Management of Mitochondrial Disease: The Role of Supplements and Emergency Protocols

Hilary Vernon, MD, PhD
Director of the Metabolism Clinic and Barth Syndrome Clinic at Kennedy Krieger Institute
&
Assistant Professor of Genetic Medicine
The Johns Hopkins University’s Institute of Genetic Medicine
Anatomy of the cell

- Each organelle has its individual function.
- Yet they are intertwined and inseparable with each other.

Mitochondria: Energy production
Nucleus: Package genes
ER: Stress, molecular management
Golgi: Molecular modification
Lysosome: Waste disposal
Functions of the mitochondria

• ATP production
• Citric Acid (Krebs) Cycle
• Fatty Acid Oxidation
• Transport of reducing equivalents
  – Malate-aspartate shuttle, etc.
• Apoptosis
• Ammonia detoxification (in liver)
Mitochondrial structure

- Outer mitochondrial membrane
  - porins that allow molecules <5000 Daltons to diffuse
- Intermembrane space
  - concentrations of small molecules is the same as the cytosol
- Inner mitochondrial membrane
  - Oxidative phosphorylation
  - ATP synthase
  - Metabolite and protein transport
  - Fusion and fission machinery
- Cristae (foldings of the inner membrane)
- Matrix (space in the inner membrane)
  - Ribosomes, tRNAs, mtDNA, biochem. Rxns

http://micro.magnet.fsu.edu/cells/
Cell Function: A balance between “breaking down and building up”

Catabolism: Use fuel to make energy
- Energy sources
- Utilizable energy
- Metabolic products
- Heat

Anabolism: Build Cellular Intermediates
- ATP
- Biopolymers
- Intermediates
- Intracellular precursors
- External nutrients
- ADP
Mitochondrial Energy Production by the Respiratory Chain

Exogenous and Endogenous Carbohydrate
Fat
Protein

ATP
Flux between cytoplasm and mitochondria

Nadege et al, Frontiers in Bioscience 14, 4015-4034, 2009
Cytoplasmic Energy Production by Glycolysis

Exogenous and endogenous Carbohydrates → Glucose → ATP → Pyruvate

Cytoplasmic to mitochondrial energy metabolism

Glucose → ATP

Pyruvate → ATP

ATP

TCA cycle

Glucose → Pyruvate → ATP

NAD+ → NADH

ATP

Cytoplasmic to mitochondrial energy metabolism
Consequences of energy failure

• Decreased ATP
  – The energy molecule of the cell
• Energy failure
• Altered cellular cascades
  – Stress responses
• Increased ROS
• Lipid peroxidation
• Apoptosis
  – Cell death
Oxidative Damage

• Acute ROS exposure
  – Inactivates the Fe-S centers of ETC complexes I, II, III, & aconitase
  – Decreases mitochondrial energy production

• Chronic ROS exposure causes oxidative damage to mitochondrial and cellular proteins, lipids, and nucleic acids

• Protein thiols, glutathione, α-tocopherol are considered to be protective against ROS
ROS: Cascade of cellular reactions

- Accumulating injury to lipids and DNA
- Accumulating organelle damage
- Change cellular signalling
- Alter Gene Expression
- Alterations in Cellular Survival

Oxidative Stress
Reactive oxygen species

Generation of reactive oxygen species is enhanced when the respiratory chain is inefficient.
Oxidative Stress

OXIDATIVE DAMAGE
- O$_2^-$
- H$_2$O$_2$
- OH
- NO
- ONOO-
- GSSG

ANTI-OXIDANT DEFENSE
- Superoxide dismutase
- Catalase
- Glutathione system
- Ascorbic acid
- α-Tocopherol
- Lipoic acid

CELL DEATH

CELL SURVIVAL

www.simd.org
Basic Principles in Mitochondrial Disease Management
Dual approaches to reduce bioenergetic deprivation

**Reduce cellular Stress of ROS**

- **Antioxidants**
  - CoQ10
  - Vitamin C
  - Vitamin E
  - Others

- **OxPhos Cofactors**
  - Carnitine
  - Riboflavin
  - Others

**Reduce cellular stress of decreased fuel**

- Avoid prolonged fasting
- Avoid Fever
- Avoid Dehydration
- Balanced healthy diet
Where do the vitamins act?

Antioxidant: Vitamin E, Lipoic acid, N-acetylcysteine, CoQ10

Bypass Defect: CoQ10, Succinate

Improve Energy Pools: Creatine

Improve Energy Transfer: Carnitine
Discussion in mitochondrial vitamin therapy: Why is this controversial?

• Few to no standard protocols for supplements many (most) mitochondrial conditions
• Few to no well controlled studies on effects of individual supplements
  – Conditions are rare
  – Endpoints for measuring success are limited
• Not clear that some supplements get to the affected tissues
• Many clinicians rely on their personal experiences
“Highest levels of Evidence”
Difficult in rare diseases

• Lack of prospective natural history studies
  – Small cohorts
  – Different clinical focuses

• Difficulty determining clinical targets for measurement of treatment outcome
  – Length of time to see an effect
  – Selecting the right target

• No biomarkers correlating to clinical status

• These are not insurmountable, but must be considered carefully
My Personal Approach to vitamin supplements

• Most important principle: “First Do No Harm”
• Keep an open mind
• Ask the following questions
  – Is there a risk to this approach
  – Is there any level of evidence supporting this approach
  – Has this approach worked in similar conditions
  – Did this child have an improvement with this approach
• Aim to keep key vitamin levels robust but still within the realm of physiologic (high normal)
  – Vitamin E, CoEnzyme Q10, Carnitine
Approaches to Bioenergetic Stress Reduction

- Therapeutic goals when energy is limited
- General health strategies
  - Optimize nutrition
    - Appropriate, well proportioned calories
    - Follow growth curves, work with trusted dietician
  - Encourage appropriate sleep
    - Listen to your body.
    - If you’re tired, rest
- Precautions during surgical procedures
- Avoid continued deprivation
  - Avoid fasting and dehydration
- Optimize muscle strength and avoid deconditioning
  - Do what you can, but do something
Mitochondrial Stress Management Strategies in LBSL: Considerations
Evidence for Mitochondrial Stress in LBSL

- Robust evidence that decompensation can occur early and in the setting of bioenergetic stress
  - With fever or intercurrent illness
- Experimental evidence that cells lacking in DARS2 have both respiratory chain dysfunction and cellular stress responses INDEPENDENTLY and INTERDEPENDENTLY
Tissue Specificity in LBSL

• Tissue specificity is seen in many conditions
  – Mitochondrial and non-mitochondrial conditions
  – Primary and Secondary mitochondrial conditions
• Not well understood
• May be related to individual energy needs of the tissue
• May be due to tissue-specific stress responses
• Certainly there are other unknown factors and a lot to learn
Body Chemistry in flux with the CNS

Provide fuel

Inflammatory signals

Manage Inflammation, reduce fever

Avoid starvation

Ketoacids
Glucose Lactate
Amino acids
Glu GluN
Essential AAs
Na,K ATPase
HCO3-
Lipids and fats

Lipids and fats

Avoid starvation
Similar approaches to bioenergetic balance

**Reduce stress of decreased fuel**
- Avoid prolonged fasting
- Surgical precautions
- Avoid Fever
- Avoid Dehydration
- Balanced healthy diet

**Reduce Stress of ROS**
- Antioxidants
- OxPhos Cofactors