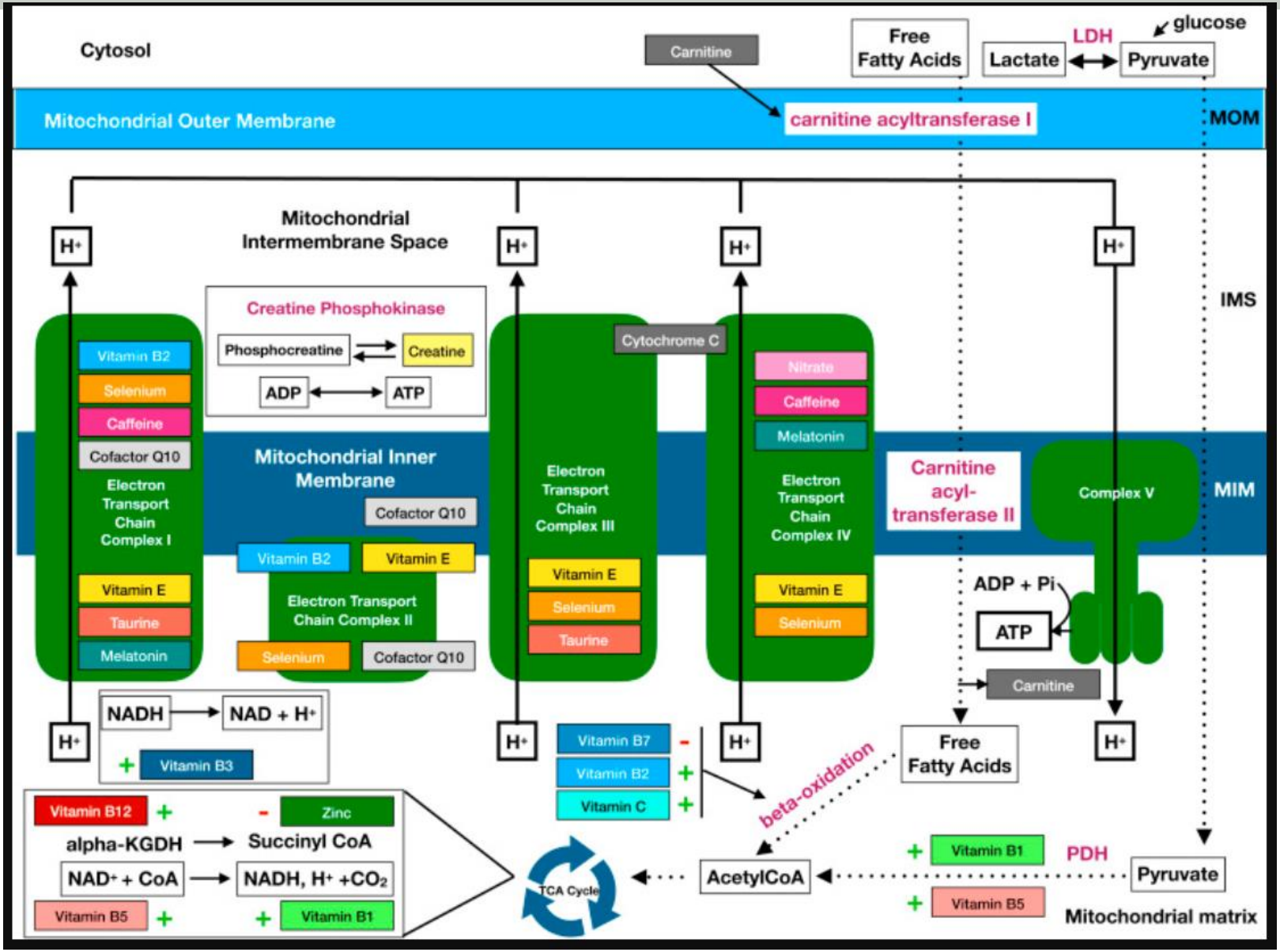
B1
B2
B3
B5
B7 (Biotin)
B12

Mitochondrion

Note the huge role of Nicotinamide adenine dinucleotide (NAD)

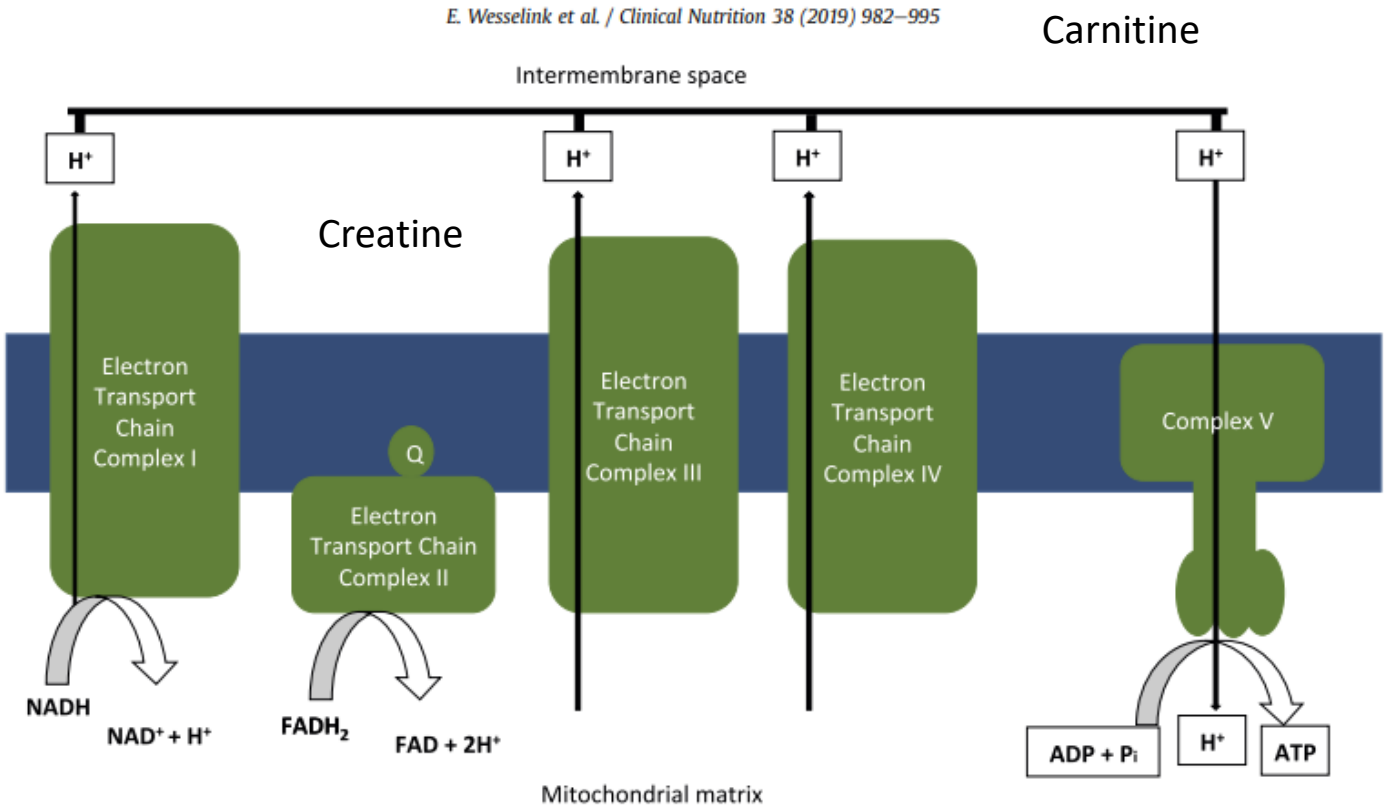
Source: https://www.mdpi.com/2072-6643/8/2/68; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4950986/

Vitamins and cofactors required along the electron transport chain according to comprehensive study



Source: *Wesselink E, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin Nutr. 2019 Jun;38(3):982-995, https://pubmed.ncbi.nlm.nih.gov/30201141/*

Summary of many of the nutrients mentioned in the previous study (Wesselink et al) ...



Complex 1: B12, Se, CoQ10, Vit E, Taurine, melatonin

Complex 2: B2, Vit E (α,-tocopherol), Se, CoQ10

Complex 3: Vit E, Se, Taurine

Complex 4: Melatonin, tocopherol, selenium (Se)

Complex 5: Mg

Source: *Wesselink E, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin Nutr. 2019 Jun;38(3):982-995; Yamanaka, R. et al. (2016). Mitochondrial Mg(2+) homeostasis decides cellular energy metabolism and vulnerability to stress. Scientific reports, 6, 30027. https://doi.org/10.1038/srep30027*

CoQ10 is critical to electron transport

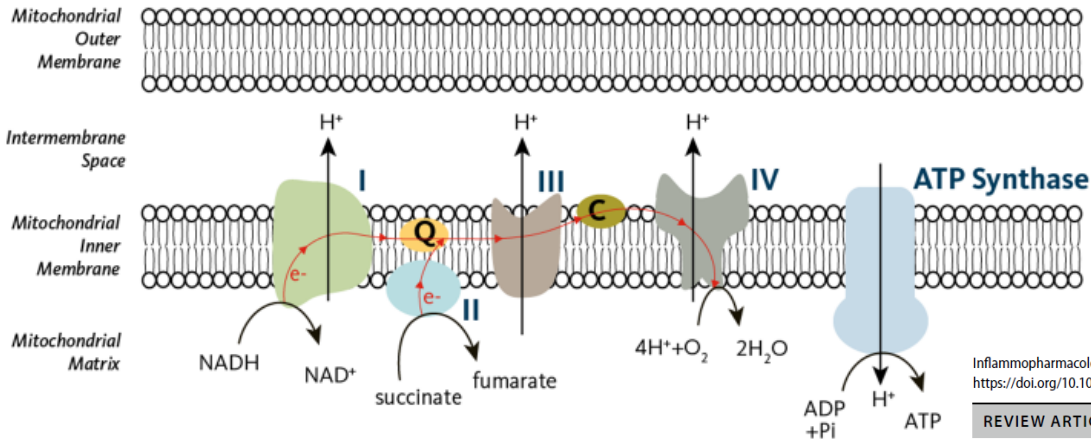
Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Reversal of mitochondrial dysfunction by coenzyme Q10 supplement improves endothelial function in patients with ischaemic left ventricular systolic dysfunction: A randomized controlled trial

Yuk-Ling Dai[a], Ting-Hin Luk[a], Kai-Hang Yiu[a], Mei Wang[a], Pandora M.C. Yip[a], Stephen W.L. Lee[a], Sheung-Wai Li[c], Sidney Tam[d], Bonnie Fong[d], Chu-Pak Lau[a], Chung-Wah Siu[a,b], Hung-Fat Tse[a,b,*]



Coenzyme Q_{10} is a lipid-soluble component of the mitochondrial inner membrane that is critical to electron transport (in red) in the mitochondrial respiratory chain. Coenzyme Q_{10} carries electrons from complexes I and II to complex III, thus participating in ATP production. *C, cytochrome C; e-, electron; H+, proton; Q, coenzyme Q_{10}.*

The Effect of Coenzyme Q_{10} on Morbidity and Mortality in Chronic Heart Failure

Results From Q-SYMBIO: A Randomized Double-Blind Trial

Svend A. Mortensen, MD, DSc,* Franklin Rosenfeldt, MD,† Adarsh Kumar, MD, PhD,‡ Peter Dolliner, MD,§ Krzysztof J. Filipiak, MD, PhD,‖ Daniel Pella, MD, PhD,¶ Urban Alehagen, MD, PhD,# Günter Steurer, MD,§ Gian P. Littarru, MD,** for the Q-SYMBIO Study Investigators

ABSTRACT

OBJECTIVES This randomized controlled multicenter trial evaluated coenzyme Q_{10} (CoQ_{10}) as adjunctive treatment in chronic heart failure (HF).

BACKGROUND CoQ_{10} is an essential cofactor for energy production and is also a powerful antioxidant. A low level of myocardial CoQ_{10} is related to the severity of HF. Previous randomized controlled trials of CoQ_{10} in HF were under-powered to address major clinical endpoints.

METHODS Patients with moderate to severe HF were randomly assigned in a 2-year prospective trial to either CoQ_{10} 100 mg 3 times daily or placebo, in addition to standard therapy. The primary short-term endpoints at 16 weeks were changes in New York Heart Association (NYHA) functional classification, 6-min walk test, and levels of N-terminal pro-B type natriuretic peptide. The primary long-term endpoint at 2 years was composite major adverse cardiovascular events as determined by a time to first event analysis.

Inflammopharmacology (2019) 27:233–248
https://doi.org/10.1007/s10787-019-00572-x

Inflammopharmacology

REVIEW ARTICLE

The effects of coenzyme Q10 supplementation on biomarkers of inflammation and oxidative stress in among coronary artery disease: a systematic review and meta-analysis of randomized controlled trials

Mohammad Vahid Jorat[1] · Reza Tabrizi[2] · Fariba Kolahdooz[3] · Maryam Akbari[2] · Maryamalsadat Salami[4] · Seyed Taghi Heydari[5] · Zatollah Asemi[6]

Received: 2 November 2018 / Accepted: 1 February 2019 / Published online: 13 February 2019

Source: https://lpi.oregonstate.edu/mic/dietary-factors/coenzyme-Q10; https://www.sciencedirect.com/science/article/pii/ S0005272816300573

Food sources of CoQ10; if a supplement: ubiquone or ubiquinol – does it matter?

The highest level of CoQ_{10} is found in heart meat, and significant amounts are found in cold water fish, beef, pork, chicken and nuts. About 10 percent of daily CoQ_{10} requirements can be obtained by eating 12 ounces of beef or pork heart, two pounds of sardines or mackerel, three pounds of beef or pork, or four pounds of peanuts. Milk, eggs, and most grains and vegetables contain small amounts of CoQ_{10} [1, 2]

The miracle of CoQ10

Ubiquinone or ubiquinol - does it matter?

Ubiquinol is the reduced form of ubiquinone. Much has been made of the need to take the reduced form over recent years, but how much does it actually matter? Both ubiquinone and ubiquinol are lipid soluble due to the presence of the 10-unit isoprene tail. They act as a redox pair where the conversion of one form to the other can be readily achieved depending on when and where their functions are needed in the body. For example, tissues that involve high aerobic activity contain more of the oxidised form (ubiquinone) than the reduced form. In blood circulation, around 95% of CoQ10 is present in the ubiquinol form. Exogenous CoQ10 is absorbed in the small intestine and enters the circulation via the lymphatic system. Before absorption, CoQ10 is converted to the reduced form ubiquinol by the enterocytes.

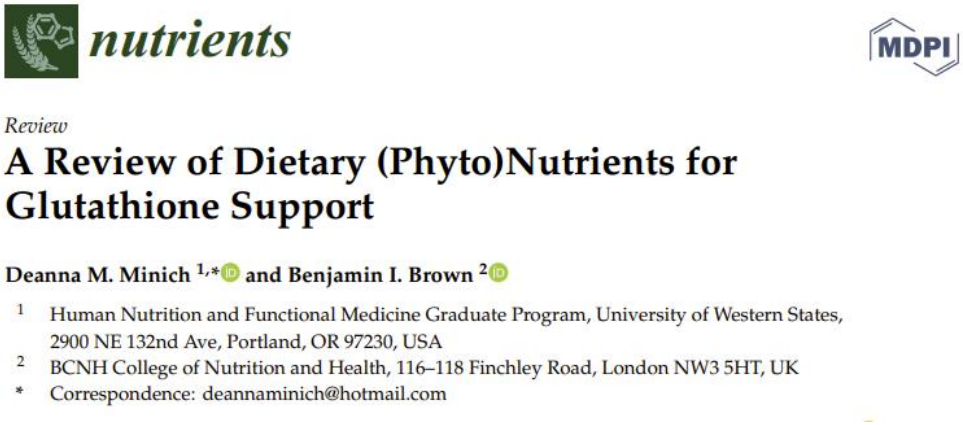
So, when taken orally, there is no great difference between the two: what counts is bioavailability. Q10 is hydrophobic, so its absorption in the GI tract is suboptimal. Fine

Source: 1. https://www.westonaprice.org/health-topics/coenzyme-q10-for-healthy-hearts/#gsc.tab=0; 2. Weber C. et al, The coenzyme Q_{10} content of the average Danish diet. *Int J Vitam Nutr Res*. 1997: 67: 123-129; 3. Only Natural, Issue 32, Summer 2019, fully referenced *(please request from Gilian)*

Glutathione our key intracellular antioxidant – crucial for the mitochondria

By evaluating levels of GSH and GSSG, as well as the GSH/GSSG ratio in blood, one can get a glimpse into the degree of mitochondrial dysfunction at a tissue level. An increased GSSG:GSH ratio is an indication of oxidative stress.

Glutathione, free (GSH)		185 mg/l	150 - 460	[*.....]
Glutathione, total		380 mg/l		
Glutathione, oxidized	**+**	**195 mg/l**	**15 - 90**	**[..... *>**



nutrients

MDPI

Review

A Review of Dietary (Phyto)Nutrients for Glutathione Support

Deanna M. Minich [1,*] and Benjamin I. Brown [2]

[1] Human Nutrition and Functional Medicine Graduate Program, University of Western States, 2900 NE 132nd Ave, Portland, OR 97230, USA
[2] BCNH College of Nutrition and Health, 116–118 Finchley Road, London NW3 5HT, UK
* Correspondence: deannaminich@hotmail.com

"… recent research suggests that when glutathione is administered in liposomal or sublingual forms it may be made more bioavailable and favorably impact systemic glutathione levels.[1]"

Source: 1. Minich DM, Brown BI. A Review of Dietary (Phyto)Nutrients for Glutathione Support. Nutrients. 2019 Sep 3;11(9):2073; Enns GM, Cowan TM. Glutathione as a Redox Biomarker in Mitochondrial Disease-Implications for Therapy. J Clin Med. 2017 May 3;6(5):50.

Support of glutathione from food sources

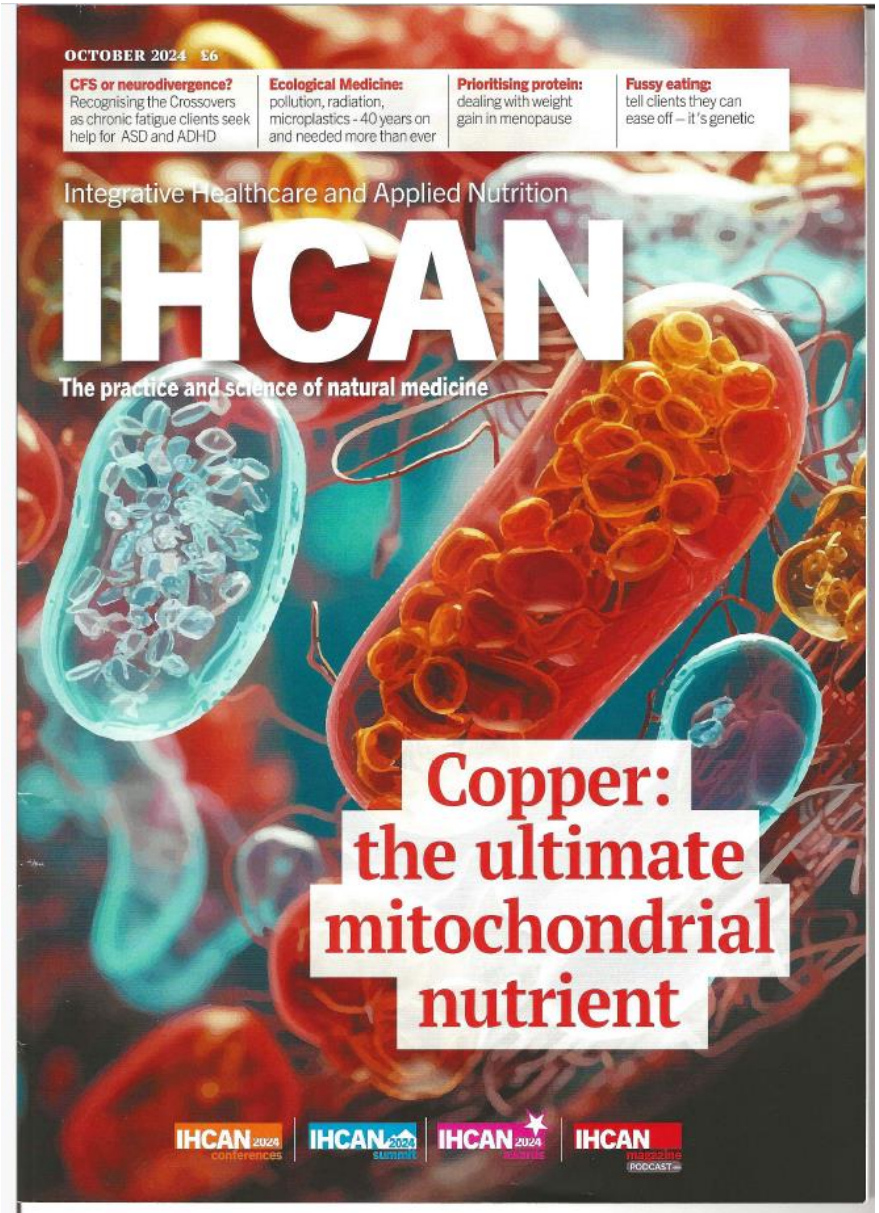
Multi-component dietary interventions specifically designed to enhance glutathione status represent an exciting opportunity for clinical medicine and future research.

Table 4. Summary of nutrients and foods for support of glutathione levels.

Nutrient and Foods	Recommended Dosage
Alpha lipoic-acid	300 mg 3× day; 200–600 mg/day [158]
Brassica vegetables	250 g/day
Curcumin	Doses up to 12 g/day safe; 1–2 g/day found to benefit antioxidant capacity; increased bioavailability with piperine [159]
Fruit and vegetable juices	300–400 mL/day
Glutathione (Liposomal)	500–1000 mg/day [43]
Glutathione (Oral)	500–1000 mg/day [41,42]
Glycine	100 mg/kg/day [63]
Green tea	4 cups/day
N-acetylcysteine	600–1200 mg/day in divided doses, but up to 6000 mg/day have been shown effective in studies [30,53,56,160]
Omega-3 fatty acids	4000 mg/day [76]
Salmon	150 g twice a week [80]
Selenium	247 µg/day of selenium enriched yeast; 100–200 ug/day. Anything above 400 ug/day watch for toxicity [103,160]
Vitamin C	500–2000 mg/day [87,88]
Vitamin E	100–400 IU/day [77,91]
Whey Protein	40 g/day [72]

Source: Minich DM, Brown BI. A Review of Dietary (Phyto)Nutrients for Glutathione Support. Nutrients. 2019 Sep 3;11(9):2073;

... often forgotten: bioavailable copper



Energy pathway is copper dependent

• "Copper is essential for life processes like energy metabolism, reactive oxygen species detoxification, iron uptake, and signalling in eukaryotic organisms.

"Mitochondria gather copper for the assembly of cuproenzymes such as the respiratory complex IV, cytochrome c oxidase, and the antioxidant enzyme superoxide dismutase. In this regard, copper plays a role in mitochondrial function and signalling involving bioenergetics, dynamics and mitophagy, which affect cell fate by means of metabolic reprogramming" (2).*

The proper assembly and functioning of the ETC [electron transport chain] is copper dependent.

* "Role of Copper on Mitochondrial Function and Metabolism" 2021 https://www.frontiersin.org/articles/10.3389/fmolb.2021.711227/full.

Bioavailable copper vital to numerous cellular processes

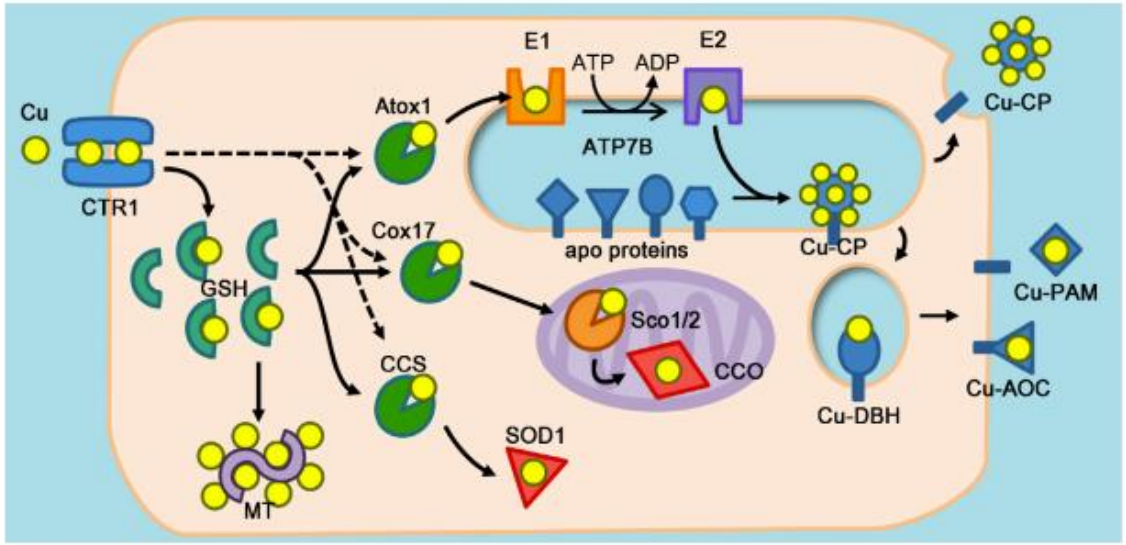


Figure 1. Major routes of intracellular copper trafficking. Copper (yellow spheres) enters the cell via the copper importer CTR1, located at the plasma membrane, and binds to thiol metabolites including glutathione (GSH). At least three different cytosolic copper chaperones (Atox1, Cox17, CCS) compete for Cu-GSH pool and sort Cu to specific destinations. Excess copper is stored as a Cu-metallothionein (MT) complex. Arrows represent the routes of intracellular copper trafficking. Alternative routes (direct transfer from CTR1 to copper chaperones) are indicated by dashed arrows. Cu-Atox1 transfers copper to the copper transporting ATPases (ATP7A and ATP7B) located in the membranes of trans-Golgi network (TGN) and secretory vesicles. ATP7B undergoes ATP-dependent conformational change from a Cu-bound state (E1) into a low affinity state (E2). Copper dissociates into lumen where it is incorporated into various copper-dependent enzymes including ceruloplasmin (CP), dopamine β-hydroxylase (DBH), peptidylglycine α-amidating monooxygenase (PAM), and other oxidoreductases.

"Copper is the major redox-active element in most biological systems. As a redox catalyst, copper is utilized in many essential cellular processes including energy production by the respiratory chain … Inadequate copper supply results in numerous metabolic defects"

Source: Hatori Y, Lutsenko S. The Role of Copper Chaperone Atox1 in Coupling Redox Homeostasis to Intracellular Copper Distribution. Antioxidants (Basel). 2016 Jul 27;5(3):25.

Caeruloplasmin the carrier of bioavailable copper into the cells: barely ever included in blood results

Biol Trace Elem Res (2008) 123:261–269
DOI 10.1007/s12011-008-8110-2

Ceruloplasmin, an Indicator of Copper Status

Miguel Arredondo · Mauricio González · Manuel Olivares · Fernando Pizarro · Magdalena Araya

Received: 13 December 2007 / Accepted: 24 January 2008 /
Published online: 13 February 2008

Abstract For clinical purposes, the non-ceruloplasmin copper fraction is routinely derived on the basis that ceruloplasmin binds six Cu atoms. However, this approach is limited because the actual ceruloplasmin copper binding is unclear. We performed direct measurement of the total serum copper and ceruloplasmin in 790 healthy individuals. We used an immunoprecipitation technique to separate ceruloplasmin and determined Cu content. With these values, we calculated the Cu/ceruloplasmin (Cp) ratio and thus generated data to support or discard the theoretical calculation of the non-ceruloplasmin fraction. Average of serum Cu and Cp levels were 18.4±4.4 μmol/l and 390±100 mg/l, respectively. The immunoprecipitation procedure allowed us to calculate a Cu/Cp ratio of 5.8, respectively, which supports the methodology of calculation that assigns a mean of six copper atoms to each ceruloplasmin molecule. With these values, we calculated that, in apparently normal adults, the non-ceruloplasmin copper (NCPC) fraction is lower than 1.3 μmol/l of Cu. In this report, we examine the Cp/Cu ratio by using Cp immunoprecipitation procedure. Our in vitro and in vivo studies indicate that, as a mean, there are 5.8 atoms of Cu per Cp molecule and that <1.3 μmol/l of Cu would correspond to the NCPC.

Keywords Ceruloplasmin · Copper · Non-ceruloplasmin copper

Abbreviations

Cp	Ceruloplasmin
Cu	copper
NCPC	non-ceruloplasmin copper

So often low when measured:

Ceruloplasmin	0.15	g/L	0.15 - 0.30

Source: Arredondo M, González M, Olivares M, Pizarro F, Araya M. Ceruloplasmin, an indicator of copper status. Biol Trace Elem Res. 2008 Summer;123(1-3):261-9.

The Cu-Cp-retinol link connects with blocks along the complexes, too: most mitochondrial proteins are Cu-dependent

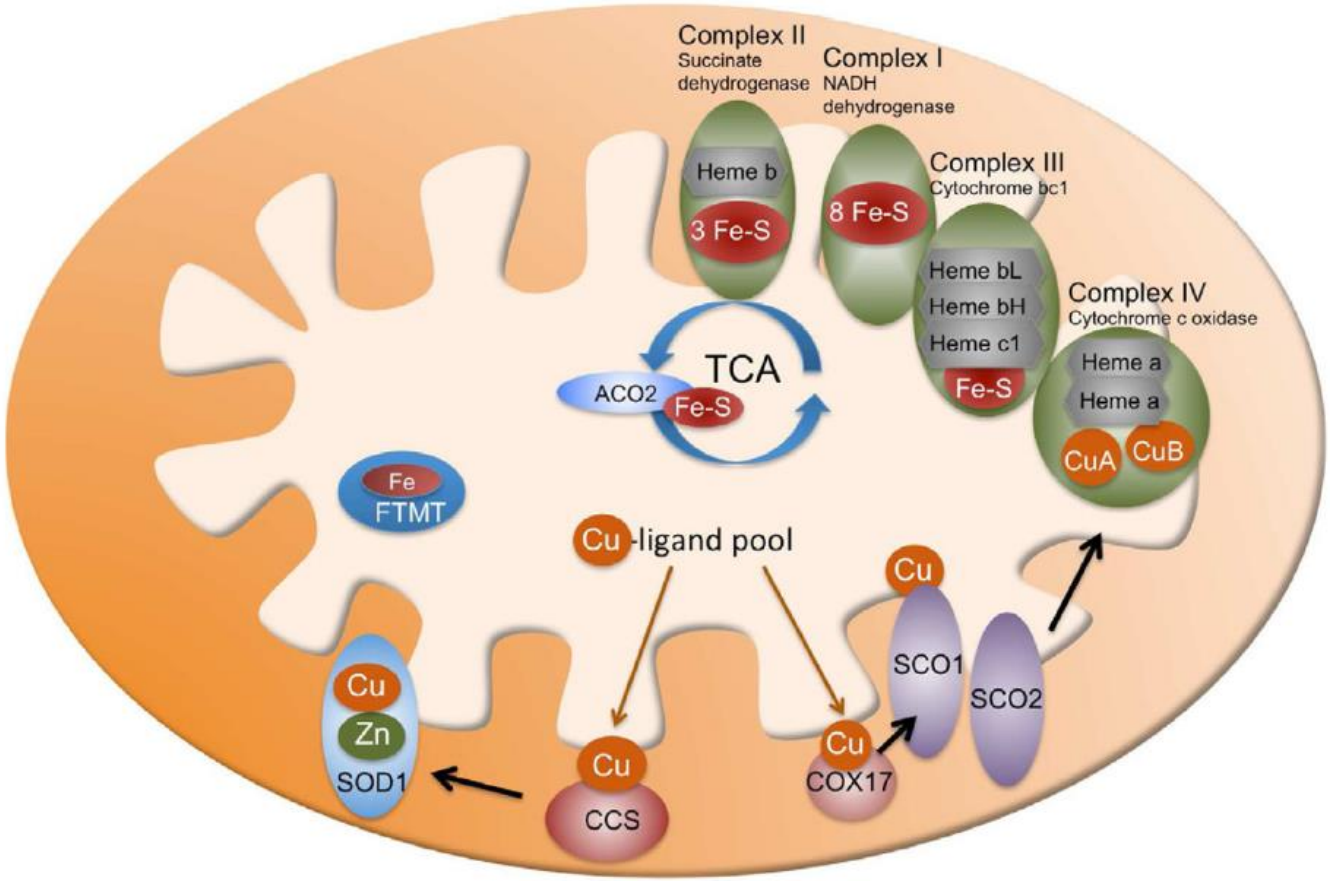


Figure 1. Mitochondrial proteins containing Fe and Cu
Complexes I to IV of the electron transport chain require Fe-S clusters, heme moieties and Cu centers to function. Complex II functions both in electron transport and also in the tricarboxylic acid (TCA) cycle. Complexes I, III and IV co-purify (not depicted here). Mitochondrial aconitase (ACO2), another TCA cycle enzyme, contains an Fe-S cluster. Complex IV acquires Cu from a copper-ligand pool in the mitochondrial matrix through the action of cytochrome c oxidase assembly factors COX17, SCO1 and SCO2. Cu-Zn superoxide dismutase (SOD1) contains Cu provided by the Cu chaperone CCS. Mitochondrial ferritin (FTMT) can store Fe.

Source: Xu W, Barrientos T, Andrews NC. Iron and copper in mitochondrial diseases. Cell Metab. 2013 Mar 5;17(3):319-28; see also https://therootcauseprotocol.com/

Retinol is the backbone of the multi-copper ferroxidase, caeruloplasmin

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"Retinol is the backbone of the ferroxidase enzyme that is so critical for chaperoning iron, and retinol loads copper into ferroxidase. Interestingly, studies of anemia have illustrated vitamin A's importance.[35] Although
we measure anemia via hemoglobin, adding iron does not meaningfully restore normal hemoglobin levels—
but vitamin A does. In addition to high-quality cod liver oil, good sources of retinol include liver, pastured eggs and butter (preferably from raw milk)."[1]

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FASEB J. 2010 Feb; 24(2): 627–636.
doi: 10.1096/fj.09-142281
PMCID: PMC2812036
PMID: 19812372

Control of oxidative phosphorylation by vitamin A illuminates a fundamental role in mitochondrial energy homoeostasis

Rebeca Acin-Perez,[*] Beatrice Hoyos,[‡] Feng Zhao,[‡] Valerie Vinogradov,[‡] Donald A. Fischman,[†] Robert A. Harris,[§] Michael Leitges,[‖] Nuttaporn Wongsiriroj,[¶] William S. Blaner,[#] Giovanni Manfredi,[*] and Ulrich Hammerling[‡]

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Associated Data

▸ Supplementary Materials

"Here we show that retinol is essential for the metabolic fitness of mitochondria."

Abstract Go to: ▸

The physiology of two metabolites of vitamin A is understood in substantial detail: retinaldehyde functions as the universal chromophore in the vertebrate and invertebrate eye; retinoic acid regulates a set of vertebrate transcription factors, the retinoic acid receptor superfamily. The third member of this retinoid triumvirate is retinol. While functioning as the precursor of retinaldehyde and retinoic acid, a growing body of evidence suggests a far more fundamental role for retinol in signal transduction. Here we show that retinol is essential for the metabolic fitness of mitochondria. When cells were deprived of retinol, respiration and ATP synthesis defaulted to basal levels. They recovered to significantly higher energy output as soon as retinol was restored to physiological concentration, without the need for metabolic conversion to other retinoids.[2]

Source: 1. https://www.westonaprice.org/health-topics/toxic-iron-and-ferroxidase-the-master-antioxidant/, 2. https://pubmed.ncbi.nlm.nih.gov/3655940/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2812036/; www.rcp123.org

Natural sources of bioavailable copper

Copper - Almonds; Avocado; Beans; Broccoli; Buckwheat; Chocolate; Crab; Dried legumes; Lamb; Mushrooms; Oysters; Pecans; Perch; Pork; Prunes; Sunflower seeds; Wholegrain cereals; Water from copper pipes. Synergistic Nutrients - Vitamin B2, B6, B12, D, Amino acids; Ca, B9, Fe, Mn, Se, Zn. Ca and K increase Cu absorption and retention. Fe inhibits Cu uptake[1]

NB Important to first build the caeruloplasmin carrier for bioavailable Cu with its retinol backbone[3]

"Our in vitro and in vivo studies indicate that, as a mean, there are 5.8 atoms of Cu per Cp molecule"

Source: 1. : Osiecki H (2014) The Nutrient Bible 9th Edition Bio Concepts Publishing Australia; http://www.alfiestrust.com/wp-content/uploads/2017/09/NutrientSourcesVitsMinsAGT.pdf; 2. *https://www.hsph.harvard.edu/nutritionsource/copper/*

References on the importance of copper in mitochondrial function

Selection

Role of Copper on Mitochondrial Function and Metabolism, 2021 https://www.frontiersin.org/articles/10.3389/fmolb.2021.711227/full.

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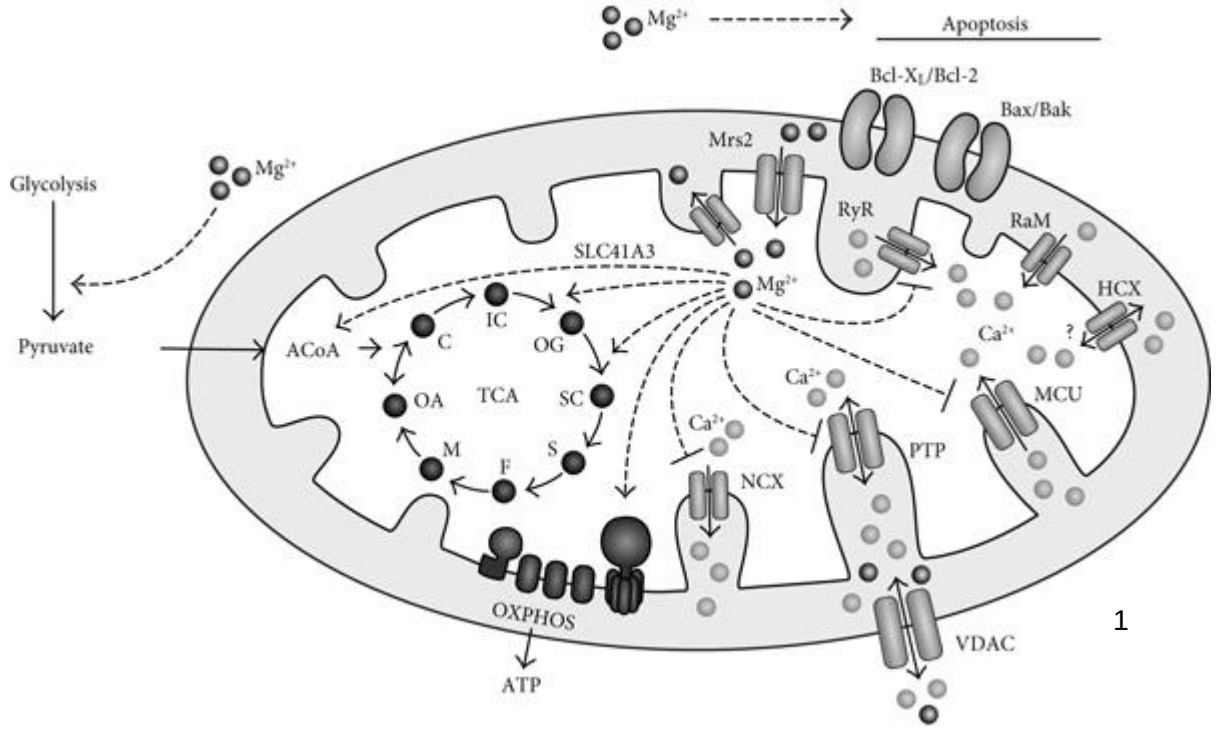
Mitochondrial copper metabolism and delivery to cytochrome c oxidase. IUBMB Life 2008, Jul;60(7):421-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2864105.

Kataoka M, Tavassoli M. **Ceruloplasmin receptors in liver cell suspensions are limited to the endothelium.** Exp Cell Res. 1984 Nov;155(1):232-40; https://pubmed.ncbi.nlm.nih.gov/6092118/

Without magnesium, no mitochondrial ATP can be generated



Vital for activating the terminal complex of the electron transport chain: without it, no mitochondrial ATP

1

Figure 1: Regulation of mitochondrial functions by Mg^{2+}. Mitochondrial Mg^{2+} activates (------>) three dehydrogenases in the mitochondrial matrix: pyruvate dehydrogenase (conversion of mitochondrial pyruvate to acetyl coenzyme A), isocitrate dehydrogenase (conversion of isocitrate to 2-oxoglutarate), and 2-oxoglutarate dehydrogenase (conversion of 2-oxoglutarate to succinyl coenzyme A). In addition, mitochondrial Mg^{2+} activates F_0/F_1-ATP synthase, which is the terminal complex of mitochondrial oxidative phosphorylation (OXPHOS). This regulatory activity contributes to mitochondrial energy metabolism.

Source: 1. Pilchova I et al. The Involvement of Mg^{2+} in Regulation of Cellular and Mitochondrial Functions. Oxid Med Cell Longev. 2017;2017:6797460. *;* R. Yamanaka, S. Tabata, Y. Shindo et al., "Mitochondrial Mg^{2+} homeostasis decides cellular energy metabolism and vulnerability to stress," *Scientific Reports*, vol. 6, article 30027, 2016

Docosahexaenoic acid appears to have an especially important role in the ETC

controls, in the group that received both light exposure and melatonin administration.

THE ROLES OF DHA AND CHOLESTEROL SULFATE IN INDUCING ELECTRON FLOW

Go to:

Lipid rafts are specialized areas of the plasma membrane that are rich in cholesterol and sphingolipids and that serve as signaling platforms by clustering proteins.[93] The omega-3 fatty acid, DHA, plays an important role in the r… 22-carbon backbone and six cis-… id occurring naturally in organisms… ty associated with the visual system… his process converts photons to el… ted that DHA possesses quantum me… n the visible to UV frequency range a… a continual stream through a proc…

DHA … captures light in the visible to UV frequency range and uses its energy to excite pi electrons and ultimately release them in a continual stream through a process termed "electron tunneling,"

The pineal gland normally contains substantial amounts of DHA.[175] In a rat model, deficiency in alpha-linolenic acid (a precursor to DHA) led to compensatory higher levels of omega-6 fatty acids in the pineal gland.[224] Furthermore, a decrease in melatonin release in response to adenosine by pinealocytes was observed in rats fed an omega-3 fatty acid-deficient diet.[62] Finally, dietary supplements in DHA increase the excretion of melatonin sulfate in the urine, indicating that synthesis of melatonin depends on adequate DHA.[47] These effects can plausibly be explained by the idea that DHA is essential for light-catalyzed sulfate synthesis by the pineal gland. We propose here, for the first time, that the pineal gland utilizes its NOS isoforms to produce sunlight-catalyzed sulfate from reduced sulfur sources.

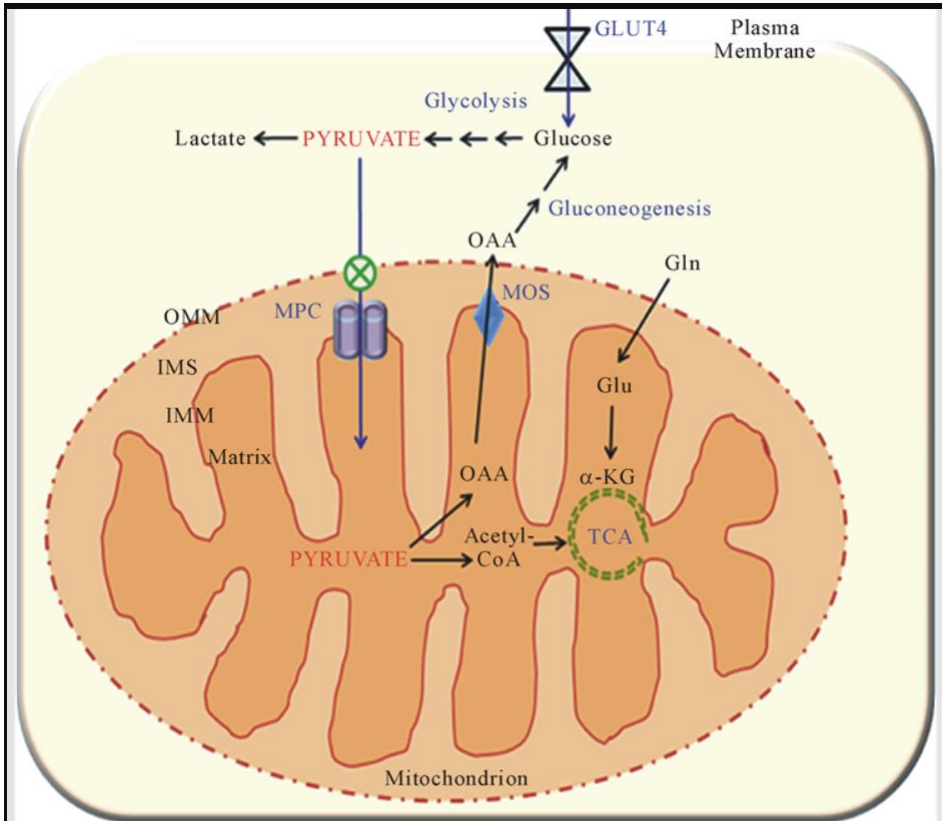
Source: Wendy A. Morley and Stephanie Seneff[1], Diminished brain resilience syndrome: A modern day neurological pathology of increased susceptibility to mild brain trauma, concussion, and downstream neurodegeneration, Surg Neurol Int. 2014; 5: 97; Crawford MA et al. A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution. Prostaglandins Leukot Essent Fatty Acids. 2013;88:5–13

Agenda

- What pathways may have become compromised?
- ATP Profile
- Mitochondrial Health Index
- **Lactate/Pyruvate Index**

Pyruvate is the product of glycolysis, and can either be transformed into lactate or transported into the mitochondria

Lactate/Pyruvate Plus test



Glucose in cells is converted to pyruvate. It can then either be transported into the mitochondria via the mitochondrial pyruvate carrier (MPC) or "turned back" and converted into lactate. Ideally most of it gets into the mitochondria. Here, you can see that the MPC is blocked, so lactate will build up in the cytosol.

Figure 1. Schematic diagram of a mitochondrion illustrating the cellular components associated with pyruvate transport and metabolism.

Source: Tang, B. (2014) The Mitochondrial Pyruvate Carrier and Metabolic Regulation. *CellBio*, **3**, 111-117.

Lactate/pyruvate ratio Plus: shows what nutrients are being used as fuel for the mitochondria (2/2)

Lactate/Pyruvate Plus

The higher the value of lactate compared to pyruvate, the more glycolysis is occurring. A higher level of pyruvate compared to lactate is a prerequisite for successful transfer of substrates in the mitochondria for oxidative phosphorylation.

The normal range for immune cells usually ranges from 1.0 – 0.7. Examples are calculated below

Ratio	Basal metabolic rate
>2.0	The cell is primarily using carbohydrates and preferentially converting them to lactate.
>1.2 – 2.0	The cell is primarily using carbohydrates and partially converting them to lactate.
1 – 1.2	The cell is primarily using carbohydrates and transporting them into the mitochondria.
0.8 – 1.0	The cell is using carbohydrates, fatty acids and amino acids. The carbohydrates are primarily being transported into the mitochondria.
<0.8	The cell is primarily using fatty acids as fuel.

BILIRUBIN	10	umol/L	0 - 20
ALKALINE PHOSPHATASE	55	IU/L	40 - 129
ASPARTATE TRANSFERASE	23	IU/L	0 - 37
ALANINE TRANSFERASE	15	IU/L	10 - 50
LDH	* 251	IU/L	135 - 225
CK	123	IU/L	38 - 204
GAMMA GT	16	IU/L	10 - 71
TOTAL PROTEIN	70	g/L	63 - 83

This may well be reflected in high LDH

Source: https://www.agilent.com/cs/library/usermanuals/public/103344-400.pdf; Prof. Dr. rer. nat. Brigitte König, MMD Labor; *mitochondrial research by Martin D. Brand and others*

Lactate/Pyruvate Index: shows what macronutrients are being used as fuel for the mitochondria (2/2)

Cell type:
Peripheral blood mononuclear cells (PBMC)

Lactate/Pyruvate Index Plus

Lactate/Pyruvate index PLUS

Test	Result	Interpretation
Lactate/Pyruvate in dormant cells	1.61	Your immune cells are primarily metabolising carbohydrates and partially (30%) converting them to lactate
Lactate/Pyruvate in activated cells	2.43	The cells are primarily using carbohydrates and converting around 80% of them to lactate

This result:
Under pressure, the fuel is largely not going into the mitochondria, it is being recycled into lactate. The buildup can be very painful (fibromyalgia-type symptoms).

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How the MCT oil C8 can help (octanoic/caprylic acid)

"MCTs don't rely on transport proteins— instead, they're absorbed directly from the intestinal lumen into the portal vein. Then they're quickly transported to the liver, where they're metabolized via beta--oxidation to produce energy and ketones.

MCTs ability to more rapidly metabolize than long-chain fats is thought to contribute to greater energy expenditure, less deposition in adipose tissue, and more efficient ketone production. This also explains why MCTs are "ketogenic."

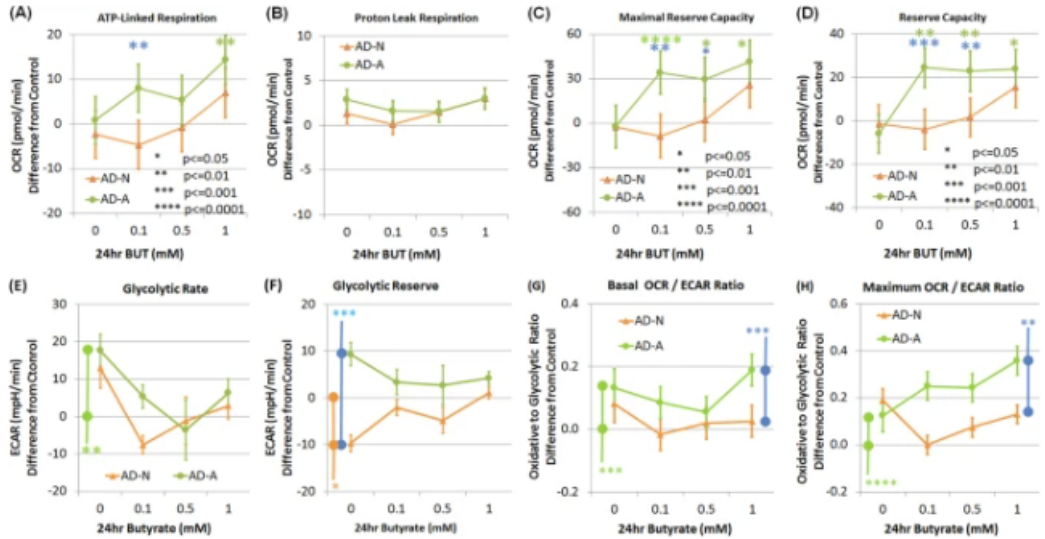
Although all MCTs are metabolized in a similar way, C8 has an even greater advantage than other MCTs. C8 can cross the mitochondrial membrane without carnitine-dependent transport, allowing for even more rapid beta-oxidation and ketone production.

A study published in April 2019 in the journal Frontiers in Nutrition measured the change in plasma ketones after an eight-hour feeding trial with different types of MCTs. Based on plasma levels of acetoacetate, beta-hydroxybutyrate, and total ketones, the study found that C8 was about three times more ketogenic than C10 and about six times more ketogenic than C12."

Source: https://www.emersonecologics.com/blog/post/c8-mct-oil-quick-source-of-energy-how-to-use-C8-MCT-oil; St-Pierre V et al. Plasma Ketone and Medium Chain Fatty Acid Response in Humans Consuming Different Medium Chain Triglycerides During a Metabolic Study Day. Front Nutr. 2019 Apr 16;6:46; https://www.mdpi.com/1422-0067/24/17/13090

Butyrate also beneficially impacts mitochondrial function

Fig. 4: Butyrate (BT) enhances the mitochondrial function in autistic lymphoblastoid cell lines (LCLs) with atypical mitochondrial function (AD-A) over and above the effect it has on control LCLs in a concentration- and exposure time-dependent manner.



ATP-linked respiration (**a**), maximal respiratory capacity (**c**), and reserve capacity (**d**) were enhanced over and above the control values for the AD-A LCLs with BT exposure, particularly for 0.1 and 1.0 mM BT concentrations. The bars adjacent to the data lines represent overall significant differences. The color of the stars and bars represents the specific comparisons. Green represents the difference between AD-A and control LCLs. Orange represents the difference between AD-N and control LCLs. Blue represents the difference between the AD-N and AD-A LCLs. Statistical significance levels: $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$, $****p \leq 0.0001$

"[Butyrate] BT positively modulates mitochondrial function, including enhancing oxidative phosphorylation and beta-oxidation and has been proposed as a neuroprotectant."

Source: Rose S, Bennuri SC, Davis JE, Wynne R, Slattery JC, Tippett M, Delhey L, Melnyk S, Kahler SG, MacFabe DF, Frye RE. Butyrate enhances mitochondrial function during oxidative stress in cell lines from boys with autism. Transl Psychiatry. 2018 Feb 2;8(1):42.

Carnitine acts as a carrier for fatty acids across the mitochondrial membrane for b-oxidation, essential for converting fat into energy

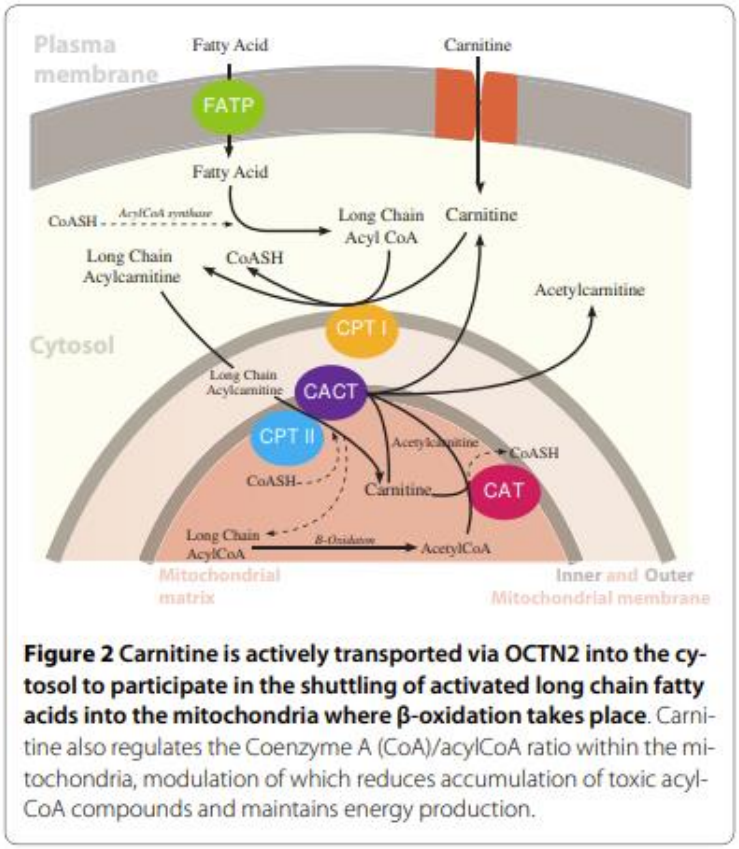


Figure 2 Carnitine is actively transported via OCTN2 into the cytosol to participate in the shuttling of activated long chain fatty acids into the mitochondria where β-oxidation takes place. Carnitine also regulates the Coenzyme A (CoA)/acylCoA ratio within the mitochondria, modulation of which reduces accumulation of toxic acyl-CoA compounds and maintains energy production.

L-carnitine is one of the key nutrients for proper mitochondrial function and is notable for its role in fatty acid oxidation. L-carnitine also plays a major part in protecting cellular membranes, preventing fatty acid accumulation, modulating ketogenesis and glucogenesis and in the elimination of toxic metabolites.

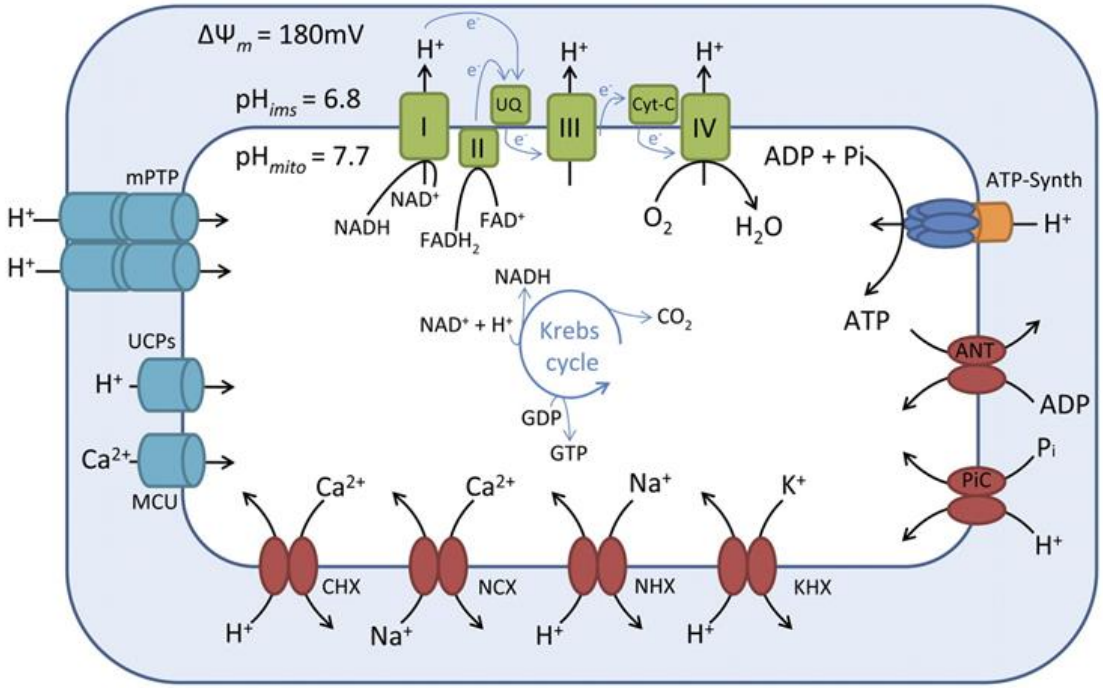
"Meat, poultry, fish, and dairy foods, and, recently, dietary supplements supply 75% of carnitine [13]. The main animal source of carnitine is red meat (which contains up to 80 µg/100 g); it is present in moderate amounts in dairy products, and at a low-to-zero level in vegetables." [3, 4]

1

Source: 1. Flanagan JL, Simmons PA, Vehige J, Willcox MD, Garrett Q. Role of carnitine in disease. Nutr Metab (Lond). 2010 Apr 16;7:30; 2. Virmani MA, Cirulli M. The Role of l-Carnitine in Mitochondria, Prevention of Metabolic Inflexibility and Disease Initiation. Int J Mol Sci. 2022 Feb 28;23(5):2717; 3. Durazzo A et al. The Nutraceutical Value of Carnitine and Its Use in Dietary Supplements. Molecules. 2020 May 1;25(9):2127.; 4. Pormsila, W.; Krähenbühl, S.; Hauser, P.C. Determination of carnitine in food and food supplements by capillary electrophoresis with contactless conductivity detection. Electrophoresis 2010, 31, 2186–2191; : https://www.mdpi.com/1422-0067/23/5/2717/htm; Osiecki H (2014) The Nutrient Bible 9th Edition Bio Concepts Publishing Australia; http://www.alfiestrust.com/wp-content/uploads/2017/09/NutrientSourcesVitsMinsAGT.pdf

Mitochondrial energy production is dependent on the correct mitochondrial membrane potential

"Mitochondria have a membrane potential of 150 -200 mV across a membrane that is 5 - 6 nm thick, giving a field strength of 30×106 V/m, equivalent to a bolt of lightning."



If the normal electrical gradient is reversed, exchange across the cell membrane will be disrupted

Imagine the damage EMFs can create …

Source: Jaime Santo-Domingo and Nicolas Demaurex (2012). The renaissance of mitochondrial pH. J Gen Physiol 2012 139:415-423; Molecular Cell Biology. 4th edition. Lodish H, Berk A, Zipursky SL, et al. New York: W. H. Freeman; 2000.

EMF prevention and support essential (1/2)

Wi-fi disrupts the voltage-gated calcium channels of our cells, leading to the internal mitochondrial production of highly corrosive peroxynitrite, which in turn causes brain fog, memory decline and neurodegeneration.

Essential Protective Measures

Prevention

Eliminating wi-fi routers from indoor spaces is paramount. However, if complete removal isn't feasible, switching off the wi-fi router at night provides a 30% reduction in stressors. Achieving optimal healing often necessitates complete elimination.

Eliminate cordless phones

Internal Protection.

a. Special tinctures are available composed of e.g. Propolis, Rosemary and Gingko: internal cellular shielding against low-frequency wavelength ranges

b. Natural vitamin C a potent antioxidant resource, fortifying our body's natural resilience against oxidative damage caused by wi-fi's impact.

EMF prevention and support essential (2/2)

1. **External protection**:
    a. There are creams you can apply that provide a degree of protection against EMFs
    b. **Specialised protective measures**, such as a custom-made "**Sleep Sanctuary**" (silver-coated cloth that works like a Faraday cage) and **wi-fi-repelling/protective clothing**
    c. **Even special soaps**

See the AONM (aonm.org) webpage for more details

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FOOD SENSITIVITY KPU TESTING WEBINARS EVENTS PRACTITIONERS CONTACT

Prof Dr Brigitte Konig explains Mitochondrial Testing

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Mitochondrial Magic – Tips for revitalising your mitochondrial health

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Dr Sarah Myhill – Mitochondria Dysfunction and Chronic Disease

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Prof Brigitte Koening – Advanced Mitochondrial Testing and Potential Therapies

Source: https://aonm.org/mitochondria-webinars/

In Part 2 we will cover other supplementary markers and potential therapeutic support

Further supplementary biomarkers:

Ratio of mtDNA to nDNA (mtDNA:nDNA)
PGC-1α for mitobiogenesis
Mitochondrial stress test
Nrf-2 as a marker for mitochondrial stress

Thanks very much for your attention!

Q&A

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