BB 422/622

OUTLINE:

Introduction and review
Transport
Glycogenolysis
Glycolysis
Other sugars
Pasteur: Anaerobic vs Aerobic

Exam-1 material

Fermentations

Exam-2 material

Pyruvate
- pyruvate dehydrogenase (ox-decarbox; S-ester)

Krebs' Cycle
- How did he figure it out?
- Overview
- 8 Steps
  - Citrate Synthase (C-C)
  - Aconitase (=, -OH)
  - Isocitrate dehydrogenase (ox-decarbox; =O)
  - Ketoglutarate dehydrogenase (ox-decarbox; S-ester)
  - Succinyl-CoA synthetase (sub-level phos)
  - Succinate dehydrogenase (=)
  - Fumarase (-OH)
  - Malate dehydrogenase (=O)
- Energetics
- Regulation
- Summary

Oxidative Phosphorylation
- Energetics (−0.16 V needed for making ATP)
- Mitochondria
- Transport (2.4 kcal/mol needed to transport H^+ out)
- Electron transport
  - Discovery
  - Four Complexes
    - Complex I: NADH → $CoQH_2$
    - Complex II: Succinate → $CoQH_2$
    - Complex III: $CoQH_2$ → Cytochrome C (Fe^{2+})
    - Complex IV: Cytochrome C (Fe^{2+}) → H_2O
- Chemiosmotic theory: Phosphorylation
  - ATPase
  - Mitchell Hypothesis
  - Binding-Change Model
  - Connection to the proton motive force
  - Net ATP production
  - Regulation

Exam-2 material

Exam-3 material

Catabolism: Lipid Degradation
- Digestion and storage
- FOUR stages lipid catabolism
  - Mobilization from adipose tissues
  - Activation of fatty acids
  - Transport into mitochondria
  - Oxidation
    - Saturated
    - Unsaturated
    - Odd-chain
- Ketone Bodies
- Oxidation in other organelles

Catabolism: Nitrogenous
- Digestion & turnover of proteins
- Urea Cycle
- Amino-acid Degradation

Lipid Degradation

Lipid Catabolism

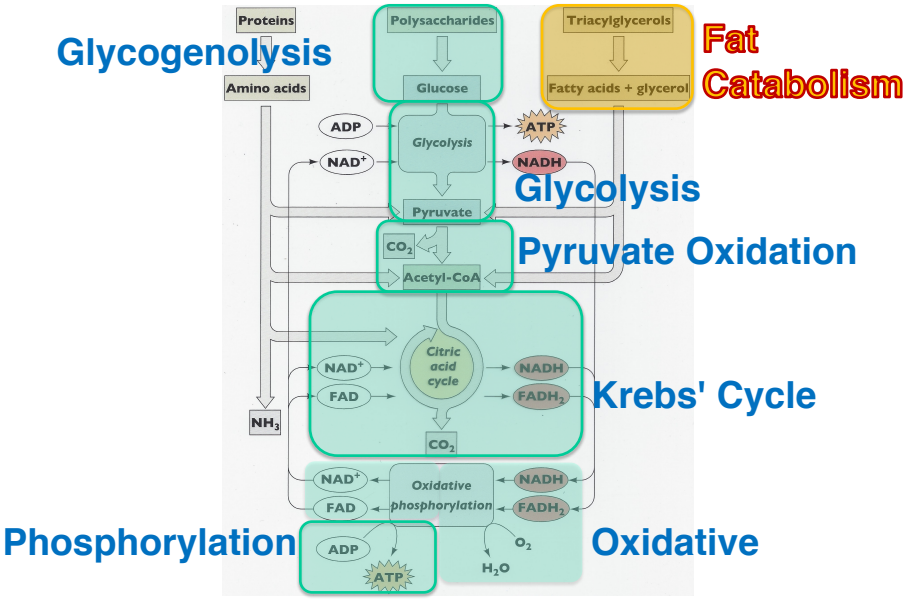
OUTLINE:

Fat Catabolism
- diet
- storage

Fatty-Acid Catabolism
- Mobilization
- Activation
- Transport
- Oxidation
  - Saturated FA
    - β-oxidation
    - energetics
  - Unsaturated FA
  - Odd-chain FA

Ketone Bodies

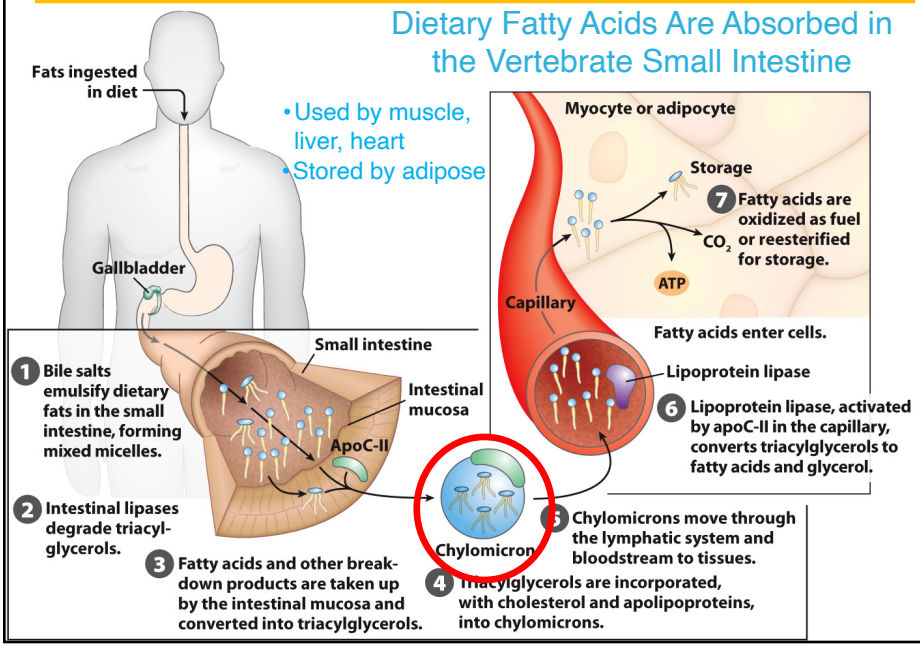
Lipid Degradation



Fat Catabolism

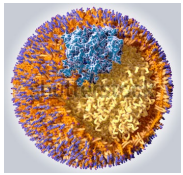
- Fat as a fuel; ingestion of the “chunks”
- How fats are mobilized and transported in animal tissues
- COMPARTMENTATION
  - How fats are oxidized in mitochondria
    - Glycerol
    - Saturated Fatty Acids
    - Un-saturated Fatty Acids
    - Odd-chain Fatty Acids
  - Blocks to oxidation in mitochondria: How “ketone bodies” are utilized
  - Fatty-acid metabolism in other organelles

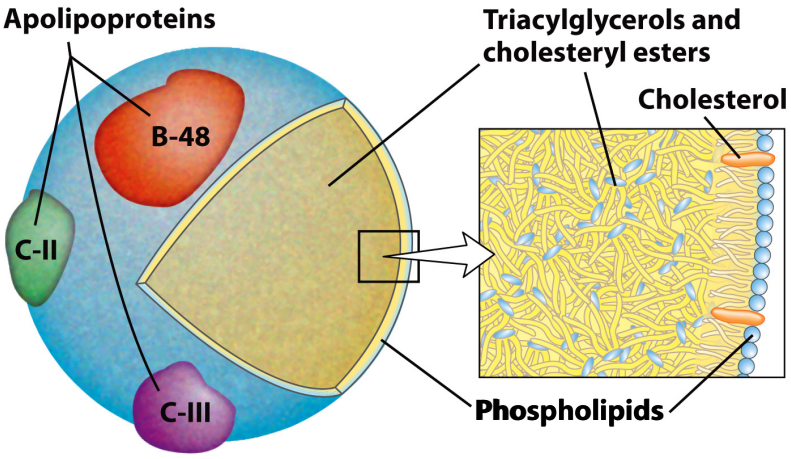
Fat Catabolism



Fat Catabolism

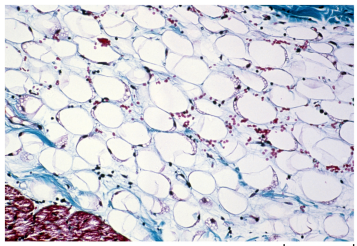
Chylomicrons

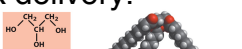


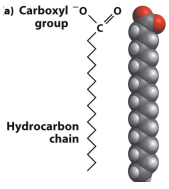


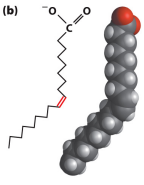
Fat Catabolism

- Fuel Storage of Fat is efficient
- The advantage of fats over polysaccharides:
  - Fatty acids carry more energy per carbon because they are more reduced.
  - Fatty acids complex or carry less water because they are relatively nonpolar.
- Glucose and glycogen are for short-term energy needs and quick delivery.
- Fats are for long-term (months) energy needs, storage, and have slow delivery.
- How are fat stores accessed?









Fatty acids come in all types: ± double bonds, long & short, odd & even, etc.

Lipid Degradation: Fatty Acids

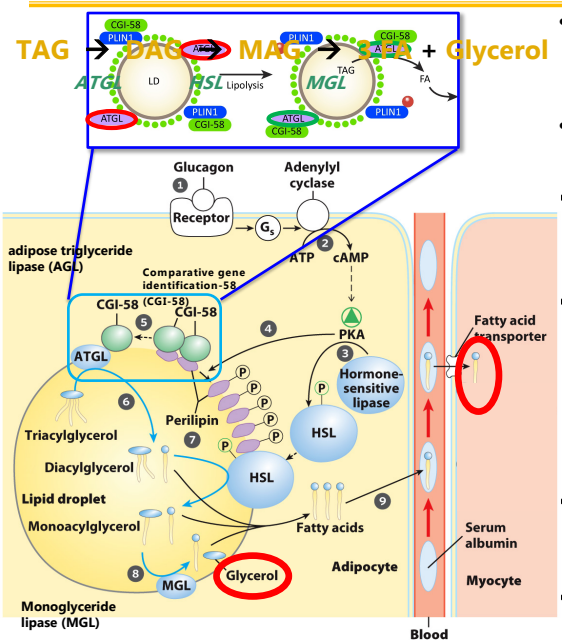
- Fatty Acid Oxidation is a Major Energy Source
- About one-third of human energy needs comes from dietary triacylglycerols (fat).
- There are differences in tissue utilization. About 80% of energy needs of mammalian heart and liver are met by oxidation of fatty acids.
- Many hibernating animals, such as grizzly bears, rely almost exclusively on fats as their source of energy.

There are FOUR stages in the catabolism of fatty acids:

1) Mobilization from tissues (mostly adipose)
2) Activation of fatty acids
3) Transport
4) Oxidation

Fatty Acid Degradation

Mobilization



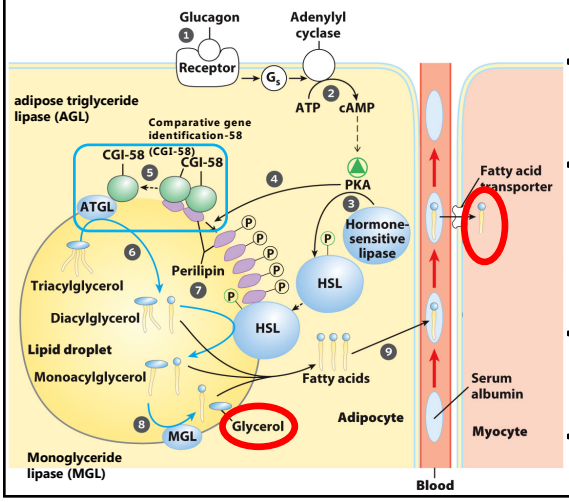
- Stored Triacylglycerides are released in response to Hormone signals
- Hormones trigger a mobilization "cascade" that activates lipases
- Lipases are activated by hormones glucagon and epinephrine. ❶
- In the case of glucagon, Protein Kinase A (**PKA**) is activated, which leads to the progressive activation of 3 lipases, one for each position on glycerol (ATGL HSL, & MGL). ❷❸❹ ❺❼ ❸❻❽
- Fats are degraded into fatty acids and glycerol in the cytoplasm of adipocytes. ❽
- Fatty acids are transported to other tissues through the blood. ❾

Fatty Acid Degradation

Mobilization

TAG → DAG → MAG → 3 FA + Glycerol

ATGL *HSL* *MGL*



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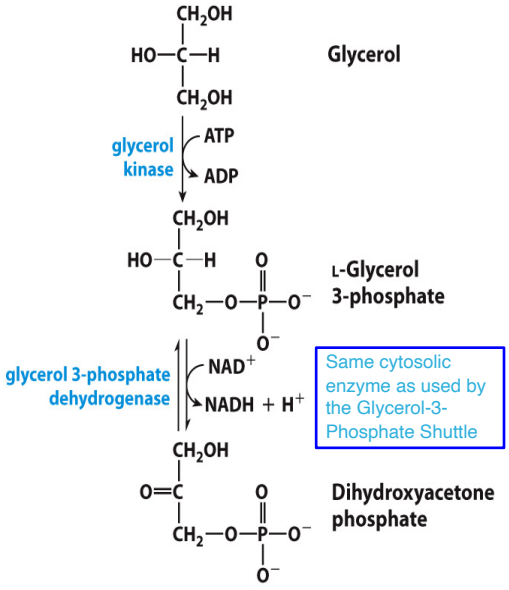
Fatty Acid Degradation

- Glycerol is a sugar alcohol and is converted to a glycolytic intermediate
- Glycerol kinase activates glycerol at the expense of ATP.
- Subsequent reactions recover more than enough ATP to cover this cost.
- Allows limited anaerobic catabolism of fats
- A redox reaction is required to convert the alcohol to a ketone. Done by glycerol-3-phosphate dehydrogenase
- We'll see this reaction again in lipid synthesis

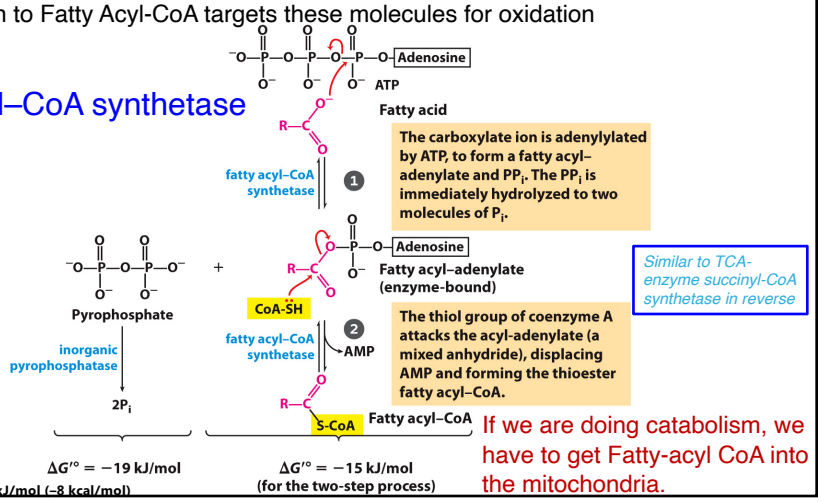


Fatty Acid Degradation

Activation

- Like the activation of sugars by phosphorylation, fatty acids must also be activated.
- Not having any alcohol groups, esterification of the carboxylate is the only chemistry available.
- A thio-ester is a higher energy bond than a simple ester: use Coenzyme A.
- Conversion to Fatty Acyl-CoA targets these molecules for oxidation

Fatty acyl–CoA synthetase



If we are doing catabolism, we have to get Fatty-acyl CoA into the mitochondria.

Lipid Degradation: Fatty Acids

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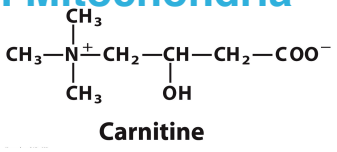
Fatty Acid Degradation

Transport

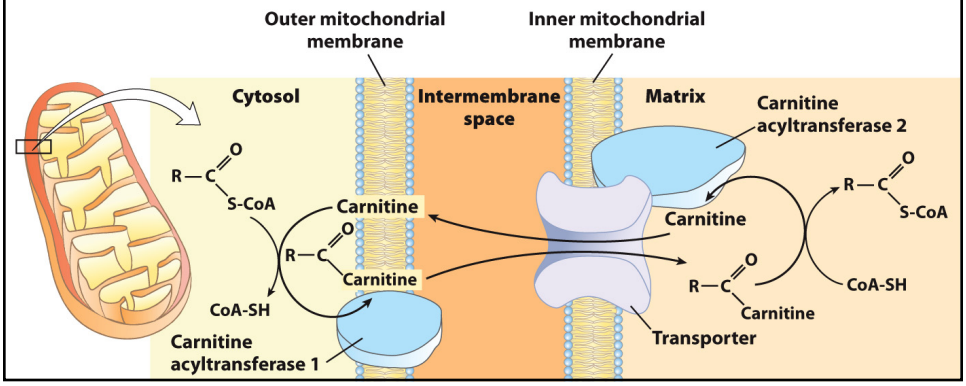
COMPARTMENTATION: Mitochondria

Acyl-Carnitine/Carnitine Transport



Carnitine

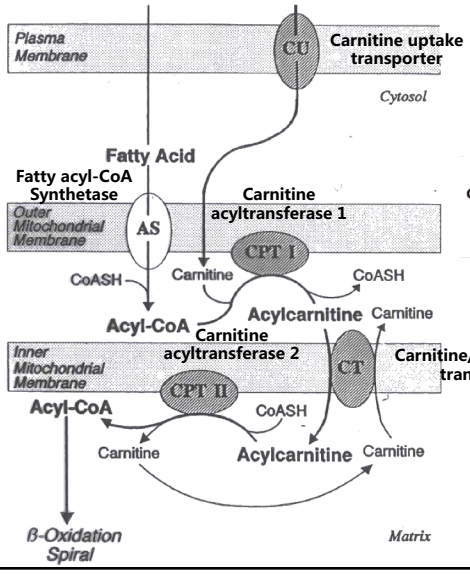
- β oxidation of fatty acids occurs in mitochondria.
- Fatty acyl-CoAs are transported via acyl-carnitine/carnitine transporter (anti-porter).



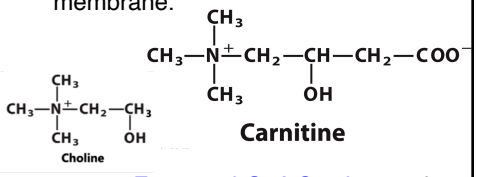
Fatty Acid Degradation

Transport

Acyl-Carnitine/Carnitine Transport



- Small (< 12 carbons) free fatty acids diffuse freely across membranes.
- Larger fatty acids are transported via fatty acid transporters on the plasma membrane.

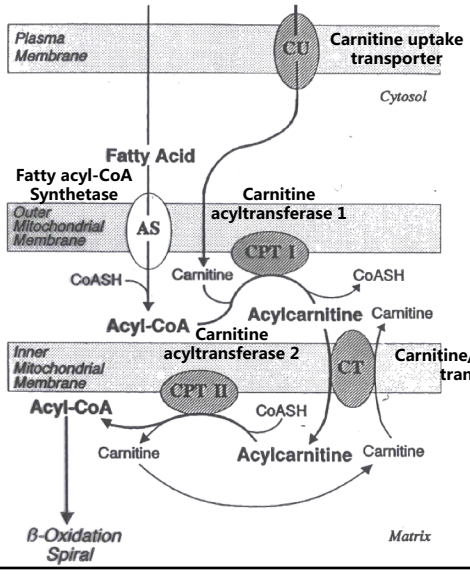


- Fatty-acyl-CoA Synthetase is attached to the OUTER mitochondrial membrane.
- Recent evidence shows that its associated with an integral membrane transporter: Fatty-acyl Transporter Protein I
- Together, they are indicated on the figure as AS.

Fatty Acid Degradation

Transport

Acyl-Carnitine/Carnitine Transport



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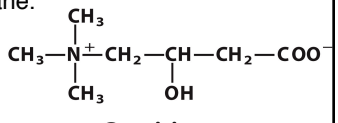

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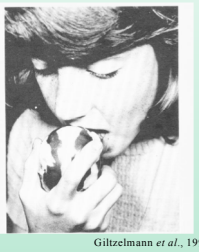
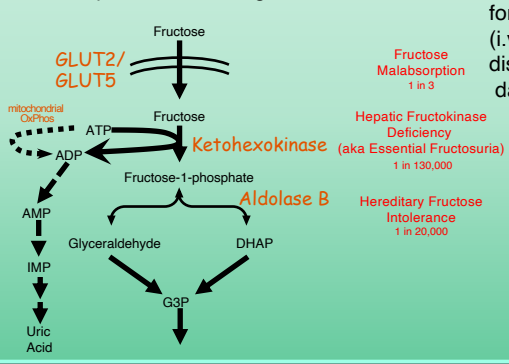
Clinical Correlations

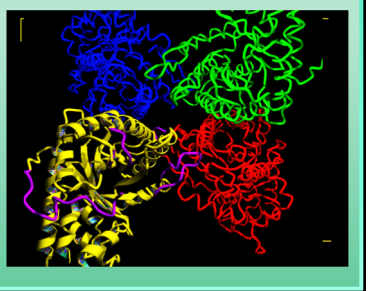
Fructose Metabolism: Malabsorption, Essential Fructosuria & Hereditary Fructose Intolerance

- Three maladies arise due to fructose metabolism.
- Only the last one, deficiency of aldolase B, can lead to death. Even small amounts of fructose lead to severe hypoglycemia, jaundice, hemorrhage, hepatomegaly, uricemia, and kidney damage.
- Fructose can account for 30-60% of carbohydrate in the Western diet. Humans have a limited capacity to handle this sugar, and show the same ATP depletion after a sugar bolus. Use of fructose, sorbitol, and xylitol for parenteral nutrition (i.v.) has been discontinued to to liver damage.



Giltzelmann *et al.*, 1995

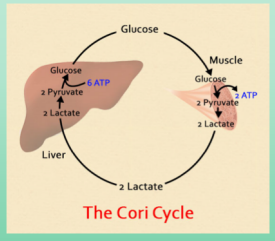




Clinical Correlations

Lactic Acidosis

- This term refers to the acidification of the blood. Blood pH dropping to anything below 7.40 causes hyperventilation, lethargy, disorientation, etc.
- Lactate is the major cause of acidosis, although any acidic metabolic intermediate, if accumulating too high, will cause this acidosis. Lactate often goes from 1.2 mM to 5 mM in the blood.
- The cause of blood [Lactate] increase can be varied, but normally it's from inadequate oxygenation. Muscle tissue easily generates large quantities of lactate, but the Cori cycle normally keeps homeostasis by converting it back to glucose through gluconeogenesis, which takes mitochondria-generated ATP. Other tissues will use the lactate and convert it back to pyruvate for combustion to CO_2 and water, which is also dependent on oxygen.



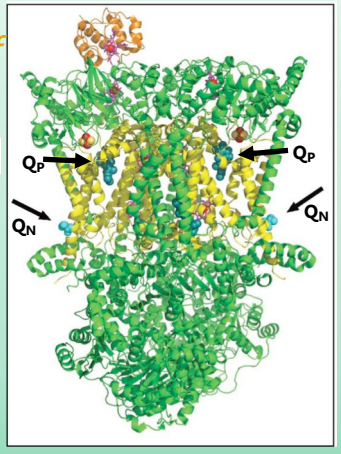
The Cori Cycle

- Finding and treating the underlying causes of the acidosis is the challenge for physicians. Otherwise, all they can do is treat the symptoms: Bicarbonate administration
- For example, treatments for diabetes often involve inhibition of gluconeogenesis (Metformin) or OxPhos (phenformin).
- Thiamin deficiency (alcoholics)

Clinical Correlations

Exercise intolerance: Q-cycle defects

- Mitochondrial disease arises from specific mutations in the gene encoding the subunit of Complex III that binds to cytochrome b's (b_H and b_L). This is the only subunit of Complex III encoded on the mitochondrial DNA.
- These patients show severe exercise intolerance.
- Often only affect muscle, suggesting a somatic mutation (not inherited from mom).



- The specific mutations have been identified. Both substitute a Gly for a bulkier acidic residue (Asp or Glu). One is at the Q_P site and one is at the Q_N site. More severe mutations have more severe outcomes and include lactic acidosis.

Clinical Correlations

Mitochondrial myopathies

- Mitochondria have their own genomic DNA and ribosomes.
- Mitochondrial DNA encodes genes for subunits of cytochrome oxidase, Complex III, ATP Synthase, and mitochondrial tRNAs
- Defects in mitochondrial genes cause a class of disorders called encephalomyopathies, which means brain/muscle abnormalities. These are the chief tissues that depend on mitochondria-derived energy.
- If tRNA genes are involved, which is the most common, then the subunits of the ETC and ATP synthase are not produced efficiently and the mitochondria have decreased activity
- Symptoms include lack of energy, muscle weakness, lactic acidosis, seizures, and other maladies. The presentation of the disease depends on the mutations and the number of mitochondria involved.