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

Hilary Vernon, MD, PhD
Director, Mitochondrial Medicine Center
Associate Professor of Genetic Medicine
John Hopkins University School of 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
Lysosome: waste disposal
Golgi: molecular modification
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 → heat → utilizable energy → metabolic products

**Anabolism**
- Build Cellular Intermediates
- Biopolymers → intermediates → intracellular precursors → external nutrients
- ATP

ATP (Adenosine Triphosphate)
- A balance between breaking down and building up
- Utilizable energy
- Energy sources
- Metabolic products
- ADP
Mitochondrial Energy Production by the Respiratory Chain

Exogenous and Endogenous Carbohydrate
Fat
Protein
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

ATP

Pyruvate
Cytoplasmic to mitochondrial energy metabolism

ATP
Glucose
Pyruvate

ATP
Pyruvate

TCA cycle
NADH
NAD+

e-

1

ATP

ATP
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

H₂O₂ → OH⁻

Fe²⁺ → Cu⁺

MnSOD

O₂⁻

H⁺

H₂O → H₂O₂

CuZnSOD

O₂⁻

H⁺

NADH → NAD⁺

complex I

1.6.99.5

complex III

1.10.2.2

Nqo1, Nqo2, Nqo3, Nqo4, Nqo5, Nqo6, Nqo7, Nqo8, Nqo9

GPX-1

mitochondrion

cytoplasm

mitochondrial membrane

Core 1

Core 2

Cyt C, ISP

15

6

9

10

11

H⁺

H₂O → H₂O₂

Cu⁺ → Fe²⁺

OH⁻
Oxidative Stress

Oxidative Damage:
- $\text{O}_2^-$
- $\text{H}_2\text{O}_2$
- OH
- NO
- ONOO-
- GSSG

Antioxidant Defense:
- Superoxide dismutase
- Catalase
- Glutathione system
- Ascorbic acid
- $\alpha$-Tocopherol
- Lipoic acid

Cell Death

Cell Survival
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
Evidence in Clinical Investigation

- Meta-Analyses
- Systematic Reviews
- Randomized Controlled Trials
- Cohort Studies
- Case-Controlled Studies
- Case Reports
- Background Information/Expert Opinion

Degree of Evidence
“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

Ketoacids
Glucose Lactate
GLUT1 MCT1 L1

Amino acids
Glu GluN
ASC A EAAT LNAA N

Manage Inflammation, reduce fever

Inflammatory signals

Hormones

Avoid starvation

Lipids and fats

Pgp MRP1 BCRP

Pgp MRP4 OAT3

Na,K ATPase

H+ K+ HCO3-

Na+, K+ 2Cl-

HCO3-
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
Anti-oxidants
OxPhos Cofactors
Questions?