My approach to mitochondria and chronic disease

- **Clinical mitochondrial therapeutic research is still in its infancy.** So there are relatively few studies investigating a mitochondrial approach to treatment.
- So the approach I have taken is to:
  - **Establish the principal therapies and remedies** for which there is evidence of improved mitochondrial function
  - **Search for studies of that therapy or remedy** used in chronic disease:
    - Metabolic disease,
    - Neurodegenerative disease,
    - Cardiovascular disease,
    - Cancer,
    - Autism.
- But just because there is no clinical trial, doesn't mean that the remedy doesn't work. It just means that there is no clinical trial…but in 10 years time there may be.

Therapies for which there is good evidence of improved mitochondrial function

- Diet: caloric restriction, fasting, ketogenic diets
- Exercise: especially endurance exercise and high intensity interval training (HIIT)
- Hyperbaric oxygen
- Therapeutic hypothermia
- Near infrared radiation: via chromophores (cytochrome c oxidase)
- Pulsed electromagnetic fields

All are beneficial at moderate dosage but can become toxic if overdone.

All references on slides on the website.

Caloric restriction (CR)

- In skeletal muscle, CR reduced mitochondrial fragmentation and normalised fission and fusion protein content.
- In injured cardiomyocytes, CR increased mitochondrial number and volume and lowered oxidative damage and apoptosis. In toxin-induced cardiac hypertrophy, CR reduced mitochondrial ROS production, upregulated antioxidants and increased activity of mitochondrial ATP-sensitive potassium channels.
- In stressed neurons or excitotoxicity, CR reduced elevated intracellular calcium levels, ROS production, caspase activity and apoptosis and reversed mitochondrial depolarisation. CR also increased eNOS, nNOS and mitochondrial protein content including mitofusins. It also increased ETC activity, enhanced antioxidant defences and increased SIRT3 expression, inhibiting the opening of the mtPTP; here CR favoured retention of calcium in the cell, demonstrating that CR is adaptogenic.
- In liver damage, CR reversed excessive mitochondrial Ca2+ accumulation and resultant opening of the mtPTP. CR also increased expression of cytochrome c oxidase (Complex IV) and formation of mitochondrial supercomplexes in hepatocytes, as well as PGC-1α, TFAM and NRF-1, and upregulated antioxidants.
- In other cells, CR promoted cardiolipin biosynthesis and aided its distribution in mitochondrial membranes and upregulated sirtuins and NAMPT, leading to increased mitochondrial biogenesis and oxidative capacity through enhanced PGC-1α, TFAM and Nrf1. It also decreased oxidative stress and increased antioxidant enzymes.

(Faitg J, Front Physiol, 2019; David CEB, J Nutr Biochem, 2018; Gültekin F, Metab B rain Dis, 2018; Amigo I, Aging Cell, 2017; Luévano-Martínez LA, Mech Ageing Dev, 2017; Kim SE, Age, 2015; Song J, J Gerontol A Biol Sci Med Sci, 2014; Picca A, PLoS One, 2013; Lanza IR, Cell Metab, 2012; Finckenberg P, Hypertension, 2012; Cerqueira FM, Free Radic Biol Bed, 2012; Kitada M, Front Endocrinol, 2019; Niemann B, Cardiovasc Res, 2010; Rodgers JT, Proc Natl Acad Sci U S A, 2007; Dai H, Pharmacol Ther, 2018)

Fasting/Time-restricted eating

- Fasting and time-restricted eating mimic the eating habits of our hunter/gatherer ancestors.
- In hepatocytes, SIRT1 activated genes coding for mitochondrial β-oxidation, but not gluconeogenesis, during fasting. However, fasting also reduced OXPHOS, with increased electron leak from Complex III and hence increased ROS production. It also decreased mitochondrial membrane potential and resistance to calcium-induced opening of the mtPTP. However, time-restricted feeding resulted in decreased ROS production but increased uncoupling, with raised proton leak and decreased OXPHOS activity, which could be reversed by insulin administration.
- In obese skeletal muscle, intermittent fasting limited mitochondrial damage and maintained efficient mitochondrial respiration. UCP3 was upregulated and required for the enhanced fatty acid β-oxidation but uncoupling itself was impaired but could be rescued by administration of tri-iodothyronine (T3). In healthy males, fasting induced increased whole-body fat oxidation, but an overall reduction in both coupled and uncoupled respiration, which could not be explained by changes in mitochondrial density.
- In ischaemic cardiomyocytes, fasting resulted in enhanced fatty acid catabolism and reduced oxidative damage and opening of the mtPTP.

(Seok S, J Clin Invest, 2018; Lettieri-Barbato D, PLoS One, 2018; Marina Prendes MG, Clin Exp Pharmacol Physiol, 2009; Seifert EL, J Biol Chem, 2008; Moreno M, FASEB J, 2003; Bézaire V, Am J Physiol Endocrinol Metab, 2001; Menezes-Filho SL, Biochim Biophys Acta Bioenerg, 2019; Sorensen M, Free Radic Res, 2006; Lambert AJ, Am J Physiol Regul Integr Comp Physiol, 2004; Hoeks J, Diabetes, 2010; Mattson MP, Ageing Res Rev, 2017; de Cabo R, New Eng J Med, 2019)

Ketogenic diet

- In cardiomyocytes, a ketogenic diet improved mitochondrial function and decrease oxidative stress and apoptosis.
- In neurons with a mutated DNA repair mechanism (to simulate epilepsy) and neurons suffering oxidative stress or ageing, a ketogenic diet increased mitochondrial biogenesis, density, volume and function by upregulating PGC1α, SIRT1, SIRT3 and UCP2, increased the NAD+/NADH ratio, normalised ATP production and decreased oxidative stress while increasing mtSOD and glutathione. It also inhibited mitochondrial fission. However, the ketogenic diet also aggravated neurodegeneration and mitochondrial deterioration, possibly due to increased mitochondrial biogenesis of generally dysfunctional mitochondria, and in peripheral neurons, a ketogenic diet reduced mitochondrial respiration and H_2O_2 production.
- In obese skeletal muscle, a ketogenic diet enriched with amino acids prevented mitochondrial dysfunction and alteration by increasing mitochondrial fusion proteins and PGC-1α decreased mitochondrial fission proteins. In non-obese muscle and mitochondrial myopathy, the ketogenic diet also improved OXPHOS, particularly enhancing cytochrome c oxidase (Complex IV), mitochondrial volume and biogenesis and prevented mitochondrial abnormalities.
- In hepatocytes, a ketogenic diet improved markers of oxidative stress, although long-term ketogenic feeding may negatively affect skeletal muscle mitochondrial physiology. Furthermore, it led to decreased levels of mtDNA and mitochondrial proteins, despite increased gene expression, indicating increased mitochondrial turnover by mitophagy.
- In brown adipose tissue, a ketogenic diet increased mitochondrial size, ETC proteins, PGC-1α, Sirt1 and UCP1.

(Guo Y, Aging Dis, 2020; Cooper MA, Exp Physiol, 2018; Hasan-Olive MM, Neurochem Res, 2019; Guo M, Front Mol Neurosci, 2018; Kephart WC, Nutrients, 2017; Newell C, Front Physiol, 2016; Hyatt HW, Front Physiol, 2016; Lauritzen KH, Neurobiol Aging, 2016; Greco T, J Cereb Blood Flow Metab, 2016; Srivastava S, IUBMB Life, 2013; Ahola-Erkkilä S, Hum Mol Genet, 2010; Jarrett SG, J Neurochem, 2008; Parry HA, Heliyon, 2018; Balietti M, Micron, 2010; Nylen K, Biochim Biophys Acta, 2009; Elamin M, Front Mol Neurosci, 2017)

Exercise and the best type

- Absolutely essential for mitochondrial health.
- All forms of exercise are beneficial but quality is more important than quantity. Endurance exercise tends to have greater mitochondrial impact than resistance exercise (Silvennoinen M, Physiol Rep, 2015). High intensity interval training (HIIT) also appears to be highly beneficial for mitochondria (De Strijcker D, J Musculoskelet Neuronal Interact, 2018; Wu LH, Sci Rep, 2017).
- Exercise mimics hypoxia by creating an acute need for more oxygen. But long walks do not help; we need a raised heartrate and shortage of breath.
- Note that if you train at high intensity for too long the exercise becomes anaerobic, which doesn't help. So HIIT alternating with low intensity exercise is preferable.
- Don't give antioxidants with exercise. PGC-1α and mtSOD were only upregulated in those NOT given vitamins C and E (Ristow M, Proc Natl Acad Sci U S A, 2009, Paulsen G, J Physiol, 2014). Similarly, Metformin can reduce the exercise-induced improvement in mitochondrial respiration (Konopka AR, Aging Cell, 2019).

Exercise and mitochondria

- The primary long-term adaptation that muscle makes to repeated metabolic demands is an increase in mitochondria. Exercise activates key stress signals that beneficially transcribe genes involved in skeletal muscle mitochondrial biogenesis, fusion and metabolism. The benefits are seen in all age groups and even in the elderly and those with chronic disease, decreasing skeletal muscle atrophy and reducing the risk or severity of disease. (Russell AP, Biochim Biophys Acta, 2014)
- A small study of healthy, sedentary older adults showed that after 4 months of exercise, all ETC Complexes in skeletal muscle were increased, but particularly Complex I, which was found to form an increased number of Supercomplexes (Greggio C, Cell Metab, 2017).
- Aerobic exercise elevated platelet mitochondrial oxygen consumption by increasing Complex I and II activity (Chou CH, Int J Cardiol, 2019).
- Among sedentary adults, aerobic exercise training altered the expression of mitochondrial fusion and fission proteins, promoting a more fused, tubular network (Axelrod CL, Acta Physiol (Oxf), 2019).
- A small study found that both endurance (treadmill) and resistance (leg presses)exercise upregulated PGC-1α (Silvennoinen M, Physiol Rep, 2015). Sirtuin expression was also upregulated after exercising (Suwa M, Metabolism, 2008; Ferrara N, Rejuvenation Res, 2008; Dai H, Pharmacol Ther, 2018).

Therapeutic hypothermia

- Mammals initially respond to cold by generating heat through shivering. With cold acclimation, this is replaced by the recruitment of UCP1-dependent heat production (non-shivering thermogenesis) in BAT and to a lesser extent in WAT (Bruton JD, J Physiol, 2010; Sepa-Kishi DM, Am J Physiol Cell Physiol, 2019).
- In humans, post-exercise cold water immersion upregulated TFAM to a greater extent than exercise alone (Aguiar PF, Cell Stress Chaperones, 2016).
- In human fibroblasts, mesenchymal stem cells and rat skeletal muscle, cold exposure stimulated increased mitochondrial activity and DNA copy number (Sugasawa T, Int J Sports Med, 2016). In skeletal muscle, there was increased PGC-1α and citrate synthase activity (Bruton JD, J Physiol, 2010).
- In hypoxic neurons, hypothermia reduced ETC Complex activity with decreased proton leak, indicating that mitochondrial respiration is more efficient (Pamenter ME, PLoS One, 2018) and decreased pro-apoptotic factors (Wu L, Mol Neurobiol, 2017).
- Hypothermia upregulated PGC-1α expression in mouse BAT but not in WAT (Chung N, J Exerc Nutrition Biochem, 2017).
- In adipose tissue, hypothermia upregulated mitochondrial biogenesis via increased noradrenaline by increasing fission and UCP-1-mediated mitophagy in BAT (Park H, J Clin Invest, 2019; Lu Y, Sci Rep, 2018). Human WAT expresses the cold receptor TRPM8; on activation by cold, it induces UCP1 expression (Rossato M, Mol Cell Endocrinol, 2014). UCP1 protects cells from cold-induced oxidative stress (Stier A, J Exp Biol, 2014).

Hyperbaric oxygen (HBO)

- In rat skeletal muscle contusion, HBO positively modulates the efficiency of skeletal muscle mitochondria, possibly by reducing the opening of the mtPTP (Cervaens M, Undersea Hyperb Med, 2018).
- In mouse skeletal muscle subjected to HBO for 1 hour, PGC-1α was increased; after exercise with HBO citrate synthase, TFAM, HSP70 and PGC-1α were upregulated compared to exercise alone (Suzuki J, Physiol Rep, 2017).
- In degenerated human intervertebral disc cells, HBO upregulated anti-apoptotic protein expression and reduced the activity of some caspases (Niu CC, J Orthop Res, 2013).
- In injured neurons, HBO suppressed mitochondrial apoptotic pathways as evidenced by upregulated anti-apoptotic proteins, reduced cytochrome c release and decreased caspase activity (Li JS, Neuroscience, 2009), possibly via the opening of mitochondrial ATP-sensitive potassium channels (Lou M, Brain Res Bull, 2006). HBO can also reverse loss of mitochondrial membrane potential (Palzur E, Brain Res, 2008) and increase ATP production (Zhou Z, J Neurosurg, 2007).
- However, HBO can induce apoptosis in lymphocytes through decreased mitochondrial membrane potential and upregulated caspases (Weber SU, Apoptosis, 2009).
- In human lung fibroblasts exposed to HBO for 2 hours per day for 5 consecutive days, despite upregulated mtSOD, mitochondrial oxygen consumption was impaired with increased electron leak, decreased activity of Complex II and compromised ATP-production following β-oxidation (Dejmek J, Physiol Res, 2018).

Red and near infrared radiation (Photobiomodulation)

- Photobiomodulation: the use of red or near-infrared light to stimulate, heal, regenerate or protect tissue.
- The radiation interacts with the chromophores in the body. Chromophores are molecules that accept photons, i.e. they absorb light, and are found in the mitochondria and in water molecules. In the mitochondria, the specific light-absorbing molecule is cytochrome c oxidase, which is Complex IV in the ETC; through upregulating cytochrome c oxidase, ATP production is increased. In addition there is increased mitochondrial biogenesis, oxygen consumption, membrane potential and NADH synthesis through a shift from anaerobic to aerobic metabolism.
- Far infrared radiation exerts biological effects primarily by altering protein structures, whereas near infrared primarily targets the mitochondria. Furthermore, the near infrared wavelength (810-830 nm) is one of the most beneficial for health as it can penetrate deeper into the body than far infrared, which is absorbed by water.
- Dangers of blue light: Blue light is emitted by all electronic devices and by fluorescent lights and LEDs. This excludes red, infrared and ultraviolet light, which are essential for the mitochondria. Blue light unbalanced by the rest of the electromagnetic spectrum is junk light. Blue light induced ultrastructural conformational changes in mitochondria, resulting in the appearance of giant mitochondria after 72 h, damaged mtDNA, increased ROS production and a delay in the cell cycle; unlike full spectrum light, blue light does not signal the nucleus to produce more antioxidants. (Godley BF, J Biol Chem, 2005; Roehlecke C, Molecular Vision, 2009)
- The absence of near infrared in artificial light sources, such as LEDs and fluorescents, is what makes these light sources so dangerous health. It is possible to buy full spectrum light bulbs or red lights but sunshine contains 40% infrared rays.
- Therapeutic infrared can be found in infrared lights and saunas. When choosing a sauna, ensure that it offers a full spectrum of infrared radiation, not just far infrared, and without emitting any EMFs.

More on near infrared (IR) radiation

- Cytochrome c oxidase (Complex IV in the ETC) reduces oxygen to water but can also reduce nitrite to nitric oxide (NO), a function that is upregulated by low intensity lR radiation. Nitric oxide functions as a signalling molecule through both intra- and extracellular pathways.
- Excess nitric oxide (NO) may hinder the synthesis of ATP as it competes with oxygen in the mitochondria. It binds with cytochrome c, preventing it from binding with oxygen. Red and infrared light prevent NO binding to cytochrome c oxidase, allowing utilisation of oxygen. The dissociation of NO from cytochrome c oxidase increases the respiration rate and protect against NO-induced cell death.
- Near IR radiation also increases the activity of the other respiratory complexes, upregulates protein synthesis and anti-oxidant enzymes, decreases apoptosis and helps regulate calcium.It generally improved mitochondrial function and antioxidant gene expression and reversed toxin-induced Complex I inhibition. Pulsed IR radiation generated a healing response by modulating mitochondrial calcium cycling.
- Photobiomodulation can act through hormesis. Transient increases in ROS from the light therapy activates cellular defence systems, activating NF-κB and promoting a low level inflammatory response and engaging the Nrf2 pathways and antioxidant response element (ARE). (Hamblin MR. Photochem Photobiol. 2018) Red light has been described as an 'exercise mimetic'.
- Near infrared is biphasic in dosage, meaning that the benefit disappears and becomes toxic when the dosage is too high. The ideal power density is around 10 milliwatts per square centimetre (1 joule every 100 seconds) for 10-20 minutes per day; most devices use between 10-20 mw/cm2. 20mw/cm2 is preferable if treating deeper in the body. Generally, pulsed is preferable to continuous wave; if pulsed, the ideal frequency is 10-40 Hertz.

(Wong-Riley MTT, J Biol Chem, 2005; Tsai SR, J Photochem Photobiol B; 2017; 170: 197–207; Sivapathasuntharam C, Neurobiol Aging, 2017; Zomorrodi R, Sci Rep, 2019; Hamblin MR, Photochem Photobiol, 2018; Poyton RO, Discov Med, 2011; Sommer AP, Ann Transl Med, 2019; Ravera S, J Biophotonics J Biophotonics, 2019; Eells JT, Mitochondrion, 2004; Kalaza KC, Neurobiol Aging, 2015; Yu Z, Metab Brain Dis, 2015; Gkotsi D, Exp Eye Res, 2014; Giuliani A, BMC Complement Altern Med, 2009; Zhang K, J Vis Exp, 2015; Salehpour F, Neurobiol Aging, 2017; Rojas JC, J Neurosci, 2008; Lumbreras V, J Neurophysiol, 2014; Amaroli A, Lasers Med Sci, 2019; Nguyen LM, Mitochondrion, 2014; Ferraresi C, Photochem Photobiol, 2015; Gavish L, Lasers Surg Med, 2004; Avci P, Sem Cut Med Surg, 2013; Huang YY, Dose Response. 2011; Sommer A, Sci Rep, 2015; Farivar S, J Lasers Med Sci. 2014; Xu C, J Cell Sci. 2014)

Pulsed electromagnetic fields (PEMFs)

- Raises expression levels of PGC-1$^{\alpha}$ in skeletal muscle, increasing mitochondrial biogenesis and respiratory capacity (Yap JLY, FASEB J, 2019).
- PEMFs increase ATP hydrolysis activity through upregulating ATPase (Chen C, Bioelectromagnetics, 2009).
- PEMFs also enhance the activity of cytochrome c oxidase (Ascherl R, Bioelectricity Bioenerg, 1985; Blank M, Bioelectromagnetics, 1992).
- Improves viability and maturation of osteoblasts but only in those with poor baseline function, indicating that PEMFs are adaptogenic (Ehnert S, Bone Rep, 2015).
- PEMF exposure mediates a significant upregulation of adenosine receptors expressed in various cells/tissues involving a reduction in pro-inflammatory cytokines (Varani K, Mediators Inflamm, 2017).

Vegetarian/vegan diets

- No studies involving mitochondria

But there are mitochondrial issues with vegan diets (and, to a lesser extent, vegetarian diets)

- No creatine, found only in animal foods. It provides the phosphate to donate to make ATP.
- No choline, found in eggs.
- No carnosine, found only in animal foods: can prevent oxidative stress and formation of AGEs and lipid oxidation products.
- Also carnitine, taurine (function of brain and heart, making bile + detoxification), tryptophan (for conversion to serotonin)
- Beta-carotene but no retinol (egg yolks and liver). Beta-carotene is less well absorbed than retinol and must be converted to retinol before it can be used as vitamin A, which may not be occurring effectively.
- Vitamin K1 but no K2. Although vitamin K1 can be converted to K2, it is K2 that is the active form.
- Vitamin B12
- Vitamin D
- Iron
- Zinc and magnesium, not as easily absorbed from plants.

As Dr Jenny Goodman says, "Even though your soul may be vegan, your body may be a carnivore".
(Staying Alive in Toxic Times, 2020)

The care and feeding of the mitochondria

Think of them as cute puppies:

- They need real food (but not too much), water, exercise
- Absence of toxins
- And lots of TLC!

Beware the ‘inner labrador’ (Dave Asprey, Bulletproof)

- Labradors have a POMC (pro-opiomelanocortin) mutation which makes them permanently and relentlessly ravenous!
- Humans don’t have this mutation but we do have an ‘inner labrador’, which wakes up whenever we are stressed or have a blood sugar dip, which may come with fasting or time-restricted eating.

Caffeine and mitochondria

- Caffeine (a methylxanthine alkaloid) is the most widely used psychostimulant in Western countries; the main active component is the diterpene kahweol. Caffeine is contained in coffee, tea, energy drinks, several soft drinks and cocoa. In excess, caffeine can promote cytotoxic stress and cell death. Because of this we tend to think it should be avoided but if we can strike the right balance it can be highly beneficial!
- Caffeine and adenosine have very similar basic structures: both have purine backbones, allowing for caffeine to bind to adenosine receptors as a competitive antagonist of adenosine. There are abundant adenosine receptors in the brain; different types can either inhibit or increase neuronal excitability.
- Caffeine concentrations are found in the brain at similar amounts to the blood, suggesting that caffeine can readily cross the blood-brain barrier, due to its hydrophobic nature.
- Caffeine can directly increase fatty acid oxidation, in part by promoting mitochondrial biogenesis and dose-dependently stimulated ketone production. In damaged neurons, caffeine upregulated endogenous antioxidants, decreasing oxidative stress, and restored ETC Complex activity and mitochondrial membrane permeability. In injured hepatocytes, caffeine improved mitochondrial bioenergetic function and prevented ROS production and lipid peroxidation. In skeletal muscle cells, caffeine promoted mitochondrial biogenesis through upregulation of PGC-1α and increased oxidative metabolism, cytochrome c oxidase (Complex IV), TCA cycle enzymes and ATP production, in part through interaction with nitric oxide synthase and through calcium signalling. In adipocytes, caffeine increased mitochondrial activity, upregulated PGC-1α and decreased oxidative stress.

(Enyart DS, Physiol Rep, 2020; Downs RM, Biochem Biophys Res Commun, 2016; Dragicevic N, Neuropharmacology, 2012; Sardão VA, Toxicol Appl Pharmacol, 2002; Vaughan RA, Nutr Metab Insights, 2012; McConell GK, J Appl Physiol, 2010; Enyart DS, Physiol Rep, 2020; Samadi M, Drug Chem Toxicol, 2019; Mishra J, Pharmacol Rep, 2014; de Oliveira MR, Neurotox Res, 2020; Rebollo-Hernanz M, Food Chem Toxicol, 2019; Fürstenau CR, Toxicol in Vitro, 2019; Vandenberghe C, Can J Physiol Pharmacol, 2017; Gonçalves DF, Life Sci, 2018; Kolahdouzan M, CNS Neurosci Ther, 2017; Downs RM, Biochem Biophys Res Commun, 2016; Laurent C, Neurobiol Aging, 2014; Hidgon JV, Crit Rev Food Sci Nutr, 2006; Lopez-Garcia E Ann Intern Med, 2008)

Mixing it up

- Mitochondria are dynamic organisms – they are never still and their numbers are always changing.
- And so should our therapy; **habituation** is a real problem when it comes to mitochondrial health.
- **Never stay on any regimen indefinitely or the body adapts and then benefit is lost.**
- For example, cycle between ketogenic and low GL healthy carbs to keep the mitochondrial flexible.

Remedies for which there is good evidence of benefit to the mitochondria (Annex A)

- Astaxanthin
- B vitamins
- β-lapachone
- Berberine
- Butyrate
- Cannabinoids
- Capsaicin
- L-carnitine
- Carnosine
- Coenzyme Q10
- Copper *
- Creatine
- Ginkgo biloba
- Ginseng
- Iron *
- Ketones
- Lipoic acid
- Magnesium
- Manganese *
- Melatonin
- Molecular hydrogen
- N-acetyl cysteine
- NAD+ and precursors
- Omega 3 fatty acids
- Pyrroloquinoline quinone
- D-ribose
- Selenium *
- Sulphoraphane
- Taurine
- Tauroursodeoxycholic acid (TUDCA)
- Vitamin A *
- Vitamin D
- Zinc *

Flavonoids and isoflavones

- Apigenin
- Baicalin/Baicalein
- Curcumin
- Epicatechin
- Epigallocatechin-3-gallate (EGCG)
- Grape seed extract
- Icariin
- Kaempferol
- Luteolin
- Milk thistle
- Myricetin
- Naringin/Naringenin
- Nobiletin
- Quercetin
- Resveratrol
- Rutin
- Genistein
- Daidzein
- Puerarin

Vitamins and minerals with *

All essential for mitochondrial function but in excess can be highly toxic.

Both mitochondrial deficiency and excess induce mitochondrial damage.

Flavonoids

A combination works best, as this is how they arise in nature. Their individual effects complement each other.

Mitochondrial dysfunction in chronic disease: general points

- What we may consider as ‘mitochondrial dysfunction’ is only truly dysfunction in the appropriate context. Under certain circumstances, they might be the cell’s appropriate response.
- There is an element of early adaptation in all chronic disease: at the first sign of a problem, the body finds a way around it but as the problem persists, eventually we succumb. Failure to appreciate that there is an initial adaptation response may be the reason for a lot of odd study results.
- Control of mitochondrial respiration, and hence dysfunction, is tissue-specific and is not uniformly altered in all disease. For example, ATP production can be deficient in skeletal muscle but not in adipose tissue, while mitochondrial biogenesis could be downregulated in the liver but not in the heart.
- Not all studies show the same element of mitochondrial dysfunction in the same tissue. No-one seems to know why.
- So for all these reasons, although many studies show an association between mitochondrial dysfunction and chronic disease, it is not seen in every study.

What do we mean by ‘Mitochondrial Dysfunction’?

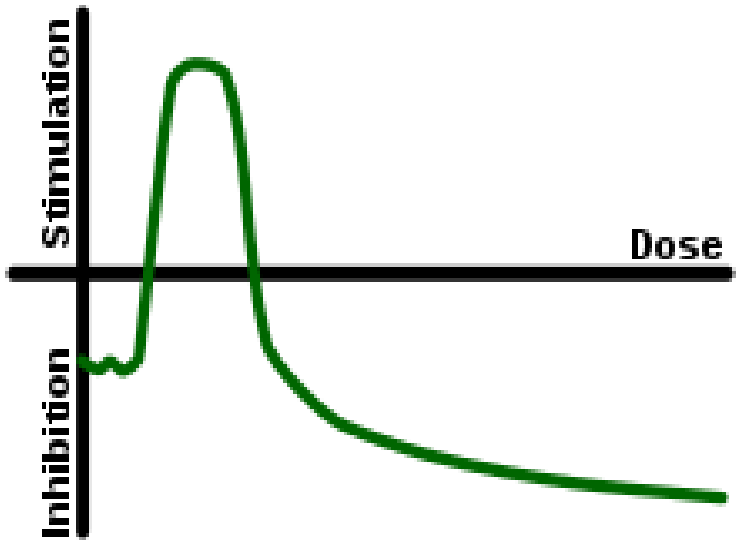
- Decreased mitochondrial biogenesis, imbalanced fission and fusion, deficient mitophagy, smaller and fragmented mitochondria.
- Decreased mtDNA content, increased mtDNA damage/mutations.
- Increased oxidative damage, particularly to cardiolipin, and/or decreased mitochondrial antioxidants.
- Inadequate amount of substrate.
- Lower metabolic flexibility.
- Impaired calcium homeostasis, disruption of MAM integrity, formation of the mtPTP leading to apoptosis.
- Impaired OXPHOS, with deficient ETC Complexes and Supercomplexes, decreased oxygen consumption, lower ATP production, upregulated UCPs.
- Decreased mitochondrial membrane potential.

Examples of therapeutic targets to combat mitochondrial dysfunction

- Upregulating the DNA-binding transcription factor PGC-1α, which in turn increases levels of Nrf1 and TFAM to induce mitochondrial biogenesis. PGC-1α is upregulated by sirtuins and by phosphorylation of the nutrient/energy sensor AMPK whenever there is a raised AMP/ATP ratio.
- Upregulating ETC Complex proteins and activity.
- Manipulating the balance between coupling and uncoupling.
- Manipulating the mitochondrial membrane potential, mtPTP opening and apoptosis.
- Upregulating mitochondrial antioxidants such as mtSOD.
- Inducing sirtuins to regulate mitochondrial activity. Sirtuin activation is dependent on NAD+ signalling.
- Inducing mitophagy to improve mitochondrial quality control.
- Manipulating the balance between NAD^+ and NADH.

Hormesis: 'The dose makes the poison' (attributed to Paracelsus)

- **What doesn't kill us makes us stronger!**
- **Hormesis is any process in a cell or organism that exhibits a biphasic response to exposure to increasing amounts of a substance or condition.** This an extension of the concept of the adaptive response. Hormesis is commonly seen in **toxicology, where low dose benefit is followed by high dose toxicity, resulting in either a J-shaped or an inverted U-shaped dose response curve.**
- Hormesis enables the body to adapt to a mild stress, making it **more resilient for the future**. It has been described as 'the mild toxicity of nature' that aids our health. It is the **mitochondria that benefit particularly from hormesis**, when it is sometimes known as mitohormesis.
- **Many mitochondrial therapies and remedies are inducers of hormesis: they all induce low levels of ROS.**
- **It follows, therefore, that where mild oxidative stress is beneficial for the body and its mitochondria, we shouldn't neutralise it by giving antioxidants.** *



More on hormesis

- Mild oxidative stress triggers beneficial mitophagy and mitochondrial biogenesis, through upregulation of AMPK and other molecules, whereas high oxidative stress triggers apoptosis.
- Similarly, plants foods contain pro-oxidants, which lead us to upregulate gene expression of endogenous antioxidants. So although plant foods contain antioxidants, their main benefit may lie in the pro-oxidants.
- Increasing your body's own endogenous antioxidant levels may be a better option for disease prevention.
- Needless to say, the existence of hormesis is widely debated but the concept is known in other areas of medicine, such as cardiology, where it is called 'pre-conditioning'. Sometimes it is called anti-fragility.
- To get our heads around this paradox we have to let go of the assumption of a linear relationship between health and toxicity.

(Frank M, Biochim Biophys Acta, 2012; Tapia PC, Med Hypotheses, 2006; Plauth A, Free Radic Biol Med, 2016; Biasutto L, Antiox Redox Signal, 2011; Barbour JA, Int J Cell Biol, 2014; Miller VJ, J Nutr Metab, 2014)

Why I am not discussing antioxidants

(although some of the remedies may have antioxidant action)

- Unless an antioxidant supplement is targeted specifically and precisely on the ETC, it is doomed to failure with respect to mitochondrial action, although it may have benefit in non-mitochondrial tissue. Furthermore it may inhibit the benefits of other therapies.
- Furthermore, not all exogenous antioxidants support the mitochondria; oral administration of vitamin C decreases muscle mitochondrial biogenesis (Gomez-Cabrera MC, Am J Clin Nutr, 2008).
- In cancer trials, results are divided over whether antioxidants are beneficial, detrimental or have no effect. An example of a detrimental effect is the finding that α-tocopherol increased the risk for a form of gastric cancer (Nouraie M, Cancer Epidemiol Biomarkers Prev, 2005)
- A combination of vitamin C (1000 mg/day) and α-tocopherol (400 IU/day) taken for 6 weeks before and after exercise by insulin resistant subjects, prevented improvement seen in controls who exercised without supplementation. The antioxidants prevent the beneficial hormetic effect of mild oxidative stress. (Ristow M, Proc Natl Acad Sci U S A, 2009; Merry TL, J Physiol, 2016)
- In a study of vitamin E forms and Alzheimer's disease, the risk of developing AD was reduced only in association with high plasma levels of β-tocopherol. The authors commented 'The neuroprotective effect of vitamin E seems to be related to the combination of different forms, rather than to α-tocopherol alone, whose efficacy in interventions against AD is currently debated'. (Mangialasche F, J Alzheimers Dis, 2010)