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

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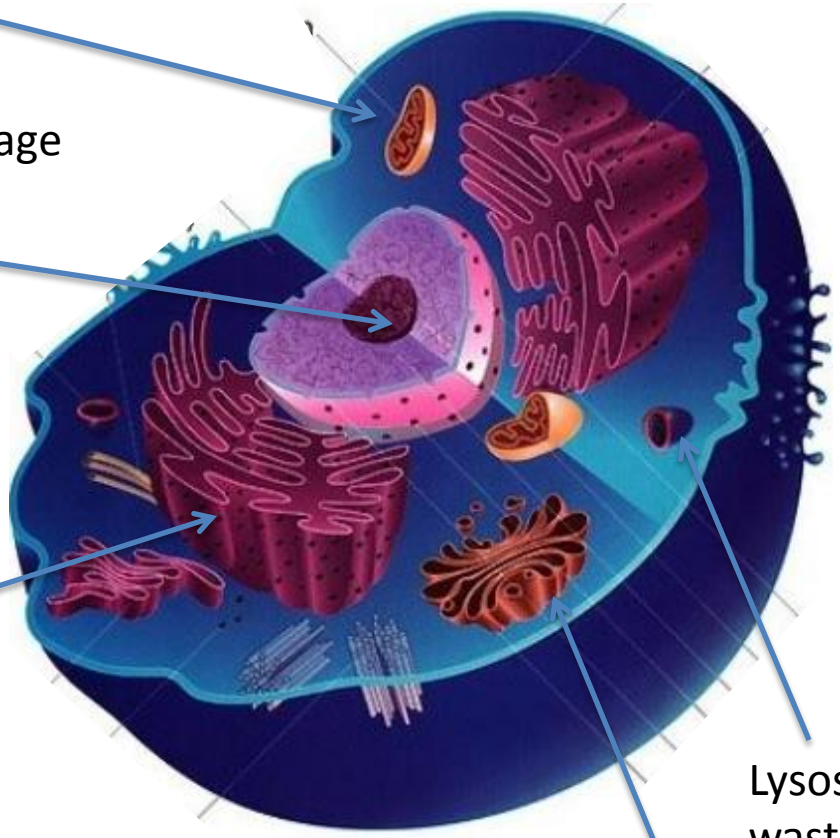
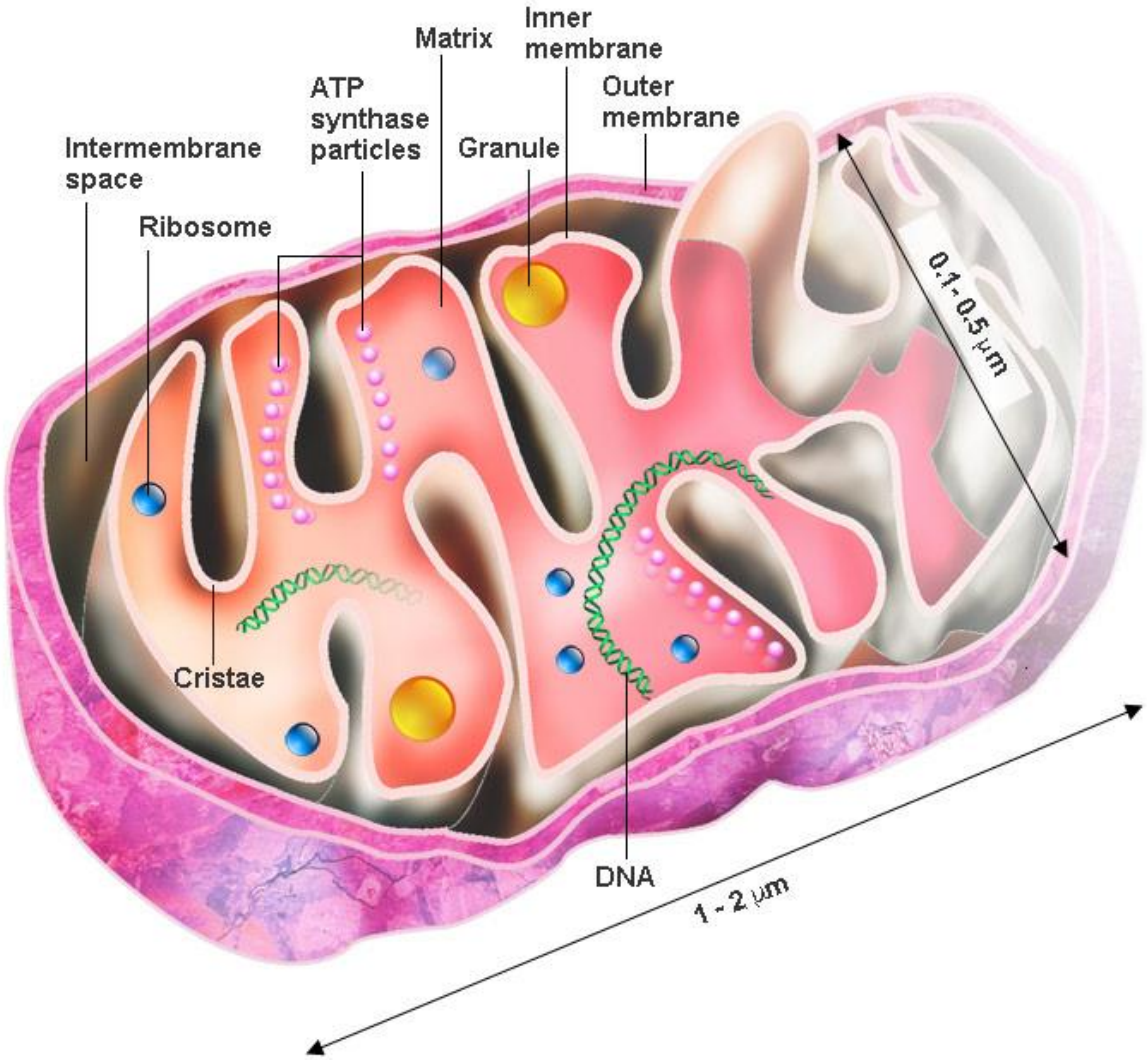
Anatomy of the cell

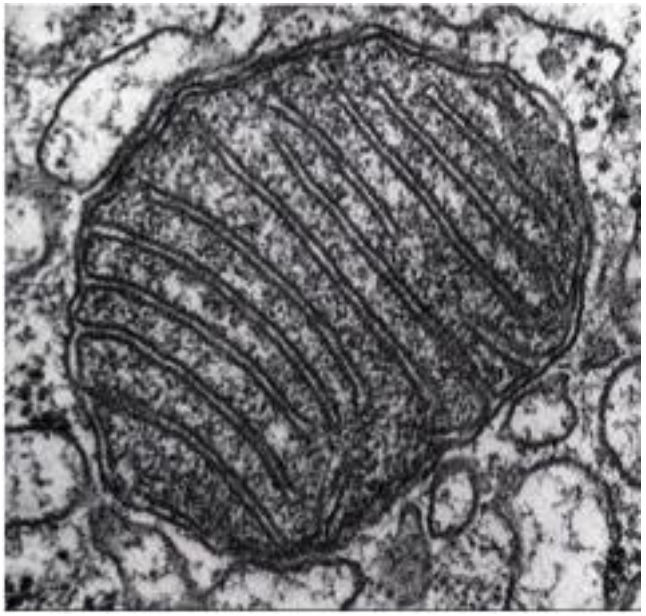


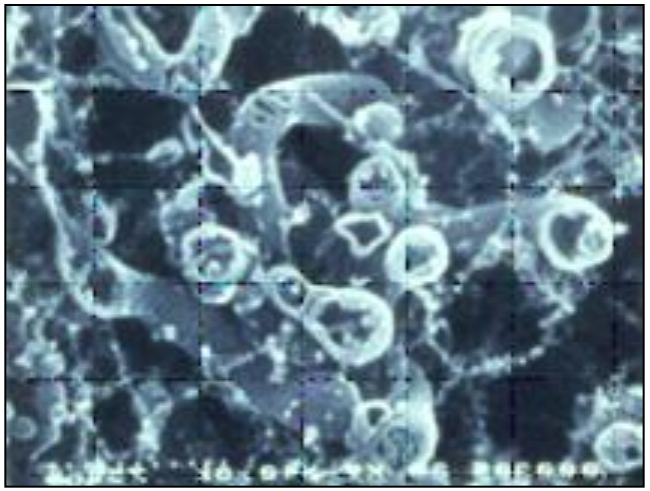
-Each organelle has it's individual function

-Yet they are intertwined and inseparable with each other

Mitochondria







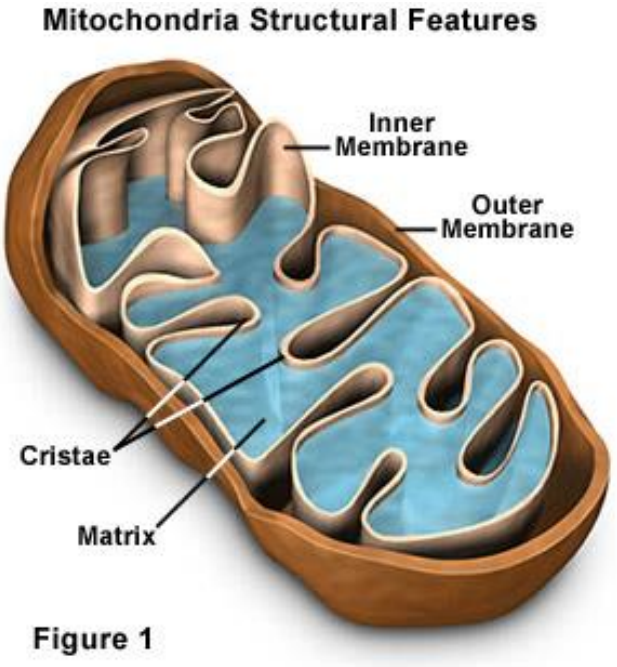
www.simd.org

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)

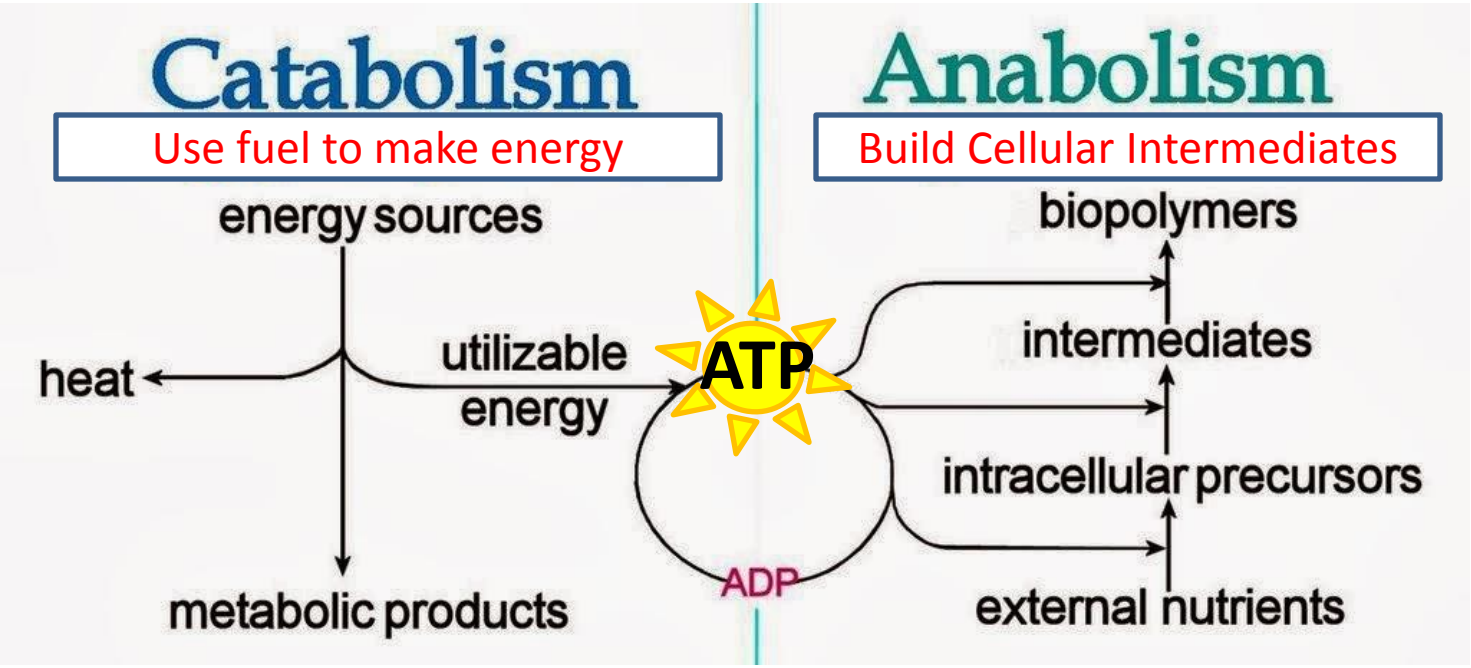
Mitochondrial structure

- 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

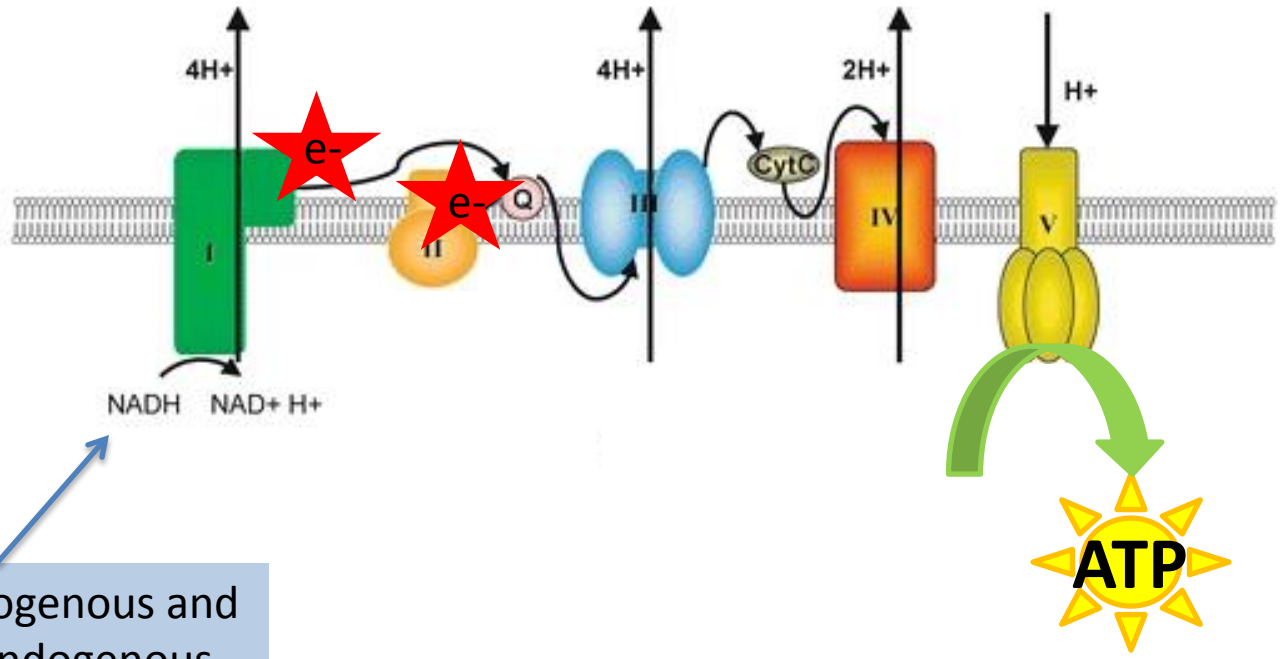


http://micro.magnet.fsu.edu/cells/

Cell Function: A balance between "breaking down and building up"

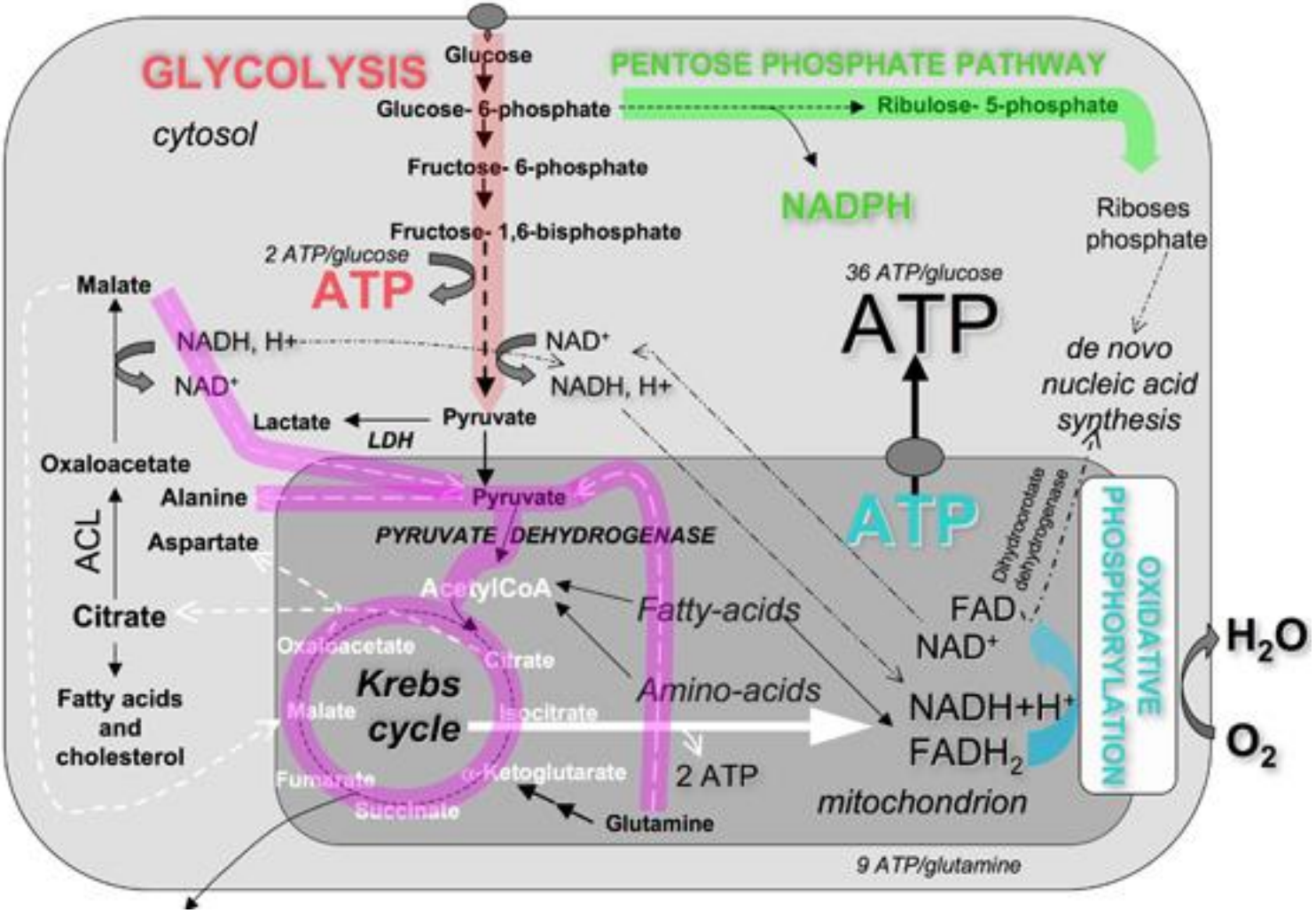


Mitochondrial Energy Production by the Respiratory Chain



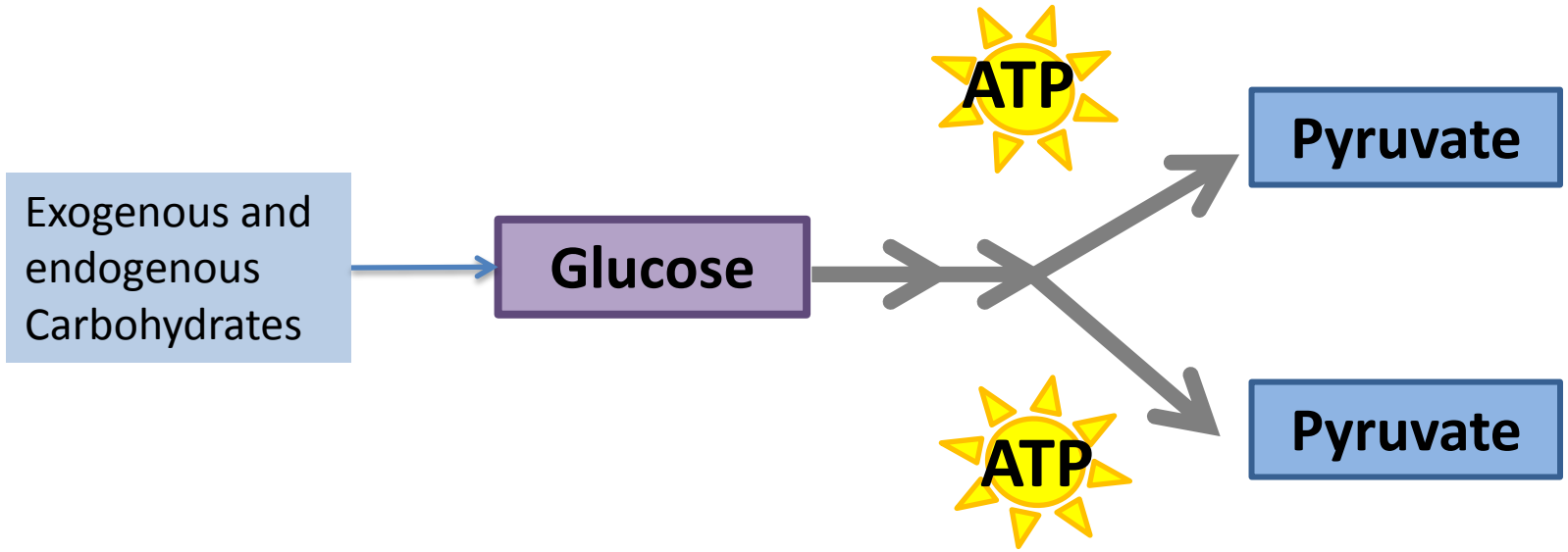
Exogenous and
Endogenous
Carbohydrate
Fat
Protein

Flux between cytoplasm and mitochondria

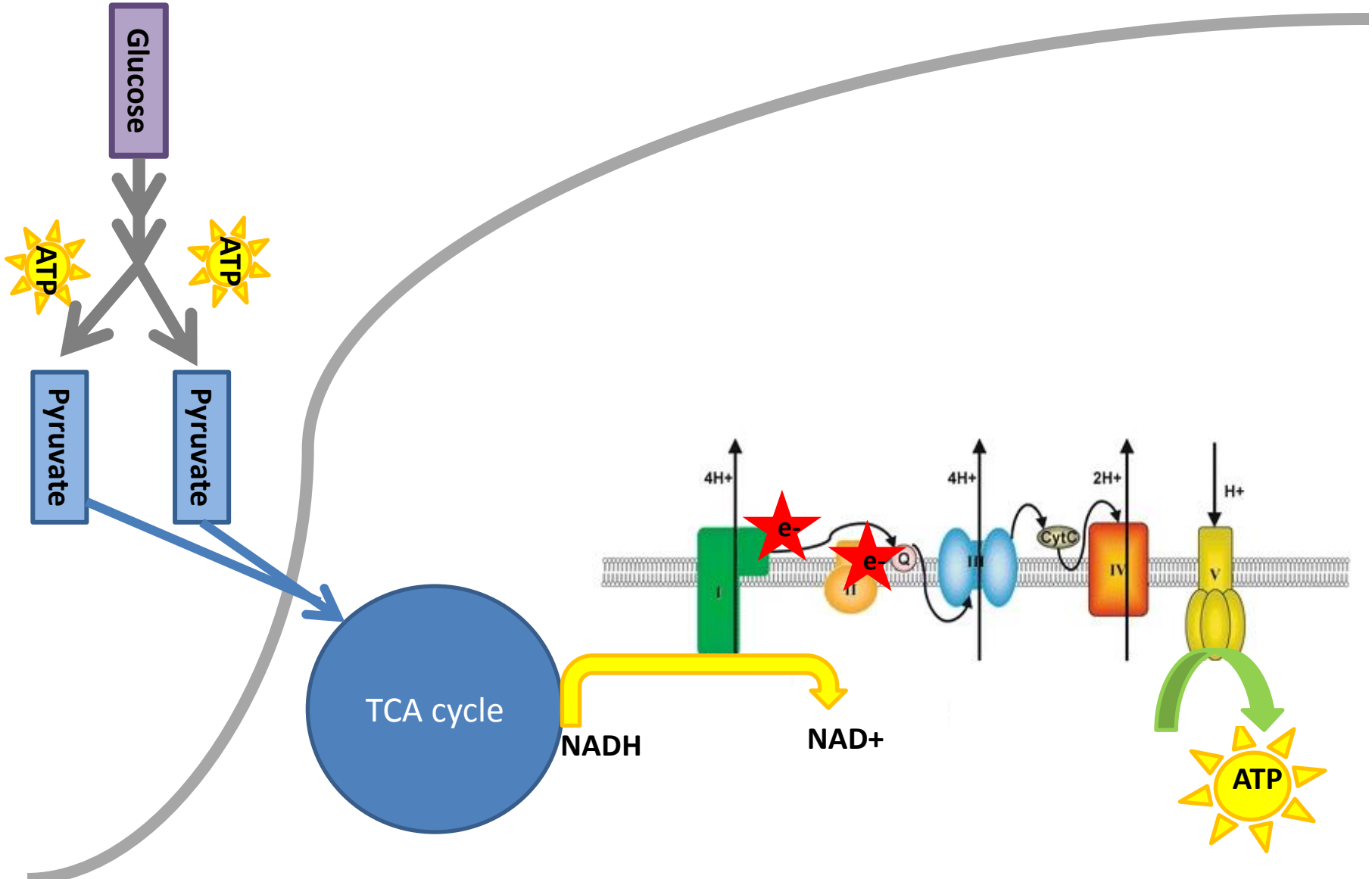


Nadege et al, Frontiers in Bioscience 14, 4015-4034, 2009

Cytoplasmic Energy Production by Glycolysis



Cytoplasmic to mitochondrial energy metabolism



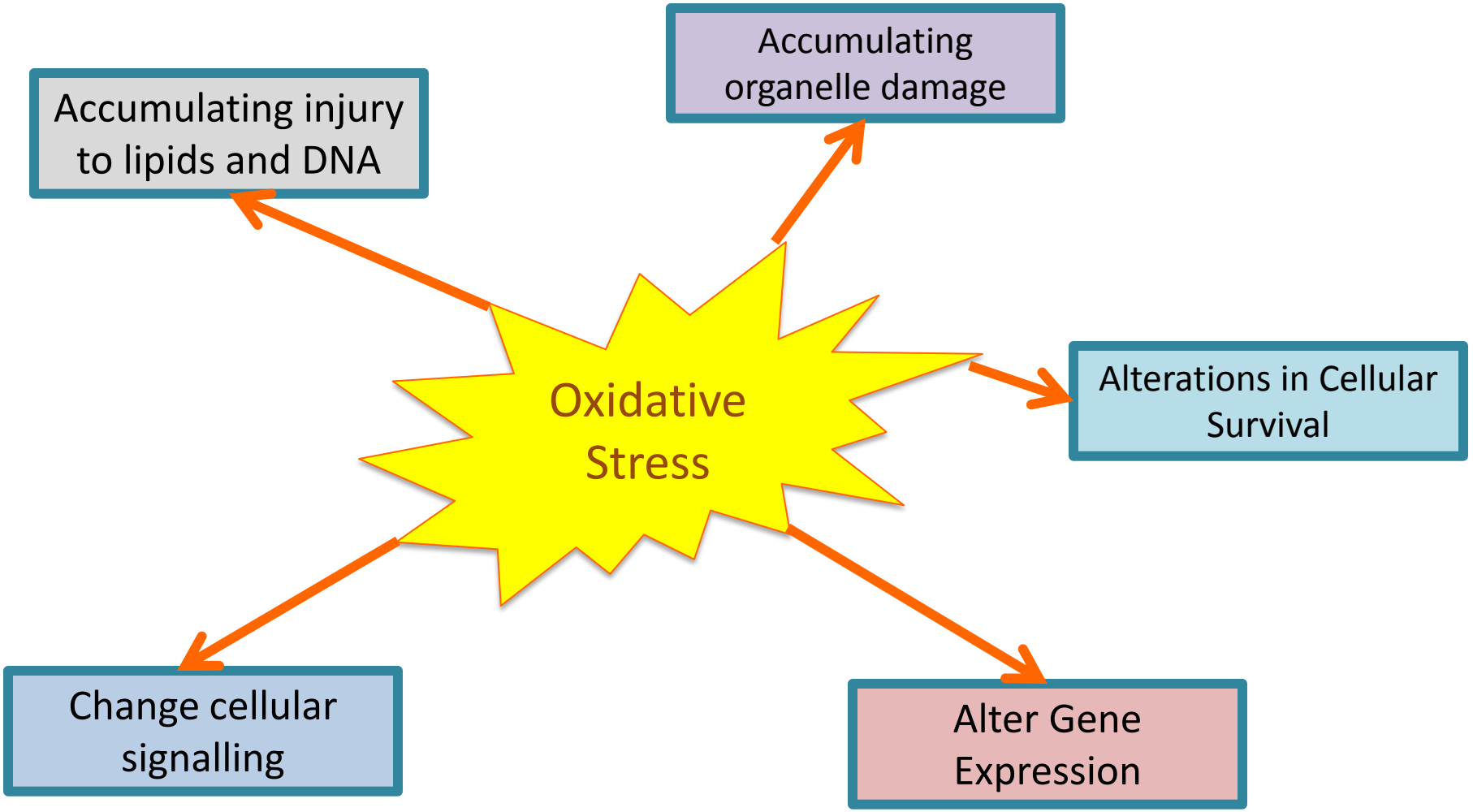
Consequences of energy failure

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

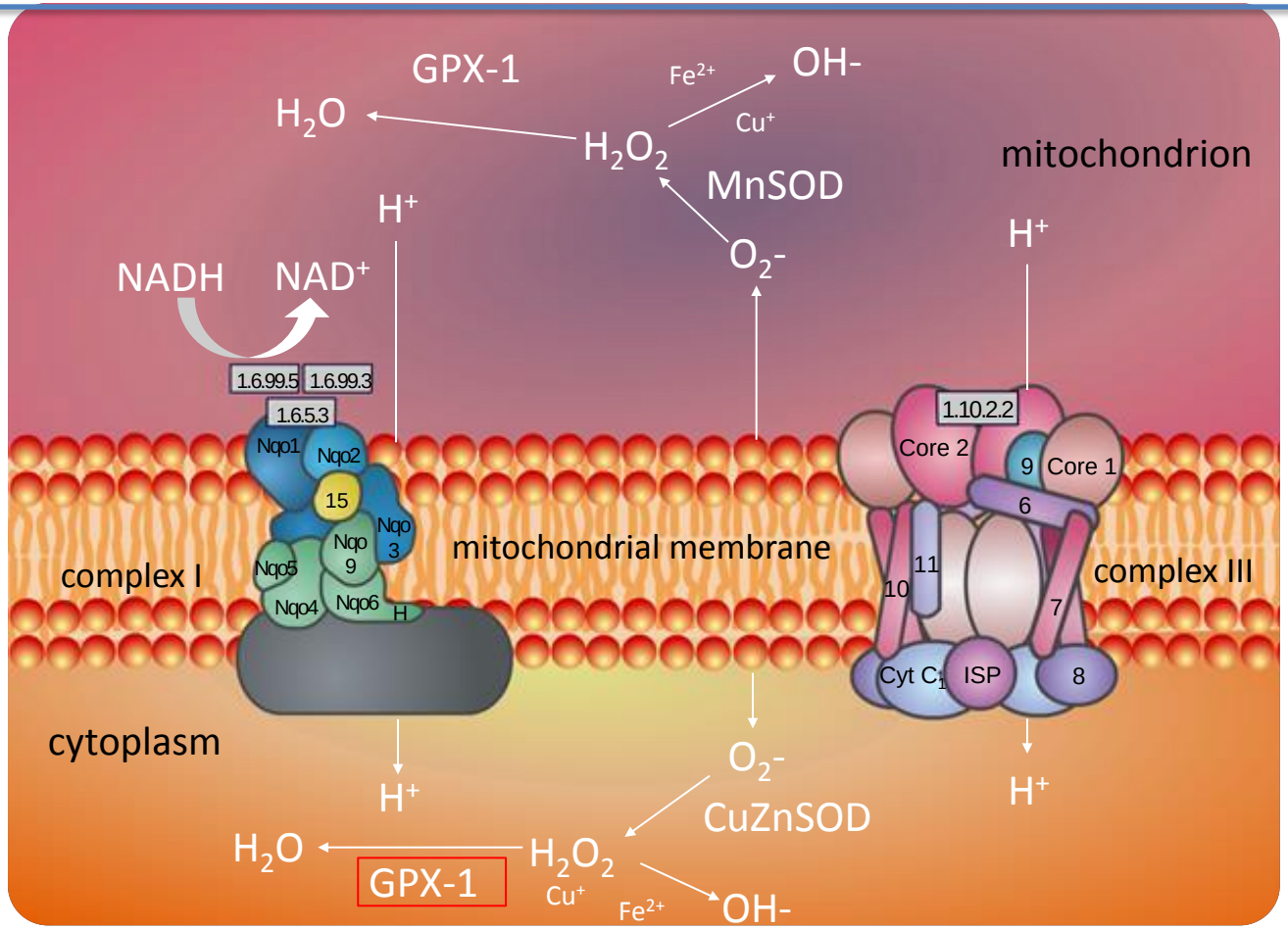
Oxidative Damage

- 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



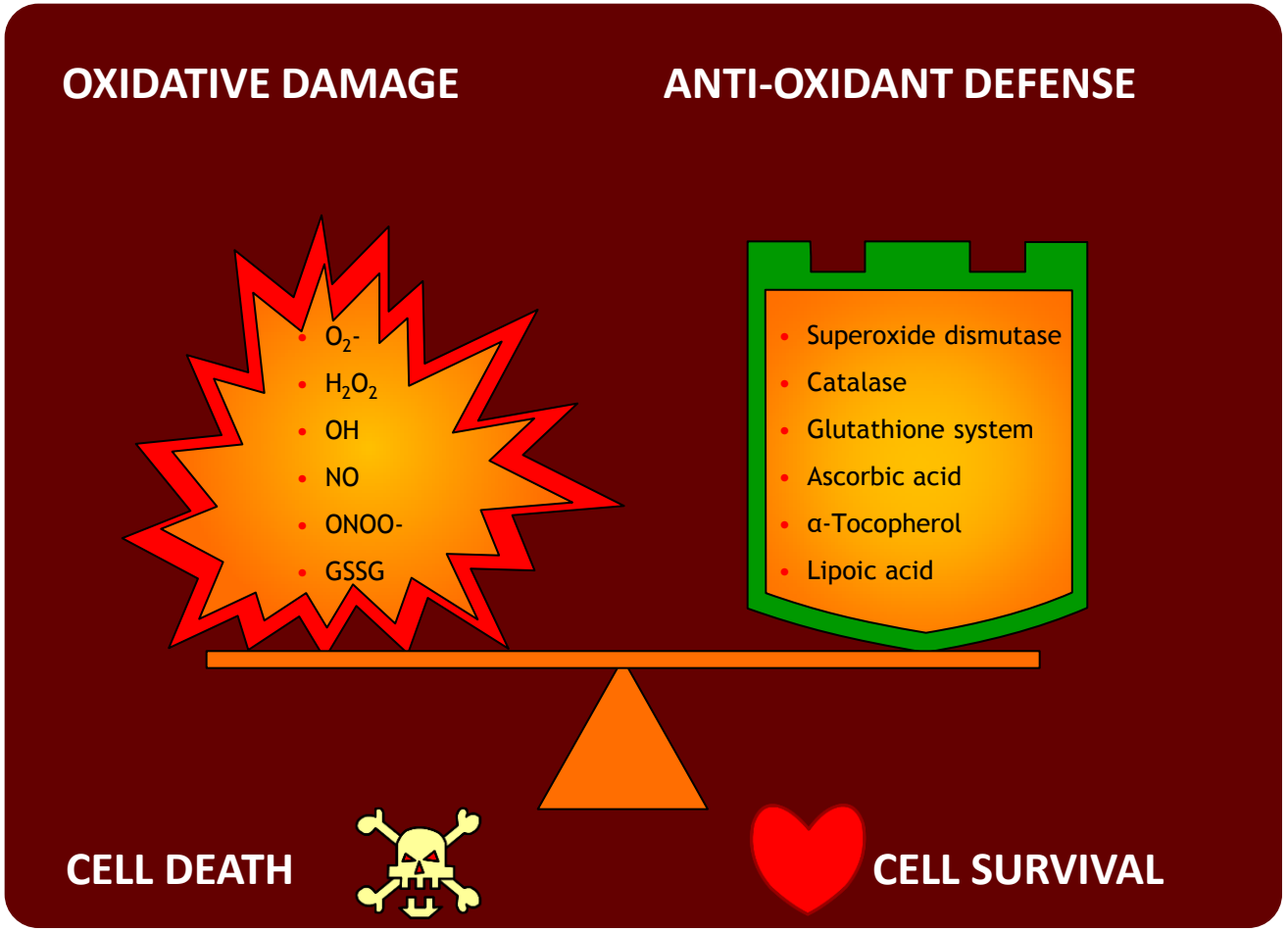
Reactive oxygen species



Case 2

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

Oxidative Stress



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

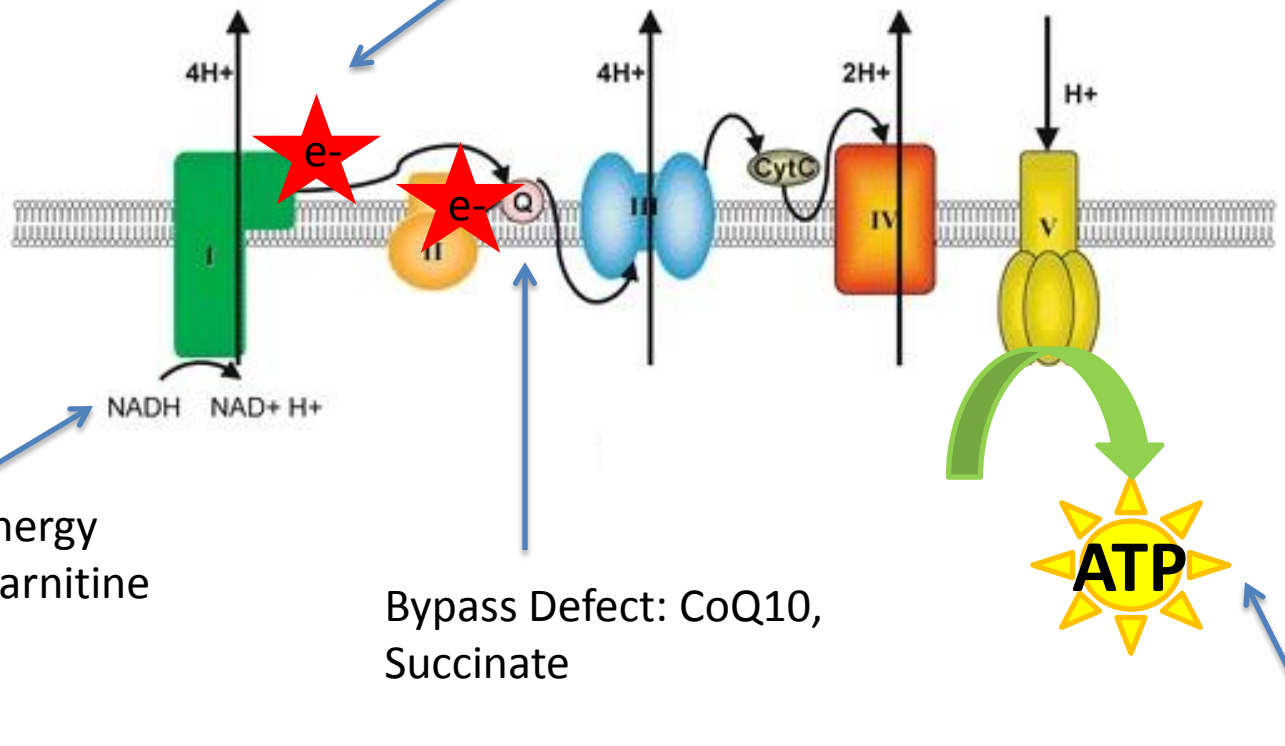
Avoid Fever

Avoid Dehydration

Balanced healthy diet

Where do the vitamins act?

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



Improve Energy Transfer: Carnitine

Bypass Defect: CoQ10, Succinate

Improve Energy Pools: Creatine

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

“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

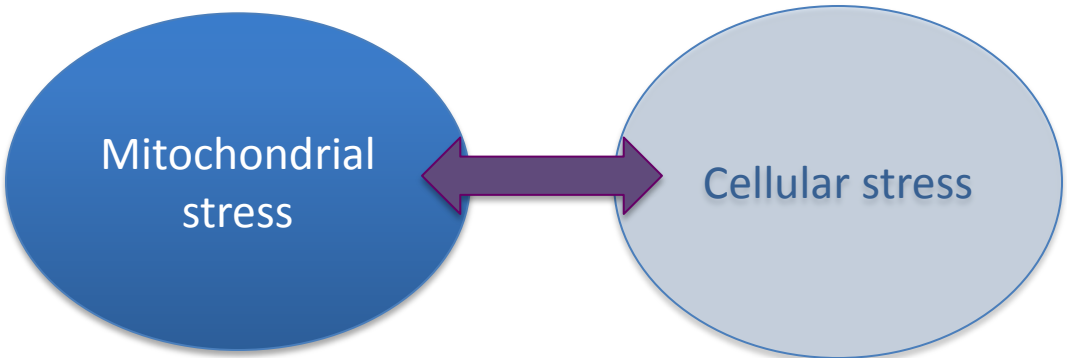
Approaches to Bioenergetic Stress Reduction

- 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

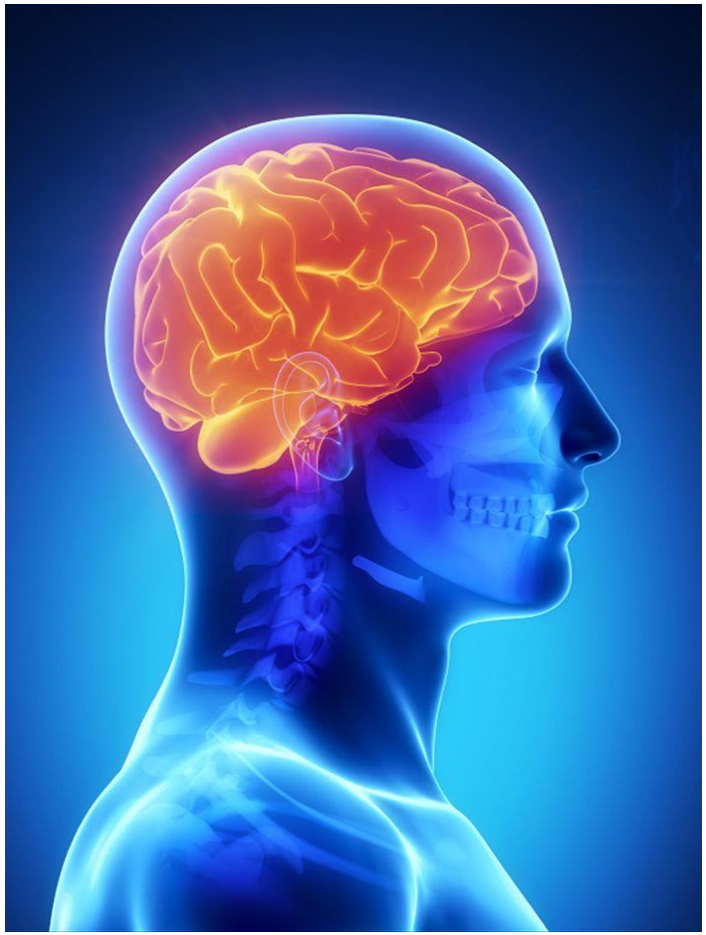
Evidence for Mitochondrial Stress in LBSL

- 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

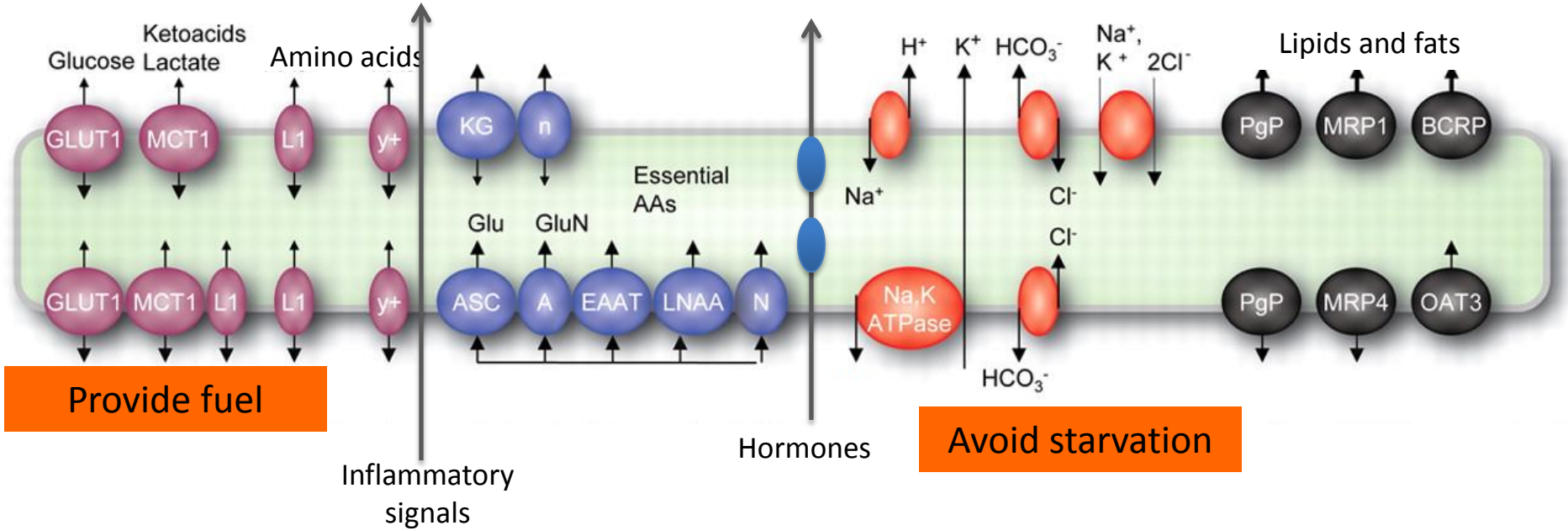


Tissue Specificity in LBSL

- 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



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