ECERI
European Cancer and Environment Research Institute

ARTAC

Environmental Medicine
Royal Academy of Medicine,Belgium
May 18 and 19, 2015

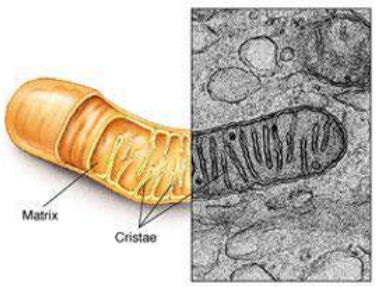
Mitochondria: Sensor of environmental aggressions

Vincent Castronovo, M.D., Ph.D.
University of Liege, Belgium

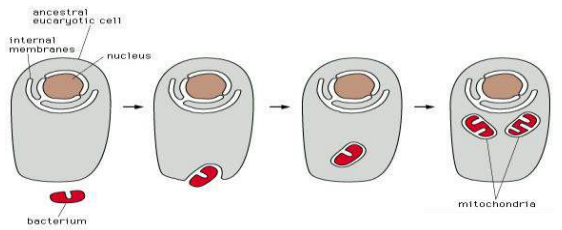
ULg

Mitochondria

The Power House of Cells



Mitochondria,
1.600.000.000 years ago…



Mitochondria, the ultimate ernergy producer of our cell is an ancestor bacteria that invented cellular respiration turning toxic oxygen into an indispensable molecule.

Mitochondria

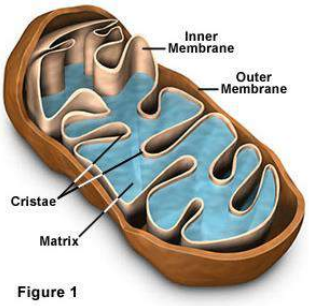
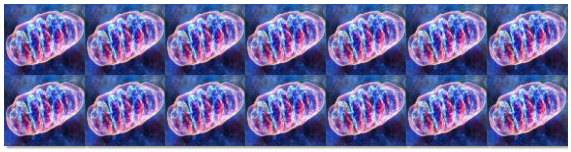
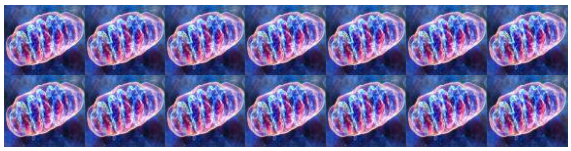
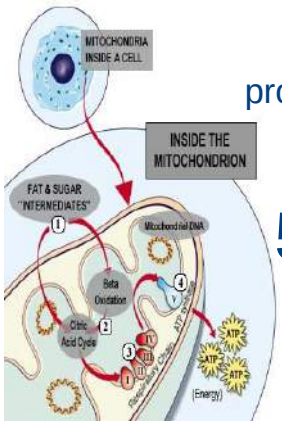


Figure 1



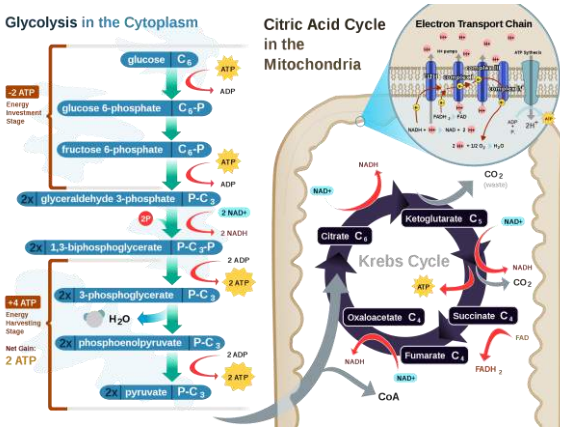
100.000.000.000.000.000
Mitochondria in a human

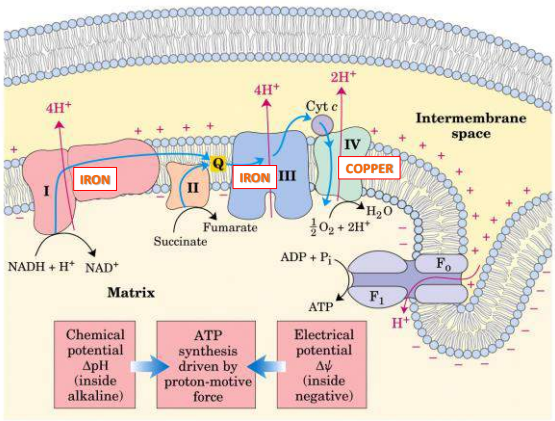




An individual produces and burns, per day, around

50 kilos of ATP

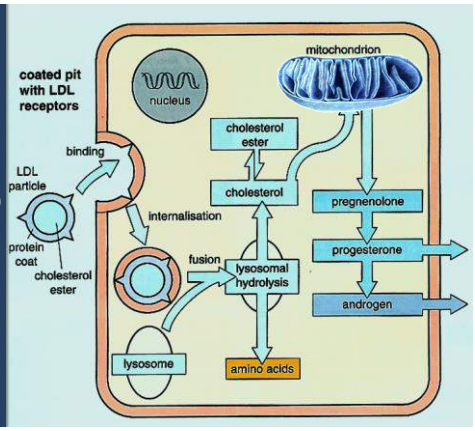




Mitochondria
A Multifunctionnal Organel

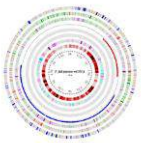
- **ATP production**
- Steroid hormone synthesis
- Detoxication
- Calcium control
- Apoptosis control

Mitochondria and Steroidogenesis



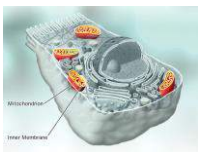
Mitochondria : The Second Genome

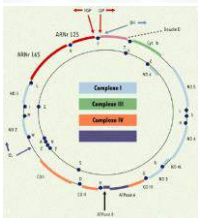
- Circular chromosomes
- 16,569 nucleotides
- Mitochondrial DNA exclusively transmitted by the mother

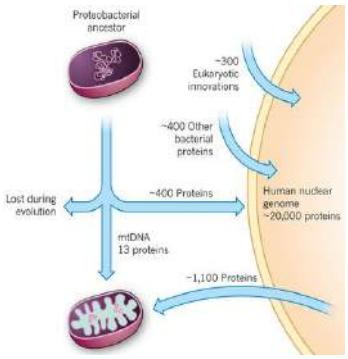


- mDNA contains 13 genes that encodes proteins from the respiratory chain
- mDNA is 10 times more fragile than nuclear DNA

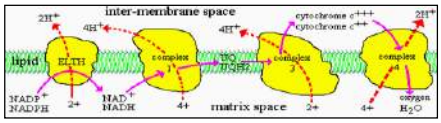
L'ADN Mitochondrial : le Second Génome

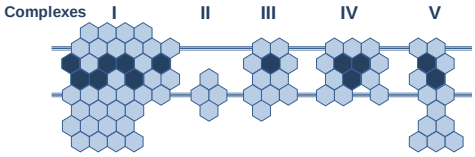






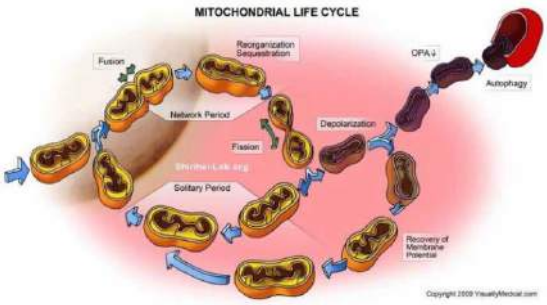
Mitochondrial Respiratory Chain



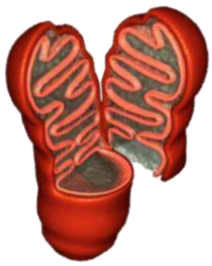


LIFE & DEATH OF MITOCHONDRIA

BIOGENESIS & MITOPHAGY

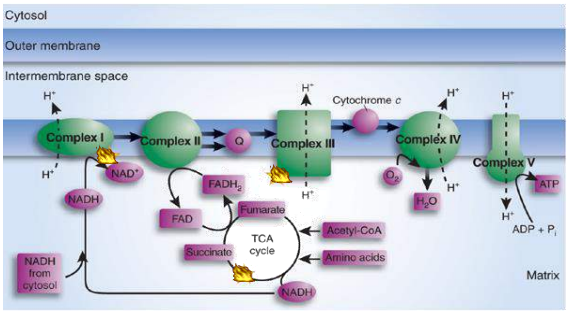


Mitochondrial Micronutrients



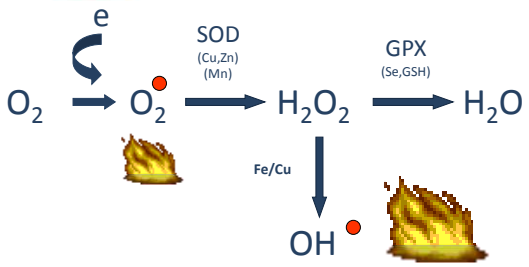
- Vitamins B1, B2, B3, B5
- Vitamins E, A, C
- Oméga-3 et -6 fatty acids
- iron
- Selenium
- Zinc
- Copper
- alpha lipoïc acid
- L-Carnitine
- Coenzyme-Q10
- Réduced Glutathion
- L-glutamin

Oxidative phosporylation can lead to premature fall of high energy electron …

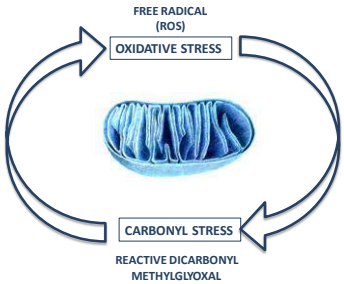


Mitochondria : Free Radicals

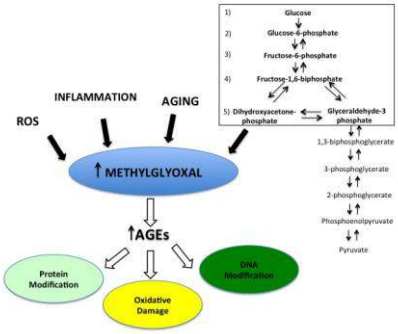
2- 10% of high energy electrons fall off the transporter chain



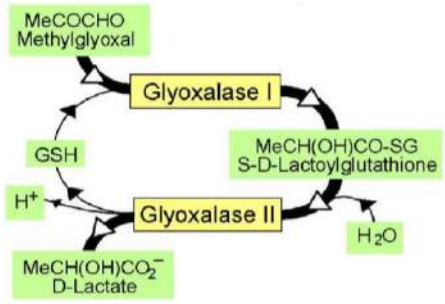
CARBPONYL STRESS AND OXIDATIVE STRESS ARE VICIOUSLY CONNECTED



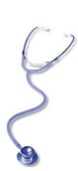
Methylglyoxal



Methylglyoxal: Detoxication



MITOCHONDRIAL MEDICINE



Mitochondrial medicine: entering the era of treatment.

Koene S, Smeitink J.

Intern Med. 2009 Feb;265(2):193-209.

Research of patients with defects in cellular energy metabolism (mitochondrial disease) has led to a better understanding of mitochondrial biology in health and disease. The obtained knowledge is of increasing importance for physicians of all medical disciplines. It assists in enabling the development of rational treatment strategies for diseases or conditions caused by mitochondrial dysfunction. The still frequently used classical interventions with vitamins or co-factors are only beneficial in some rare mitochondrial disease conditions, like coenzyme Q biosynthesis defects. For that reason alternative strategies to correct disturbed energy metabolism have to be developed. New approaches in this direction include nutrition and exercise therapies, alternative gene expression, enzyme-replacement, scavenging of potentially toxic compounds and modulating cell signalling. The effect of some of these interventions has already been explored in humans whilst others are still at the level of single cell research. We review the state of the art of the development of mitochondrial treatment strategies and discuss what steps need to be taken to efficiently approach the huge burden of disease caused by dysfunctional mitochondria.

Parr and Martin *Human Genomics* 2012, 6:3
http://www.humgenomics.com/content/6/1/3

REVIEW Open Access

Mitochondrial and nuclear genomics and the emergence of personalized medicine

Ryan L Parr* and Luis H Martin

Abstract

Developing early detection biosensors for disease has been the long-held goal of the Human Genome Project, but with little success. Conversely, the biological properties of the mitochondrion coupled with the relative simplicity of the mitochondrial genome give this organelle extraordinary functionality as a biosensor and places the field of mitochondrial genomics in a position of strategic advantage to launch significant advances in personalized medicine. Numerous factors make the mitochondrion organelle uniquely suited to be an early detection biosensor with applications in oncology as well as many other aspects of human health and disease. Early detection of disease translates into more effective, less expensive treatments for disease and overall better prognoses for those at greater risk for developing diseases.

Keywords: Mitochondrial genomics, Mitogenome, Genomic deletions, Cancerization field, Biosensor, Heteroplasmy

Review series

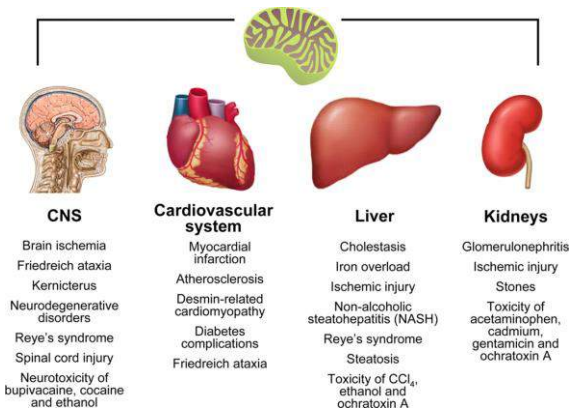
The role of mitochondria in aging

Ana Bratic[1,2] and Nils-Göran Larsson[1,2]

[1]Department of Mitochondrial Biology, Max Planck Institute for Biology of Ageing, Cologne, Germany. [2]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden.

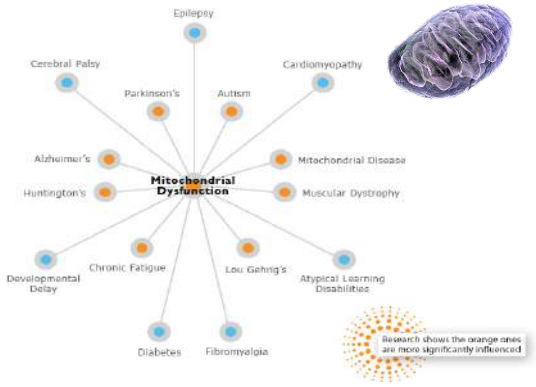
Over the last decade, accumulating evidence has suggested a causative link between mitochondrial dysfunction and major phenotypes associated with aging. Somatic mitochondrial DNA (mtDNA) mutations and respiratory chain dysfunction accompany normal aging, but the first direct experimental evidence that increased mtDNA mutation levels contribute to progeroid phenotypes came from the mtDNA mutator mouse. Recent evidence suggests that increases in aging-associated mtDNA mutations are not caused by damage accumulation, but rather are due to clonal expansion of mtDNA replication errors that occur during development. Here we discuss the caveats of the traditional mitochondrial free radical theory of aging and highlight other possible mechanisms, including insulin/IGF-1 signaling (IIS) and the target of rapamycin pathways, that underlie the central role of mitochondria in the aging process.

The Journal of Clinical Investigation Volume 123 Number 3 March 2013



CNS	Cardiovascular system	Liver	Kidneys
Brain ischemia	Myocardial infarction	Cholestasis	Glomerulonephritis
Friedreich ataxia	Atherosclerosis	Iron overload	Ischemic injury
Kernicterus	Desmin-related cardiomyopathy	Ischemic injury	Stones
Neurodegenerative disorders	Diabetes complications	Non-alcoholic steatohepatitis (NASH)	Toxicity of acetaminophen, cadmium, gentamicin and ochratoxin A
Reye's syndrome	Friedreich ataxia	Reye's syndrome	
Spinal cord injury		Steatosis	
Neurotoxicity of bupivacaine, cocaine and ethanol		Toxicity of CCl_4, ethanol and ochratoxin A	

MITOCHONDRIAL MEDICINE

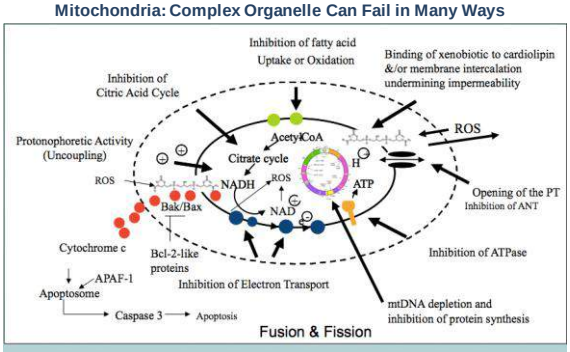


Mitochondrial diseases *generally have been thought of as a spectrum of primarily inherited conditions afflicting roughly 1 in every 2,000–5,000 people; about 1 in 200 people in the general population are thought to carry potentially pathogenic mitochondrial DNA mutations.*

Mitocondrial diseases can be also acquired and are the results of a variety of factors that can be associated:

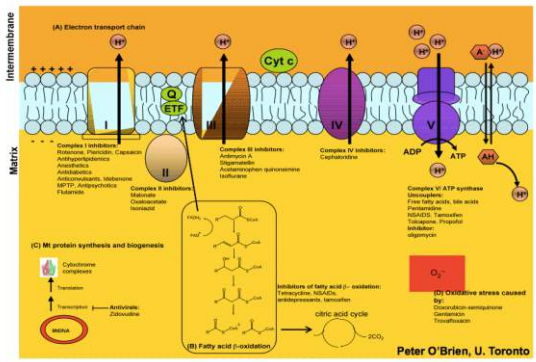
- **Micronutients deficiencies**
- **Pharmacological Drugs**
- **Heavy metals**
- **Pesticides**
- **Electromagnetic fields**

Mitochondria: Complex Organelle Can Fail in Many Ways



Dykens & Will, Drug Discovery Today, 12:777-785, 2007.

Pharmacological Drugs Affect Mitochondria



Some of the 44 Drugs Withdrawn Since 1960

Drug name	Withdrawn	Remarks
thalidomide	1960s	teratogenicity
lysergic acid diethylamide (LSD)	1960s	abused
diethylstilbestrol	1970s	teratogenicity
phenformin and buformin	1978	lactic acidosis
ticrynafen	1982	hepatitis
zimelidine	1983	Guillain-Barré syndrome
methaqualone	1984	addiction and overdose
triazolam	1991	UK - psychiatric
fenfluramine	1997	hepatotoxicity
dexfenfluramine	1997	hepatotoxicity
terfenadine	1998	arrhythmias
mibefradil	1998	interactions
troglitazone	2000	hepatotoxicity
alosetron	2000	constipation
cisapride	2000s	arrhythmias
cerivastatin	2001	rhabdomyolysis
rapacuronium	2001	bronchospasm
rofecoxib	2004	myocardial infarction
Adderall XR)	2005	Canada - stroke
hydromorphone	2005	overdose with alcohol
pemoline	2005	hepatotoxicity
natalizumab	2005-2006	CNS viral inflammation

TOXICOLOGICAL SCIENCES
doi:10.1093/toxsci/kft102
Advance Access publication April 29, 2013

REVIEW

Mitochondria as a Target of Environmental Toxicants

Joel N. Meyer,*,1 Maxwell C. K. Leung,* John P. Rooney,* Ataman Sendoel,† Michael O. Hengartner,† Glen E. Kisby,‡ and Amanda S. Bess*

*Nicholas School of the Environment, Duke University, Durham, North Carolina; †Institute of Molecular Life Sciences, University of Zurich, Zurich, Switzerland; and ‡Department of Basic Medical Sciences, Western University of Health Sciences, Lebanon, Oregon

1To whom correspondence should be addressed at Nicholas School of the Environment, Duke University, Box 90328, A354 LSRC, Research Dr, Durham, NC 27708-0328. Fax: (919) 668-1799. E-mail: joel.meyer@duke.edu.

Received January 23, 2013; accepted April 23, 2013

Many diseases have been identified as caused by mitochondrial dysfunction, and many pharmaceuticals have been identified as previously unrecognized mitochondrial toxicants. A much smaller but growing literature indicates that mitochondria are also targeted by environmental pollutants.

The Scientific World Journal
Volume 2012, Article ID 136063, 14 pages
doi:10.1100/2012/136063

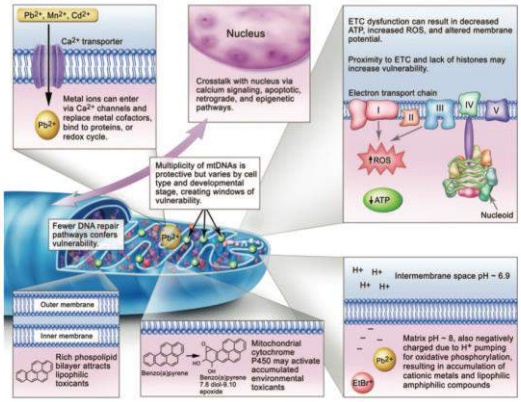
The ScientificWorldJOURNAL

Research Article

Mitochondrial Electron Transport Chain in Heavy Metal-Induced Neurotoxicity: Effects of Cadmium, Mercury, and Copper

Elena A. Belyaeva, Tatyana V. Sokolova, Larisa V. Emelyanova, and Irina O. Zakharova

I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry of Russian Academy of Sciences, Thorez pr. 44, 194223 Saint-Petersburg, Russia



Arch Toxicol. 2015 Feb;89(2):147-53. doi: 10.1007/s00204-014-1431-3. Epub 2015 Jan 6.

Mitochondrial functional impairment in response to environmental toxins in the cardiorenal metabolic syndrome.

Jia G[1], Aroor AR, Martinez-Lemus LA, Sowers JR.

Author information

Abstract

Environmental toxins can promote cardiovascular, metabolic, and renal abnormalities, which characterize the cardiorenal metabolic syndrome (CRS). Heavy metals, such as mercury and arsenic, represent two of the most toxic pollutants. Exposure to these toxins is increasing due to increased industrialization throughout much of the world. Studies conducted to understand the impact of environmental toxins have shown a major impact on mitochondrial structure and function. The maladaptive stress products caused by these toxins, including aggregated proteins, damaged organelles, and intracellular pathogens, can be removed through autophagy, which is also known as mitophagy in mitochondria. Although the underlying mechanisms involved in the regulation of mitophagy in response to pollution are not well understood, accumulating evidence supports a role for maladaptive mitochondrial responses to environmental pollution in the pathogenesis of the CRS. In this review, we discuss the ongoing research, which explores the mechanisms by which these toxins promote abnormalities in mitophagy and associated mitochondrial dysfunction and the CRS.

Front Biosci. 2007 Jan 1;12:1079-93.

Pesticides and impairment of mitochondrial function in relation with the parkinsonian syndrome.

Gomez C[1], Bandez MJ, Navarro A.

Author information

Abstract

The Parkinsonian syndrome induced by pesticides is associated with the impairment of mitochondrial function. Toxicants that inhibit selectively NADH-dehydrogenase activity, as rotenone or pyridaben, also show a selective inhibition of O2 uptake and respiratory control in rat brain mitochondria in the presence of NAD-dependent substrates. The IC50 of rotenone and pyridaben for complex I inhibition were in the range 1.7-2.2 microM. The determination of NADH-cytochrome c reductase, succinate-cytochrome c reductase and cytochrome oxidase activities in rat brain submitochondrial showed again the selective inhibition of Complex I by rotenone and pyridaben, whereas paraquat produced a non-selective inhibition affecting all the respiratory chain complexes. In rat brain mitochondria, rotenone and pyridaben markedly decreased mtNOS functional activity with NAD-dependent substrates but not when the substrate was succinate. This observation suggest than mtNOS activity is regulated by the activity of complex I. This regulation and the role of mitochondrial NO diffusion as a signal for mitochondrial biogenesis could have a role in the etiopathology of Parkinson's disease.

Hum Exp Toxicol. 2014 Mar;33(3):251-63. doi: 10.1177/0960327113493300. Epub 2013 Jun 17.

Mechanisms of muscular electrophysiological and mitochondrial dysfunction following exposure to malathion, an organophosphorus pesticide.

Karami-Mohajeri S[1], Hadian MR, Fouladdel S, Azizi E, Ghahramani MH, Hosseini R, Abdollahi M.

Author information

Abstract

Muscle dysfunction in acute organophosphorus (OP) poisoning is a cause of death in human. The present study was conducted to identify the mechanism of action of OP in terms of muscle mitochondrial dysfunction. Electromyography (EMG) was conducted on rats exposed to the acute oral dose of malathion (400 mg/kg) that could inhibit acetylcholinesterase activity up to 70%. The function of mitochondrial respiratory chain and the rate of production of reactive oxygen species (ROS) from intact mitochondria were measured. The bioenergetic pathways were studied by measurement of adenosine triphosphate (ATP), lactate, and glycogen. To identify mitochondrial-dependent apoptotic pathways, the messenger RNA (mRNA) expression of bax and bcl-2, protein expression of caspase-9, mitochondrial cytochrome c release, and DNA damage were measured. The EMG confirmed muscle weakness. The reduction in activity of mitochondrial complexes and muscular glycogen with an elevation of lactate was in association with impairment of cellular respiration. The reduction in mitochondrial proapoptotic stimuli is indicative of autophagic process inducing cytoprotective effects in the early stage of stress. Downregulation of apoptotic signaling may be due to reduction in ATP and ROS, and genotoxic potential of malathion. The maintenance of mitochondrial integrity by means of artificial electron donors and increasing exogenous ATP might prevent toxicity of OPs.

Neurochem Res. 2006 Aug;31(8):1021-5. Epub 2006 Jul 25.

Mitochondrial respiratory dysfunction and oxidative stress after chronic malathion exposure.

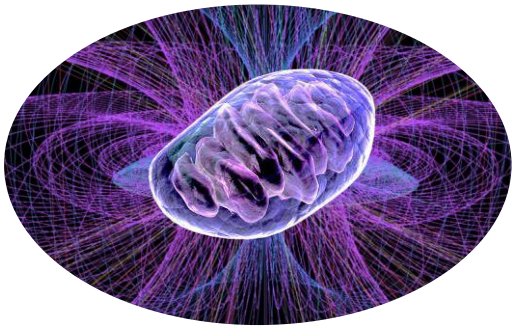
Delgado EH[1], Streck EL, Quevedo JL, Dal-Pizzol F.

Author information

Abstract

Malathion is a pesticide used on a large scale and with high potential risk for human exposure. However, it is reasonable to hypothesize that while the malathion is metabolizing reactive oxygen species (ROS) can be generated and subsequently there is onset of an oxidative stress in central nervous system (CNS) structures: hippocampus, cortex, striatum and cerebellum of intoxicated rats due to mitochondrial respiratory chain disfunctions. The present study was therefore undertaken to evaluate malathion-induced lipid peroxidation (LPO), superoxide production from sub-mitochondrial particles and the activity of complexes II and IV of the mitochondrial respiratory chain. Malathion was administered in doses of 25, 50, 100 and 150 mg malathion/kg. After malathion administration LPO increased in hippocampus and striatum. This was accompanied by an increase in the formation of superoxide in submitochondrial particles in the hippocampus. Complex IV suffered significant inhibition of its activity. We could demonstrate in this study that malathion induces oxidative stress and it could be due to inactivation of mitochondrial respiratory complexes.

Mitochondria and Electromagetic Fields



Pubmed 19/5/2015: 77 publications

The effects of prenatal exposure to a 900-MHz electromagnetic field on the 21-day-old male rat heart.

Türedi S1, Hancı H, Topal Z, Unal D, Mercantepe T, Bozkurt I, Kaya H, Odacı E.
Electromagn Biol Med. 2014 Aug 28:1-8.

The growing spread of mobile phone use is raising concerns about the effect on human health of the electromagnetic field (EMF) these devices emit. The purpose of this study was to investigate the effects on rat pup heart tissue of **prenatal exposure to a 900 megahertz** (MHz) EMF. For this purpose, pregnant rats were divided into experimental and control groups. Experimental group rats were exposed to a 900 MHz EMF (1 h/d) on days 13-21 of pregnancy. Measurements were performed with rats inside the exposure box in order to determine the distribution of EMF intensity. Our measurements showed that pregnant experimental group rats were exposed to a mean electrical field intensity of 13.77 V/m inside the box (0.50 W/m2). This study continued with male rat pups obtained from both groups. Pups were sacrificed on postnatal day 21, and the heart tissues were extracted. **Malondialdehyde, superoxide dismutase and catalase values were significantly higher in the experimental group rats, while glutathione values were lower.** Light microscopy revealed irregularities in heart muscle fibers and apoptotic changes in the experimental group. **Electron microscopy revealed crista loss and swelling in the mitochondria**, degeneration in myofibrils and structural impairments in Z bands. Our study results suggest that exposure to EMF in the prenatal period causes oxidative stress and histopathological changes in male rat pup heart tissue.

PLoS One. 2012;7(8):e42332. doi: 10.1371/journal.pone.0042332. Epub 2012 Aug 1.

Exposure to 1950-MHz TD-SCDMA electromagnetic fields affects the apoptosis of astrocytes via caspase-3-dependent pathway.

Liu YX[1], Tai JL, Li GQ, Zhang ZW, Xue JH, Liu HS, Zhu H, Cheng JD, Liu YL, Li AM, Zhang Y.

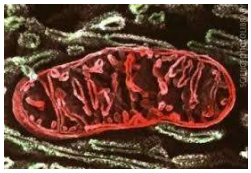
Author information

Abstract

The usage of mobile phone increases globally. However, there is still a paucity of data about the impact of electromagnetic fields (EMF) on human health. This study investigated whether EMF radiation would alter the biology of glial cells and act as a tumor-promoting agent. We exposed rat astrocytes and C6 glioma cells to 1950-MHz TD-SCDMA for 12, 24 and 48 h respectively, and found that EMF exposure had differential effects on rat astroctyes and C6 glioma cells. A 48 h of exposure damaged the mitochondria and induced significant apoptosis of astrocytes. Moreover, caspase-3, a hallmark of apoptosis, was highlighted in astrocytes after 48 h of EMF exposure, accompanied by a significantly increased expression of bax and reduced level of bcl-2. The tumorigenicity assays demonstrated that astrocytes did not form tumors in both control and exposure groups. In contrast, the unexposed and exposed C6 glioma cells show no significant differences in both biological feature and tumor formation ability. Therefore, our results implied that exposure to the EMF of 1950-MHz TD-SCDMA may not promote the tumor formation, but continuous exposure damaged the mitochondria of astrocytes and induce apoptosis through a caspase-3-dependent pathway with the involvement of bax and bcl-2.

Evaluation of Mitochondrial Status

- Lactic acid dosage
- Oxidative stress evaluation (Urinay 8 OH guanosine)
- Circulating Mithochondrial DNA



PLoS One. 2013 May 31;8(5):e64413. doi: 10.1371/journal.pone.0064413. Print 2013.

Circulating mitochondrial DNA as biomarker linking environmental chemical exposure to early preclinical lesions elevation of mtDNA in human serum after exposure to carcinogenic halo-alkane-based pesticides.

Budnik LT[1], Kloth S, Baur X, Preisser AM, Schwarzenbach H.

Author information

Abstract

There is a need for a panel of suitable biomarkers for detection of environmental chemical exposure leading to the initiation or progression of degenerative diseases or potentially, to cancer. As the peripheral blood may contain increased levels of circulating cell-free DNA in diseased individuals, we aimed to evaluate this DNA as effect biomarker recognizing vulnerability after exposure to environmental chemicals. We recruited 164 individuals presumably exposed to halo-alkane-based pesticides. Exposure evaluation was based on human biomonitoring analysis; as biomarker of exposure parent halo-methanes, -ethanes and their metabolites, as well as the hemoglobin-adducts methyl valine and hydroxyl ethyl valine in blood were used, complemented by expert evaluation of exposure and clinical intoxication symptoms as well as a questionnaire. Assessment showed exposures to halo alkanes in the concentration range being higher than non-cancer reference doses (RfD) but (mostly) lower than the occupational exposure limits. We quantified circulating DNA in serum from 86 individuals with confirmed exposure to off-gassing halo-alkane pesticides (in storage facilities or in home environment) and 30 non-exposed controls, and found that exposure was significantly associated with elevated serum levels of circulating mitochondrial DNA (in size of 79 bp, mtDNA-79, $p=0.0001$). The decreased integrity of mtDNA (mtDNA-230/mtDNA-79) in exposed individuals implicates apoptotic processes ($p=0.015$). The relative amounts of mtDNA-79 in serum were positively associated with the lag-time after intoxication to these chemicals ($r=0.99$, $p<0.0001$). Several months of post-exposure the specificity of this biomarker increased from 30% to 97% in patients with intoxication symptoms. Our findings indicate that mitochondrial DNA has a potential to serve as a biomarker recognizing vulnerable risk groups after exposure to toxic/carcinogenic chemicals.

How to improve mitochondrial functions

- Optimization of mitochondrial micronutrient status
- Nutritional chelation of heavy metal
  - Alpha lipoic acid(3 times 600 mg/day)
  - Reduced glutathion (2 times 1g/day)
- Regular aerobic physical exercise

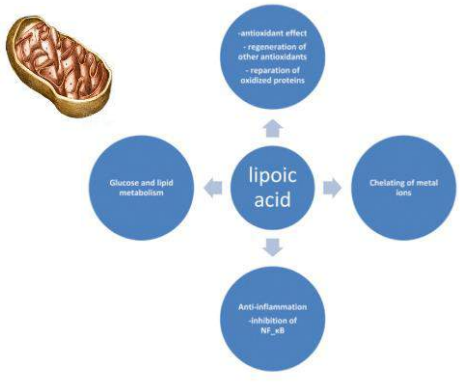
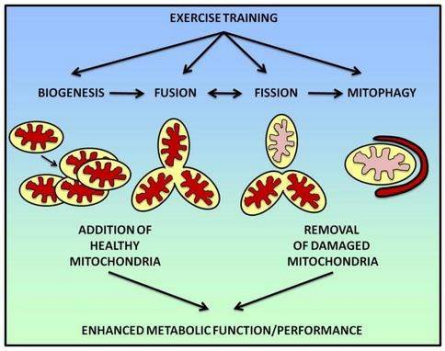


FIGURE 1 | Selected biological actions of lipoic acid.



Thank you for listening!