Functional Medicine University's Functional Diagnostic Medicine Training Program

Mod 4 * FDMT 531A

Biochemistry of Energy

By Wayne L. Sodano, D.C., D.A.B.C.I., & Ron Grisanti, D.C., D.A.B.C.O., M.S.
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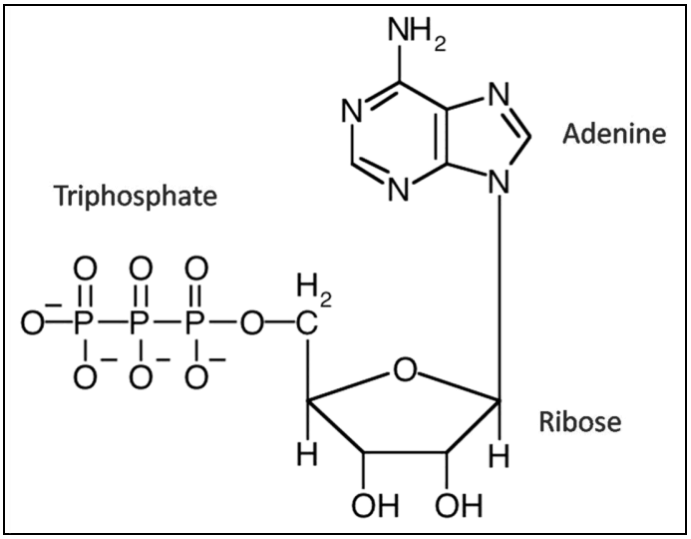
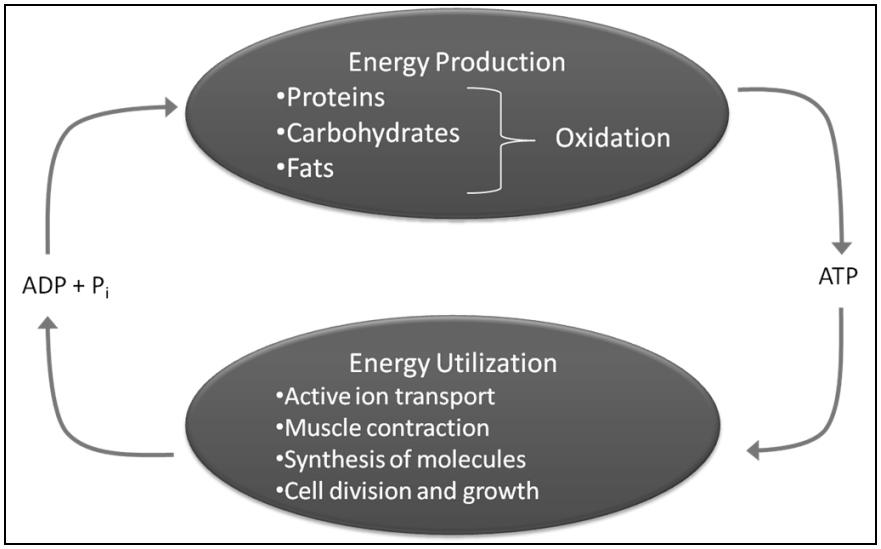
Contents

Required reading: "The Use of D-Ribose in Chronic Fatigue Syndrome and Fibromyalgia: A Pilot Study"
This article may be downloaded with this lesson or on the FMU website library.

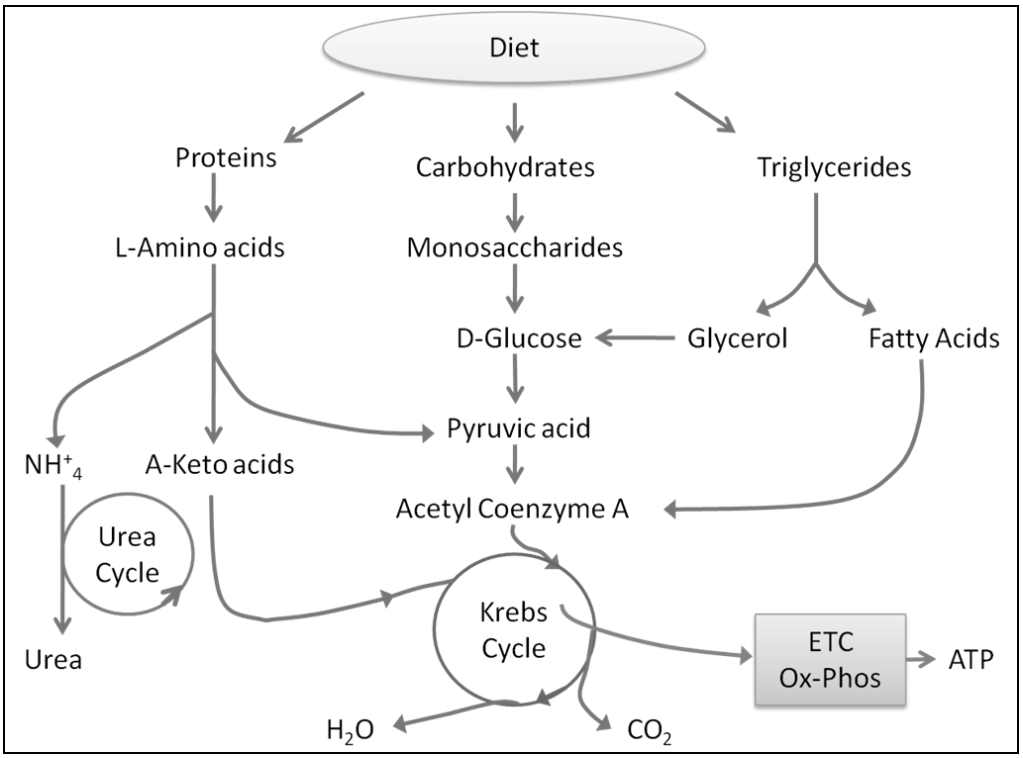
Adenosine Triphosphate (ATP)

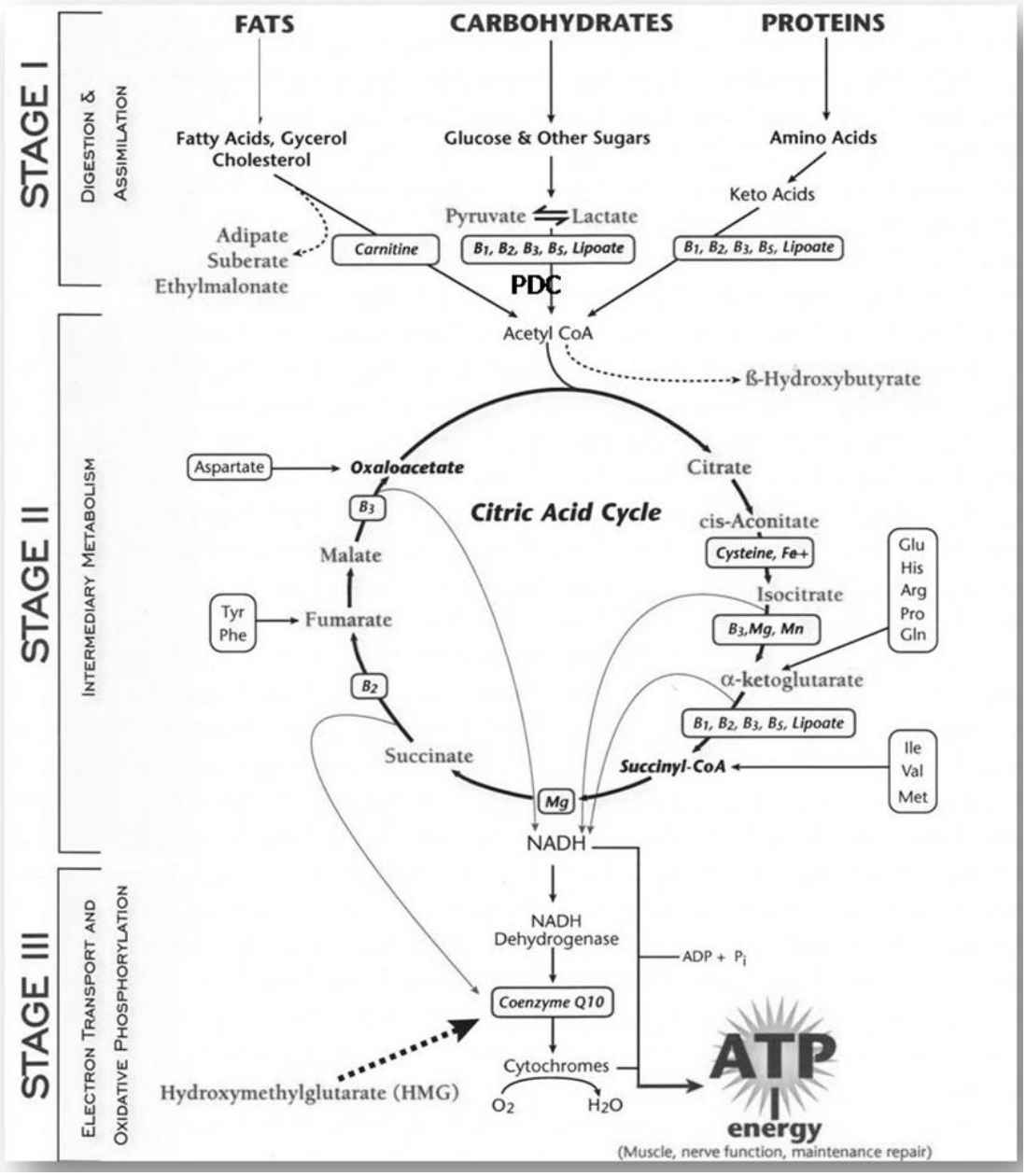


Adenosine Triphosphate (ATP) is the energy current of the body and is present in all cells. ATP is composed of ribose, adenosine and three phosphate radicals. Energy derived from the oxidation of proteins, fats and carbohydrates is used to convert ADP to ATP. ATP is then used to perform vital functions of the body. The overall process is a follows:



The Krebs cycle, along with the electron transport chain, is the main pathway in which the energy stored in food is released by the cells to make their own energy, that being ATP. An overall view of this process is illustrated below:





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It is important to note that the metabolism of carbohydrates, fats and proteins to the final ATP product is dependent upon vitamins, minerals, amino acids and certain supplements to drive the chemical reactions. An example of this is Coenzyme Q10 and its role in the electron transport chain. A deficiency in Co-Q10 will stall the electron transport chain and therefore cause decrease in ATP production. From a functional medicine perspective, understanding the pathways of energy production will provide insight about nutritional deficiencies and mitochondrial energy production and diseases associated with mitochondrial dysfunction. Some examples of mitochondrial diseases include: fibromyalgia, chronic fatigue syndrome, Alzheimer disease, Parkinson disease and bipolar disorder.

Carbohydrate Metabolism for Energy

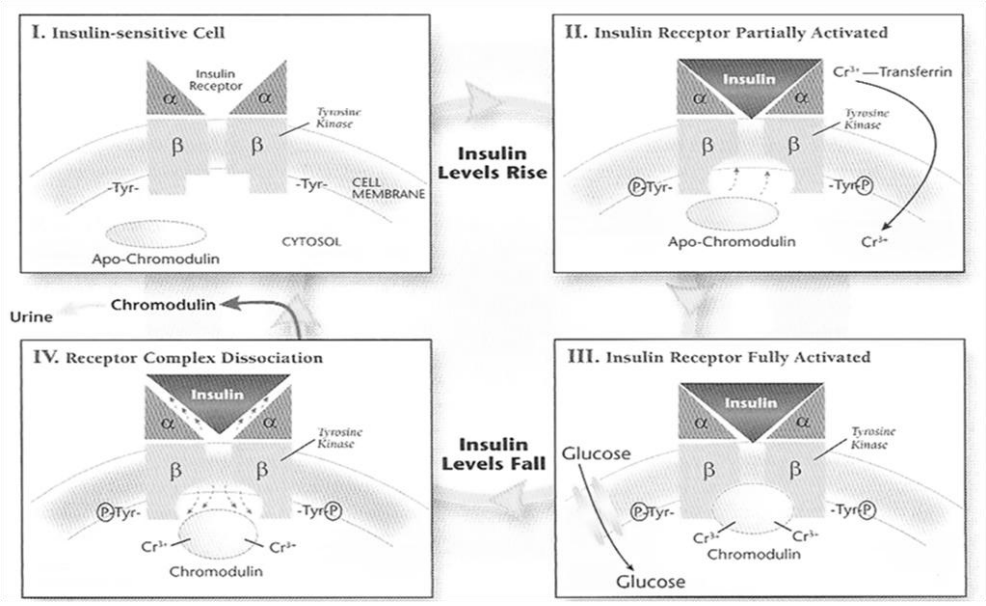
With proper digestion and a normal functioning liver, glucose becomes the main carbohydrate for transport to the tissues cells. Glucose must first be transported across the cell membrane before it can be utilized. Glucose is passed across the cell membrane to the cytoplasm by a process called facilitated diffusion. Insulin increases facilitated diffusion of glucose and is the main controller of glucose transport into the cell.

Chromium

Chromium and insulin work together. As insulin is released into the blood stream, chromium transport to insulin-sensitive cells is increased.

- Adequacy Assessment:
  - RBC, whole blood, urine, hair, insulin, blood glucose
- Optimal forms:
  - Nicotinate, chloride, histidine or picolinate salts
- Clinical indications of deficiency:
  - Blood sugar dysregulatory conditions
- Food Sources:
  - Whole grains, legumes, nuts, yeast, meats

- Unlike most essential elements that have multiple metabolic functions, the only known role for chromium is in potentiating insulin receptor tyrosine kinase.



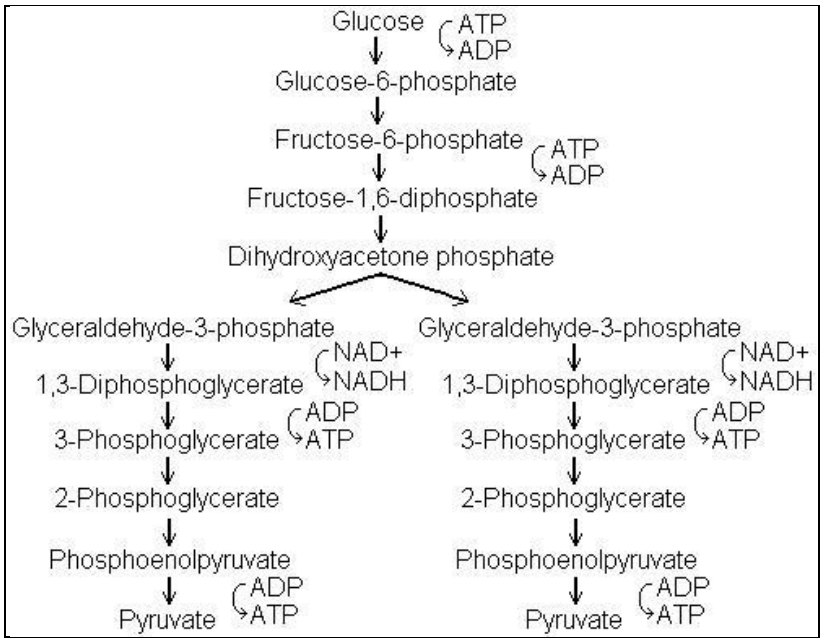
Ref: Laboratory Evaluations for Integrative & Functional Medicine, 2nd ed., Lord & Bradley

The rising & falling of blood insulin triggers actions mediated by chromium binding in insulin-sensitive cells. With the dissociation of insulin, the receptor ejects chromodulin, a portion of which escapes the cell to appear in urine as an end product of the entire signaling cycle.

- Assessing Chromium Status
  - Total body chromium is so low that analytical tissues have limited accurate direct measures.
  - Functional assessment appears to be the best choice.
    - Elevated blood glucose & insulin
    - Abnormal glucose-insulin tolerance test
  - Hair and RBC can show long term exposure to exogenous chromium.

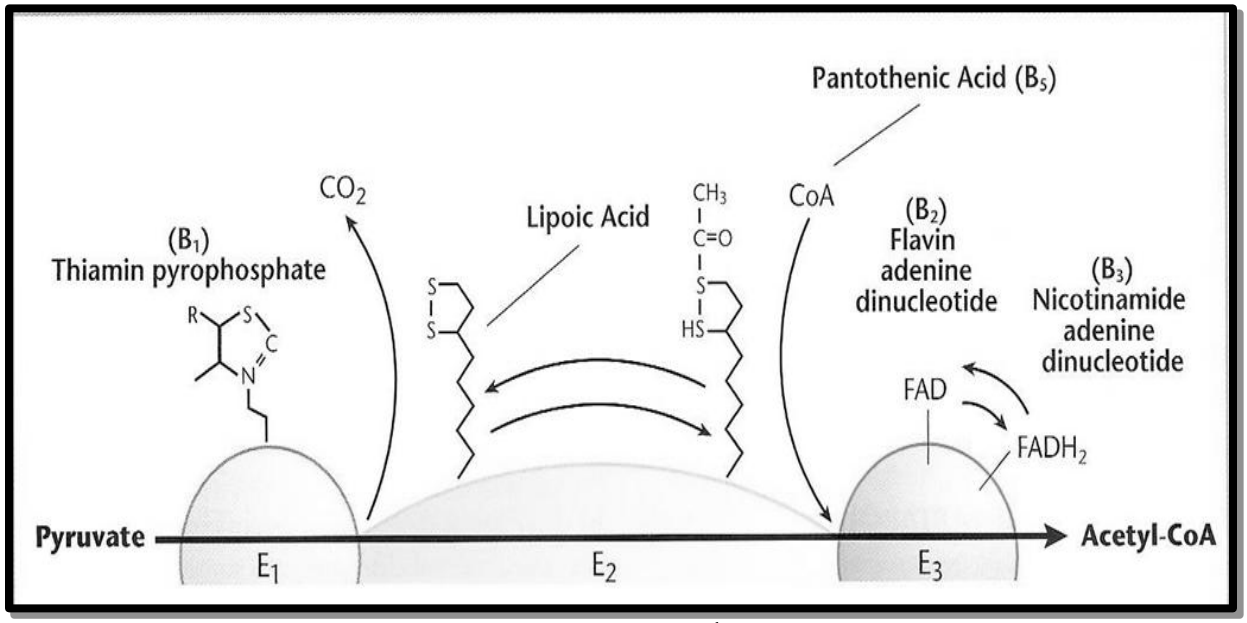
- Repletion
  - Chromium picolinate 200-1000 ug/day is effective supplementation for treating diabetes.
  - The form of chromium derived from yeast called chromium-glucose tolerance factor (GTF) is not effectively absorbed.

After entry of glucose into the cell, the oxidation of glucose to pyruvate occurs through the process of glycolysis. Glycolysis occurs by 10 successive chemical reactions. The initial steps in glycolysis involve the addition of two phosphates to the glucose molecule. During this process two ATP molecules are utilized. After the addition of the phosphate, the molecule is then split into two three-carbon molecules which are then converted into pyruvate. The net yield of the metabolism of one molecule of glucose is two pyruvic acids, two ATP and four hydrogens (NADH).



Under aerobic conditions, pyruvic acid is transported into the mitochondria and transformed to acetyl-CoA. Mitochondrial conversion of pyruvate to acetyl-CoA requires the pyruvate dehydrogenase comoplex. The enzyme complex contains three enzyme subunits and associated cofactors. The acetyl-CoA then enters the tricarboxylic acid cycle (TCA), also known as the Krebs cycle.

Pyruvate Dehydrogenase Complex



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Cofactors for the PDC

Vitamin B1 (Thiamin)

Active form:	Thiamin pyrophosphate (TPP)
Biochemical role:	Decarboxylation
Example:	Pyruvate →Acetyl –CoA + CO2
Deficiency tests:	alpha-keto acids – urine; Erythrocyte Transketolase Index
Adult repletion:	50 to 200 mg/d

Physiological Function: The two primary functions of thiamin are alpha-keto decarboxylation and transketolation. Decarboxylation reactions are an integral part of carbohydrate metabolism.

Lipoic Acid (Thioctic Acid)

Active Forms:	R-α-lipoic acid; dihydrolipoic acid
Biochemical role:	Keto acid dehydrogenase cofactor and glutathione recycling
Example:	Pyruvate→ Acetyl-CoA + CO2 GSH → GSSG
Adult repletion:	100 to 1,800 mg/d

Physiological Function: As a primary component of the lipoyl subunits, lipoic acid is required to carry out oxidative decarboxylation reactions catalyzed by several alpha-keto acid enzyme complexes – pyruvate dehydrogenase (PDC). Besides its function in dehydrogenase activities, it is also a powerful antioxidant that has been found to quench reactive oxygen species. It functions as a recycler of endogenous antioxidants, like glutathione and vitamin C.

Vitamin B5 (Pantothenic Acid)

Active form:	Coenzyme A (CoA)
Biochemical role:	Carrier for acyl groups
Examples:	Acetyl-CoA, Fatty acyl-CoA
Adult repletion:	100 to 1,000 mg/d

Physiological function: By utilizing 3 ATP's and cysteine, pantothenic acid is converted into its active form, coenzyme-A in the liver. It functions as the acyl carrier in keto acid and fatty acid oxidation. All oxidation pathways for carbohydrate, fat and protein require coenzyme-A to carry acetate, keto-acids, or fatty acid intermediates during key oxidative steps.

Vitamin B2 (Riboflavin)

Active form:	Flavin mononucleotide (FMN) Flavin adenine dinucleotide (FAD)
Biochemical role:	Redox – Central energy pathways
Adult repletion:	50 to 200 mg/d

Physiological Function: Riboflavin is primarily involved in energy production in the respiratory chain and in oxidative-reduction reactions. Riboflavin is converted to its coenzyme forms, (FMN) and flavin adenine dinucleotide (FAD), which accept and transfer electrons. FMN and FAD-linked enzymes are involved in many essential reactions, including mitochondrial respiration, citric-acid cycle, ATP synthesis and fatty acid metabolism.

Vitamin B3 (Niacin)

Active Forms: Nicotinaminde adenine dinucleotide(NAD), Nicotinamide adenine dinucleotide phosphate $NADP^+$

Adult repletion: 100 to 1,000 mg/d

Physiological Function: The two main forms of vitamin B3 are niacinamide and niacin. Its active coenzyme forms are nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Vitamin B3 maintains cellular redox state via NAD and NADP, which function as coenzymes in oxidation and reduction reactions. NADP serves as a hydrogen donor and NAD serves as an electron acceptor. NAD and NADP cycle between their reduced forms, $NADH + H^+$ and $NADPH + H^{50.}$ Many oxido-reductase enzymes that utilize NADP and NAD function in catabolic pathways.

Note: Niacin's beneficial effect on reducing triglycerides and VLDL and LDL are performed by decreasing fatty acid mobilization from adipose tissue triglyceride and inhibiting hepatocyte diacylglycerol acyltransferase and triglyceride synthesis.

NOTE: **From a functional medicine perspective, diet and exercise are the key modulators of the pyruvate dehydrogenase complex.**

Under anaerobic conditions, the majority of pyruvic acid is converted into lactic acid. The enzyme involved in this conversion is *lactic dehydrogenase.*

Clinical Pearl: **(Reactive Hypoglycemia)**

LDH is an intracellular enzyme used to support the diagnosis of injury or disease involving the heart, red blood cells, liver, kidneys, lungs, skeletal muscle and brain. The isoenzymes of LDH are used to differential the source of the injury/disease. Low levels of LDH and a decreased fasting glucose are associated with reactive hypoglycemia, also known as postprandial hypoglycemia. The causes of most cases of reactive hypoglycemia are still open to debate, however, research suggest that certain people may be more sensitive to the body's normal release of adrenaline , which causes many of the symptoms of hypoglycemia (hunger, shakiness, nervousness, sweating, dizziness, light-headedness, sleepiness, confusion, difficulty speaking, anxiety and weakness). A deficiency of glucagon secretion has also been implicated. From a functional medicine perspective, reactive hypoglycemia is associated with hormonal imbalances, in particular, adrenal dysfunction and HPA (hypothalamus-pituitary-adrenal) axis dysfunction.

Pentose Phosphate Pathway

A secondary pathway in which glucose can provide energy is through the Pentose Phosphate Pathway. This pathway is responsible for as much as 30% of glucose breakdown in the liver and fats cells. This pathway is independent of the TCA cycle and is an alternative pathway for energy production. The hydrogen generated can enter the oxidative phosphorylation pathway to form ATP. More often the energy derived from the PPP is used for synthesis of fat and other substances. The primary functions of the pentose-pathway are:

1. To generate reducing equivalents, in the form of NADPH, for reductive biosynthesis reactions in the cells. $NADP^+$ (nicotinamide adenine dinucleotide phosphate) reduced to NADPH is used for synthesis of fats from carbohydrates. One of the other uses of NADPH in the cell is to prevent oxidative stress. It reduces the coenzyme glutathione, which converts relative hydrogen peroxide to water.

2. To provide the cells with ribose-5-phosphate for the synthesis of nucleotides and nucleic acids.

The overall reaction for the pentose-phosphate pathway is:

Glucose 6-phosphate + 2 $NADP^+$ + H_20 → ribulose 5-phosphate + 2NADPH + $2H^+$ + CO_2

Clinical Pearl

D-ribose is a naturally occurring 5-carbon sugar that is present in all living cells. In the body, D-ribose is synthesized via the pentose-phosphate pathway. Supplementation with D-ribose may allow the cell to bypass the rate-limiting steps of the pathway, thereby providing a precursor for ATP and nucleotide synthesis.

Required reading: "The Use of D-Ribose in Chronic Fatigue Syndrome and Fibromyalgia: A Pilot Study"
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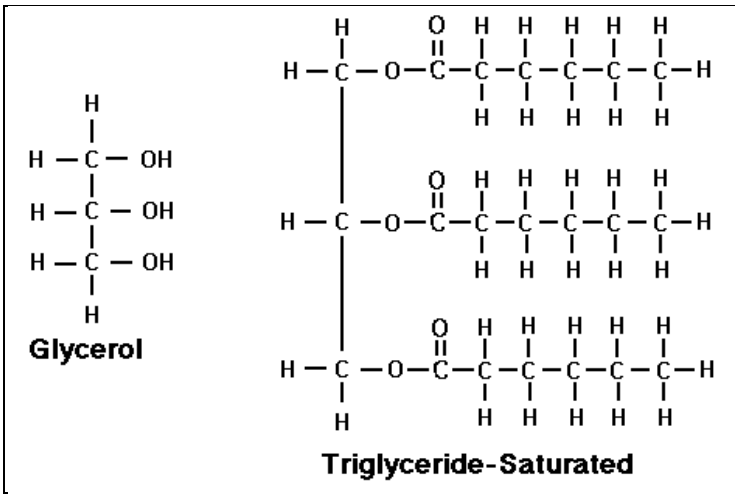
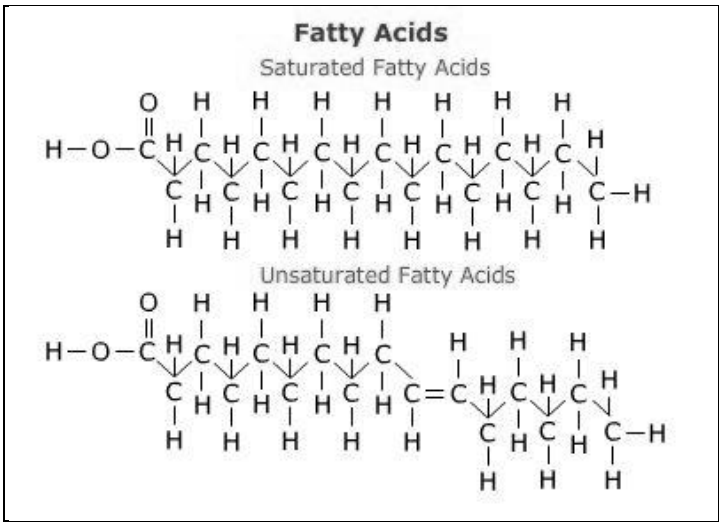
Lipid Metabolism For Energy

Lipids can be classified as neutral fats (triglycerides), phospholipids and sterol derivatives (cholesterol, steroid hormones, vitamin D, bile acids). The basic functional group of triglycerides and phospholipids is fatty acids. Fatty acids are long-chain hydrocarbon organic acids. Fatty acid compounds are chemically represented by the formula R---COOH, where R stands for an alkyl chain composed of carbon and hydrogen atoms. Fatty acids serve as a major source of energy for the body. They are also involved in intracellular regulation that modifies the cell's response to external stimuli. An example of this is displayed in prostaglandins. (Note: Cholesterol does not contain fatty acids; however, it has similar chemical and physical properties to other lipids. Cholesterol, phospholipids and triglycerides are used to form cell membranes.)

Triglycerides are mainly used to provide energy, that is, to make ATP for a variety of metabolic functions.



Triacylglyerols (triglycerides) are carried by lipoproteins to the tissues, where hydrolysis releases their fatty acids from the glycerol backbone. The glycerol enters the glycolytic pathway as glycerol-3-phosphate for glucose breakdown. The fatty acids are processed for energy in a different fashion.



Fatty acids enter the cell and are activated in the cytosol at the expense of 2 ATP's. The activated fatty acids are linked to Coenzyme A. [Recall that Coenzyme A is synthesized in a five step process from pantothenic acid (B5)]. With the help of carnitine, fatty acids are transported into the mitochondria.

Activated fatty acid→CoA-S-fatty acid (also called fatty acyl-CoA)

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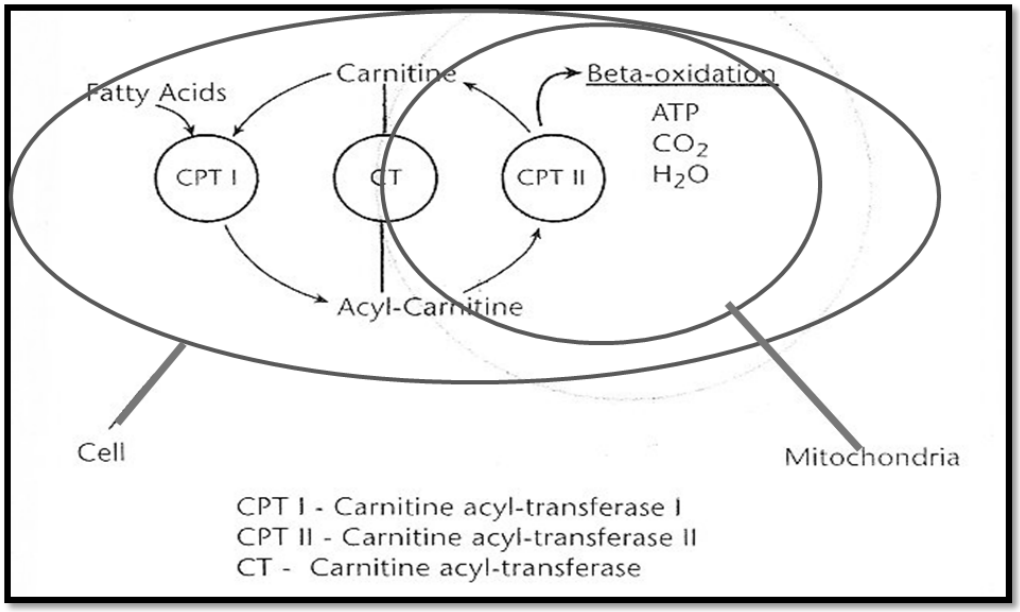
Carnitine

Biochemical Role: Fatty acid transport across cell membranes
Adult repletion: 250 to 1,000 mg/TID



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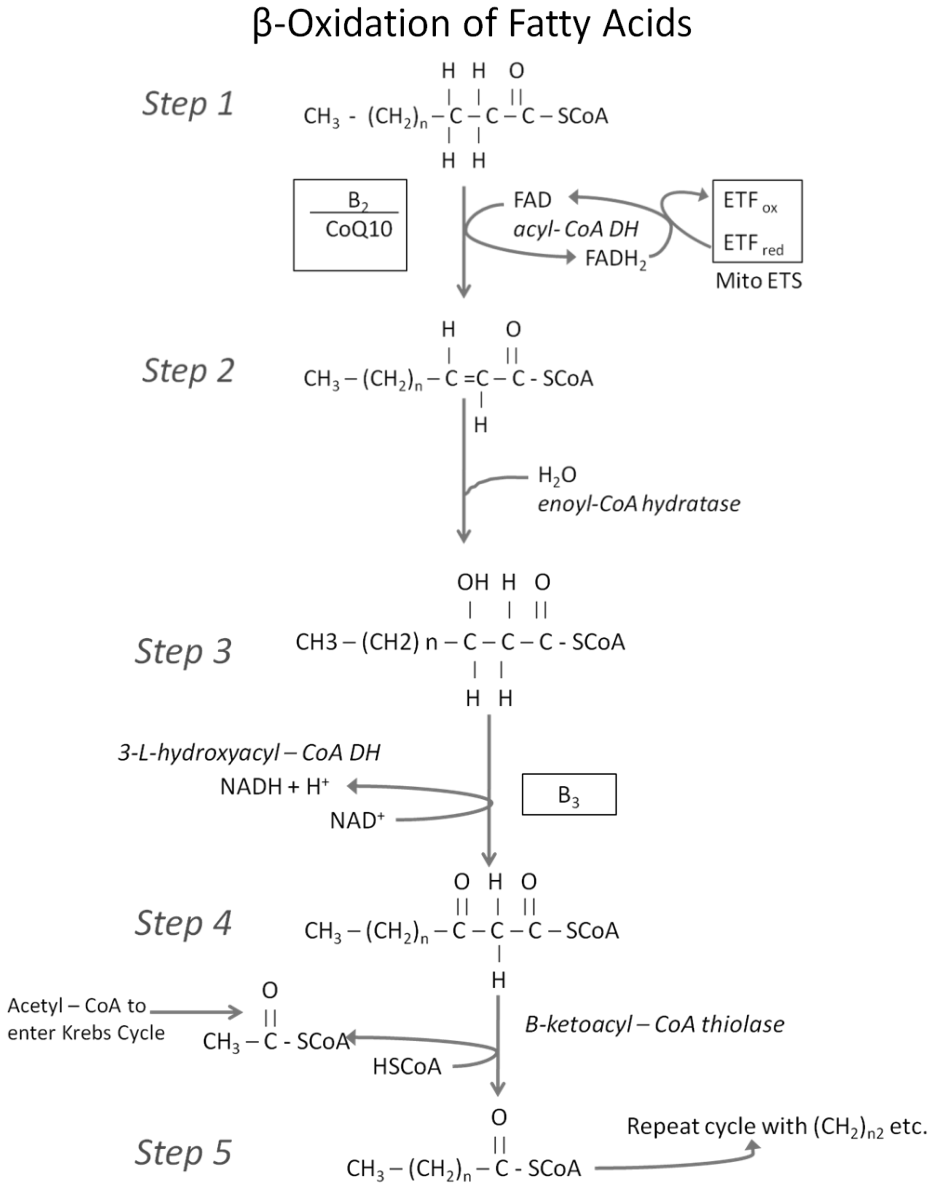
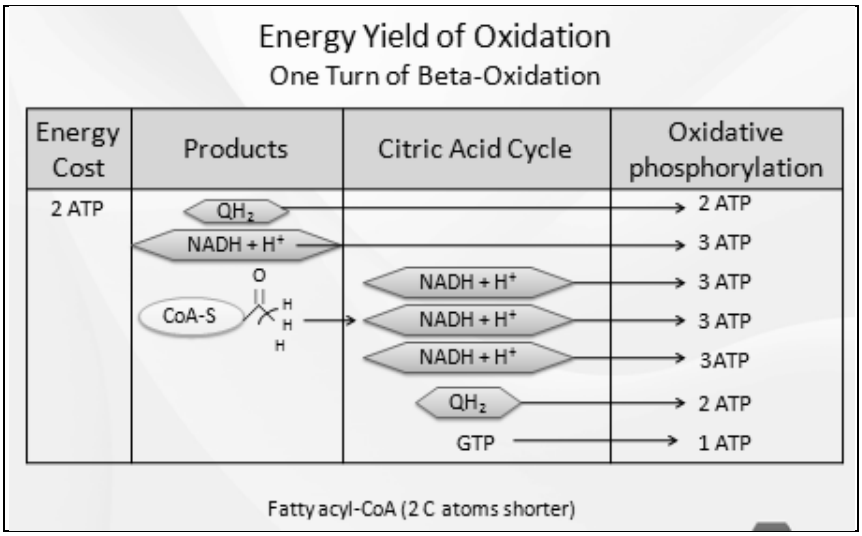
Carnitine and Beta-Oxidation

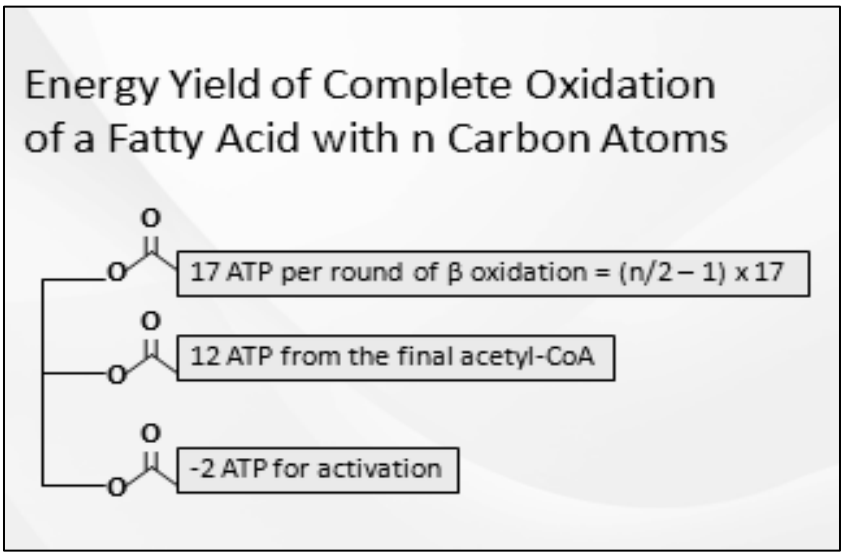
Fatty acids are converted to fatty acyl-carnitine for transport across the inner membrane of the mitochondria. Carnitine then 'flips' the fatty acid through the membrane to the inside of the mitochondria. Enzymes oxidize fat into ATP, carbon dioxide, and water.

Once inside the mitochondria, the fatty acids are degraded to acetyl-CoA by a process called ***beta-oxidation.*** The acetyl-CoA molecules formed by beta-oxidation of fatty acids will then enter the Krebs cycle for energy production.

*There are five steps to **beta-oxidation***:







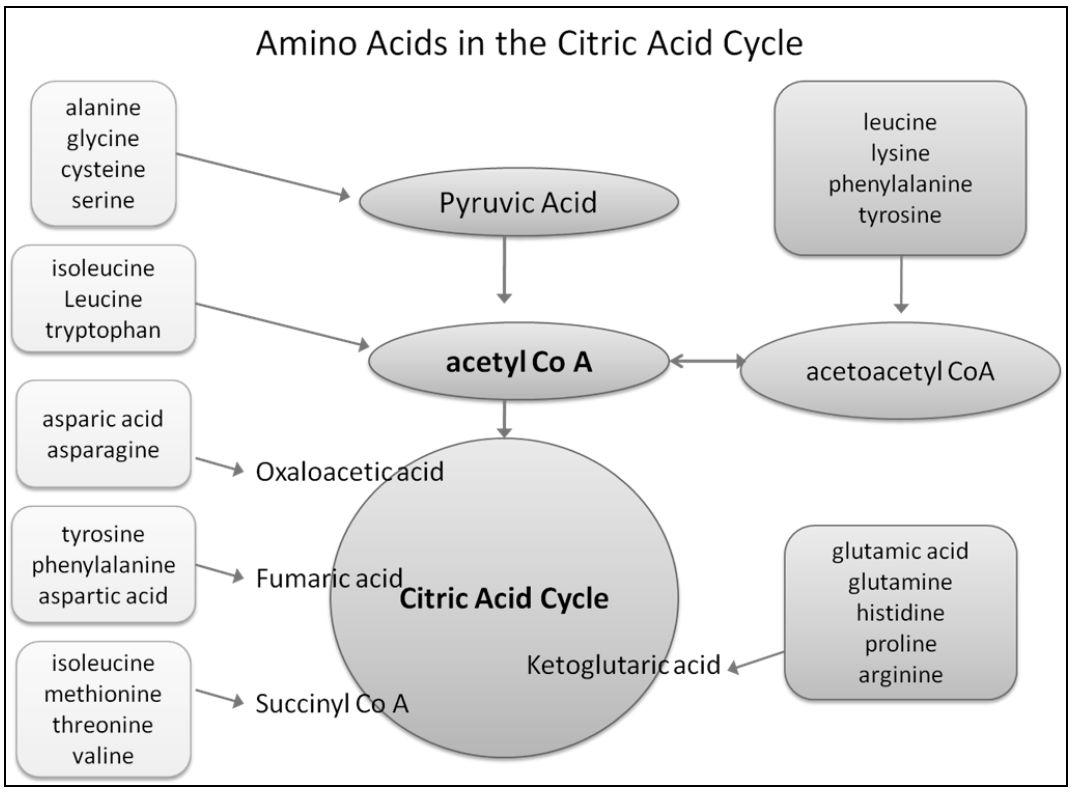
Protein Metabolism for Energy

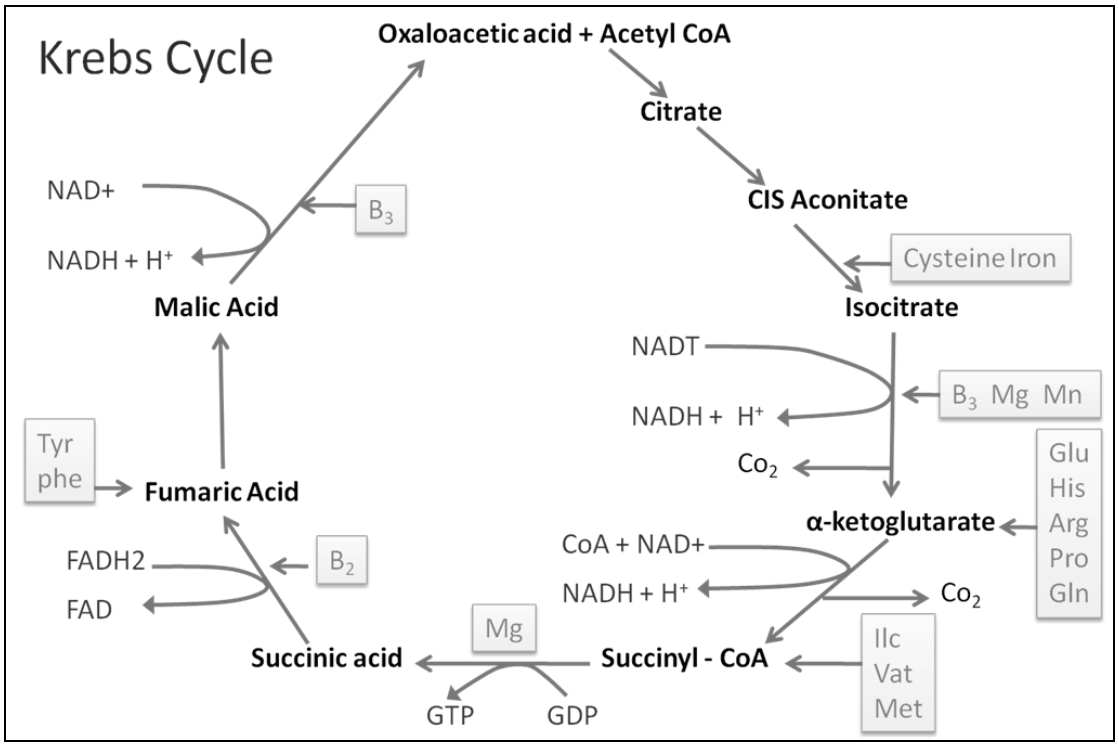
After the cells of the body are filled with stored protein, any additional amino acids can be degraded and used for energy or stored as fat or glycogen. The degradation of proteins occurs though a process called deamination, which is the removal of the amino group from the amino acid. This process almost exclusively occurs in the liver. The resulting keto acids can enter the Krebs cycle for further metabolism. The conversion of amino acids to keto acids is called ketogenesis. (Examples of keto acids are: pyruvic acid, acetoacetic acid and levulinic acid)

The conversion of amino acids into glucose or glycogen is called gluconeogenesis. 18 to 20 amino acids have structures that allow them to be converted to glucose and 19 of the 20 amino acids can be converted to fatty acids. From an energy production perspective, the body almost entirely uses carbohydrates and fats for energy.

Clinical Pearls:

1. The minimum adult recommendation for daily protein intake is about 60 to 75 grams
2. Adrenal stress, that is, increase secretion of glucocorticoids causes the breakdown of protein tissue.
3. Insulin is necessary for protein synthesis.





The beginning stage of the Krebs cycle starts with acetyl-CoA combining with oxaloacetic acid to form citric acid. The Coenzyme A that is released can be used again to form more acetyl-CoA from pyruvic acid. A total of eight reactions take place in the Krebs cycle. As the reactions take place, several molecules of water are added and carbon dioxide and hydrogen atoms are released. Not a great amount of energy is produced in the Krebs cycle, however, a significant amount of hydrogen atoms are released, which is then used by the electron transport chain and oxidative phosphorylation to produce a significant amount of ATP. These hydrogen atoms are combined with NAD^+ and FAD^+ to form $NADH + H^+$ and $FADH_2$, which proceed to the electron transport chain.

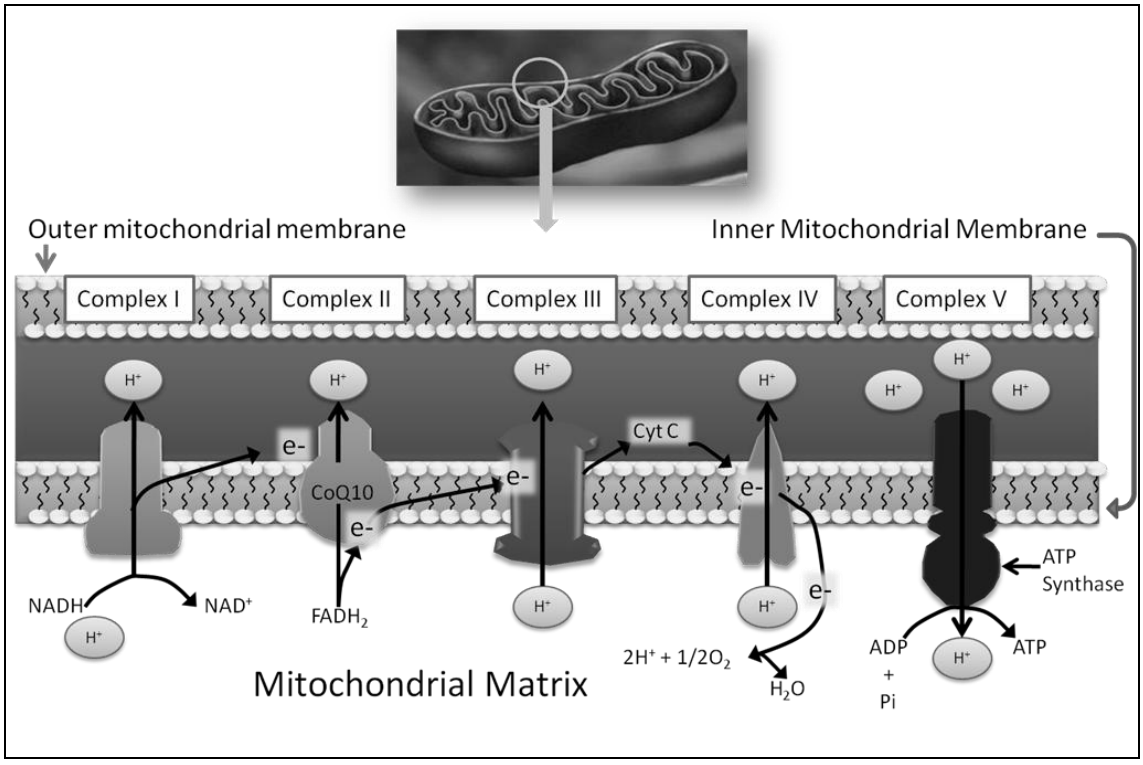
Electron Transport Chain and Oxidative Phosphorylation

The mechanism by which the mitochondria form ATP is called chemiosmosis or the chemiosmotic mechanism. As you recall that NAD^+ is reduced to NADH plus a hydrogen ion. The hydrogen atom released from NADH will have its electrons removed by the electron transport chain to form a hydrogen ion. The hydrogen ions are pumped into the outer chamber creating a strong negative electrical potential (recall that electric potential energy can be defined as the capacity for doing work which arises from position or configuration). The high concentration of positively charged hydrogen ions along with the strong electrical potential difference across the inner membrane causes hydrogen ions to flow into the substance of the ATP Synthase molecule which causes the formation of ATP from ADP.

The most important electron acceptors are: flavoprotein, ubiquinone (CoQ 10), iron sulfide proteins and the cytochromes (B, C1, C, A and A3). Each electron moves from one acceptor to another until it reaches cytochome A3, which is called cytochrome oxidase. Cytochrome oxidase is capable of giving up two electrons that reduces elemental oxygen to an ionic form, which then combines with hydrogen ions to form water.

$$2 \text{ electrons} + \tfrac{1}{2}\, O_2 + 2\, H^+ \rightarrow H_2O$$

The reason why we cannot live without oxygen is because oxygen is the final electron acceptor. Without oxygen accepting the final electrons, the electron transport chain will stop and, therefore, energy production will cease. A small percentage of electrons can escape along the electron transport chain, creating reactive oxygen species (ROS) by prematurely and incompletely reducing oxygen. The ROS will cause tissue damage when there is an imbalance in antioxidants.

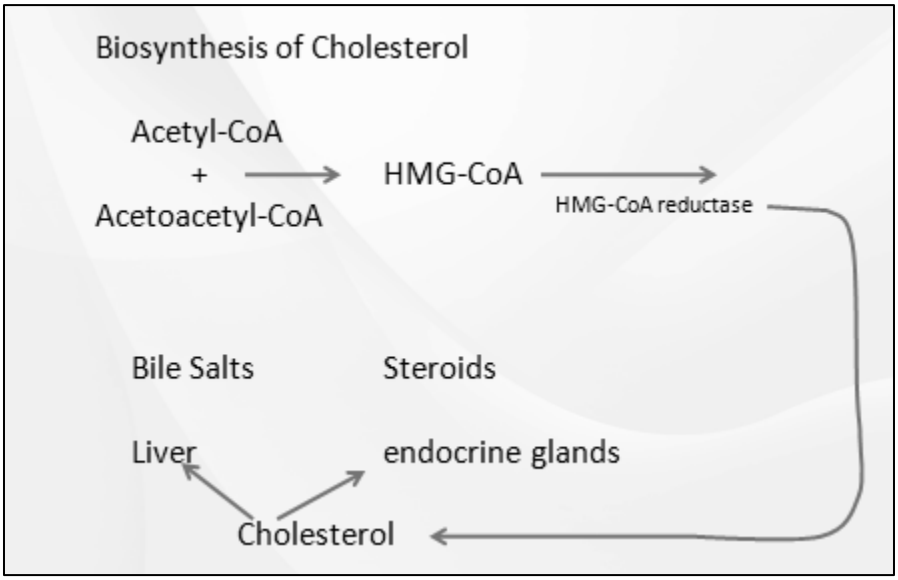


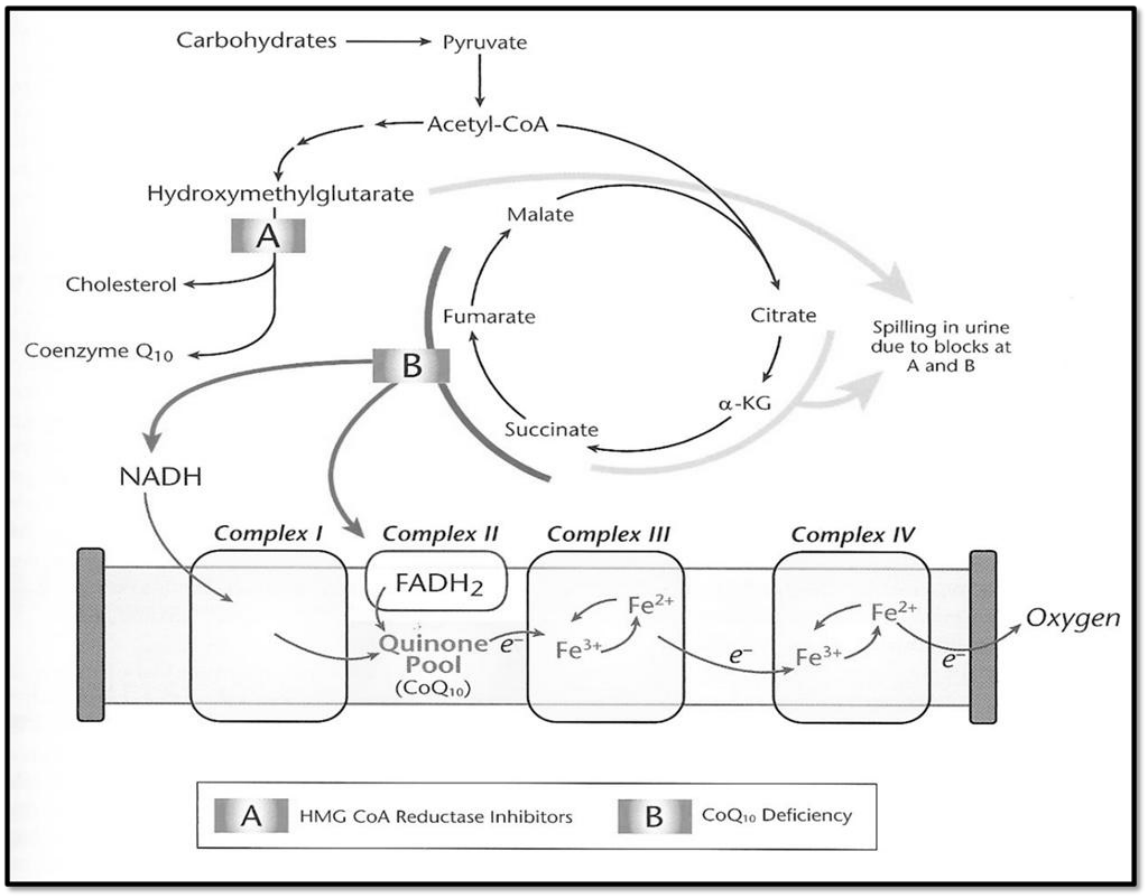
Coenzyme Q10

Common name:	Coenzyme Q10 (CoQ10), ubiquinone
Biochemical Role:	Oxidative phosphorylation
Adult repletion:	10 to 300 mg/D

Physiological Function: The primary function of CoQ10 is to shuttle electrons through the electron transport chain (ETC) in the mitochondrial inner membrane. The tissue that has the largest, most critical energy demand – the heart – will first show effects of conditional deficiency of the coenzyme.

Assessment of Status: CoQ10 synthesis is dependent on the availability of hydroxy-methylglutarate (HMG). Thus, if HMG is low it will slow the rate of CoQ10 synthesis. Statin drugs block the conversion of HMG to cholesterol and to CoQ10.





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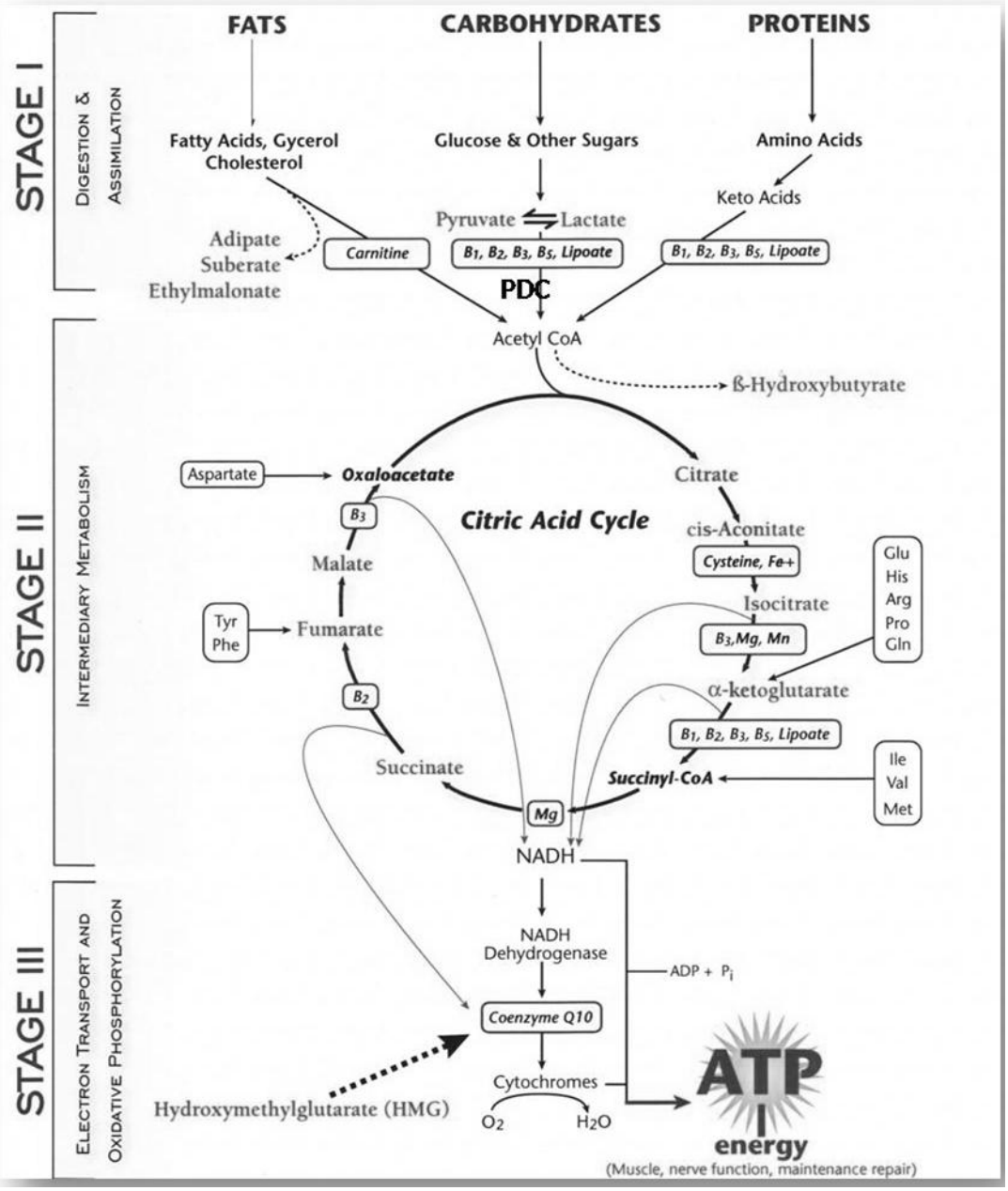

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3. http://themedicalbiochemistrypage.org/; Michael W. King, PhD (reprints with permission)
4. Textbook of Medical Physiology, 11th ed., Arthur C. Guyton, M.D.†, John E. Hall, PhD