Unit IX – Problem 1 – Biochemistry: Energy Systems

- **ATP (Adenosine Tri-Phosphate)**: it is the currency of energy (providing the energy required for muscle contraction) and it is constituted of the following:
  - Adenine.
  - Ribose (5-carbons sugar).
  - One, two or three phosphate bonds (AMP, ADP and ATP respectively).
    Notes:
    - ✓ Both adenine and ribose constitute adenosine.
    - ✓ A phosphate group is linked to adenosine through phosphoester bond.
    - ✓ Phosphate groups are linked to each other by phosphanhydride bonds. These are high-energy bonds which means that they provide a great amount of energy (-7.3 kcal/mol → negativity means that it is an exergonic reaction) when broken down.
    - ✓ The most potent source of energy is phosphenol pyruvate which is providing (-14.8 kcal/mol) when broken down. Notice that phosphenol pyruvate is the precursor of pyruvate in glycolysis (it is converted to pyruvate through the action of pyruvate kinase enzyme).
- **There are three exercise energy systems (duration and intensity of exercise will determine which of these systems must be utilized):**
  - **Creatine phosphate (CP):**
    - ✓ CP is stored in muscles in limited amounts.
    - ✓ The high-energy bond between phosphate and creatine is broken. The released phosphate will convert available ADP into ATP thus providing energy which is utilized primarily for quick, maximal exercises lasting about 1-6 seconds. Notice that in the beginning, there is a small amount of ready ATP stored in the muscle (this will provide energy only for 1 second after which CP system will be activated and it will provide energy for 6 seconds).
    - ✓ ATP and CP are known as phosphagens and together they represent the ATP-CP energy system.
    - ✓ Types of exercises activating this energy system: bench press, jump squat and sprinting.
  - **Anaerobic glycolysis (also known as the lactic acid system):**
    - ✓ The process of glycolysis occurs in the cytosol and converts one molecule of glucose (a 6-carbon sugar) into two molecules of pyruvate (generating a net of two ATPs throughout the process: four ATPs are generated in the energy-generation phase but 2 ATPs will be already consumed in the energy-investment phase).
    - ✓ The glucose which is needed for this process is provided from:
      - ❖ Blood glucose (nutrients).
      - ❖ Muscle glycogen (providing glucose which is only utilized by the muscle itself).
      - ❖ Liver glycogen (providing glucose to the blood especially in fasting conditions).
    - ✓ The rate-limiting enzyme in glycolysis is PFK (Phosphofructokinase) which is:
      - ❖ Stimulated by: fructose 2,6 bisphosphate.
      - ❖ Inhibited by: ATP and citrate.
    - ✓ What happens to PFK in liver and muscle when glucose level is low?
      - ❖ In liver: glucagon will activate a phosphatase enzyme which will convert fructose 2,6 bisphosphate to fructose-6-phosphate. Therefore, PFK will be inhibited and this will slow down glycolysis.

- In muscle: epinephrine will activate a kinase enzyme which will convert fructose-6-phosphate to fructose 2,6 bisphosphate. Therefore, PFK will be activated and this accelerates glycolysis.

✓ When is this system activated? →when the activity is longer than a few seconds or it is too intense (such as weight lifting). There is a high rate of ATP energy production but this energy lasts only for few minutes (1-2 minutes).

✓ Notice that lactic acid is the end product of this energy system resulting in fatigue of muscles. Causes of fatigue are:

- Decreased levels of energy substrates.
- Disturbed acid-base balance: due to lactic acidosis.
- Increased core body temperature: leading to dehydration.
- Disturbed electrolyte balance: through high rate of sweat loss.

- **Oxygen (aerobic) energy system: it is divided into the following:**

✓ Aerobic carbohydrate metabolism:

- Starts in the following sequence: glycolysis → Krebs cycle → electron transport system.
- Providing a long-term energy when the event lasts for less than 30 minutes.

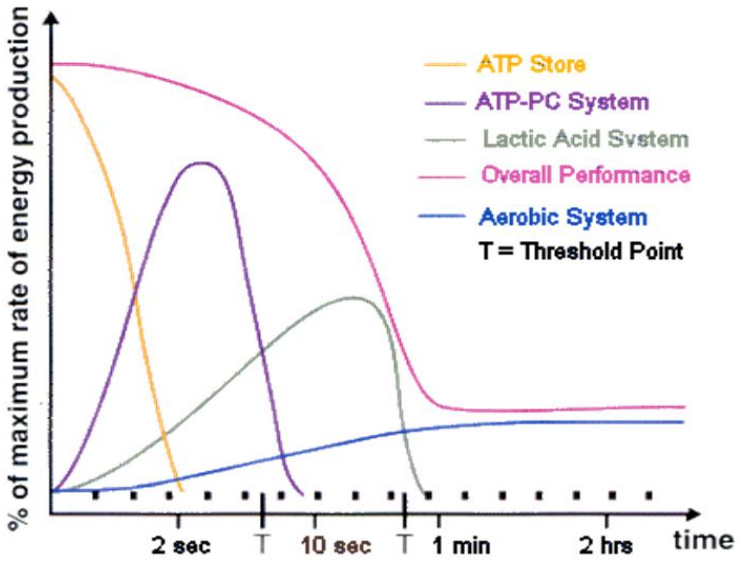
✓ Fat oxidation (fatty acid β-oxidation):

- Starts in the following sequence: β-oxidation → Krebs cycle →electron transport system.
- Sources of fat/triglycerides:
  - Adipose tissues.
  - Muscle triglycerides.

  Notice that fat stores will be released from these two location through the action of an enzyme known as hormone-sensitive lipase (which is inhibited by insulin). You have to differentiate between this enzyme and lipoprotein lipase which is stimulated by insulin and aims to break down triglyceride into fatty acids and glycerol so they can enter adipose tissue and then will be converted back into triglycerides to be stored there.
- It has the highest total energy capacity (providing energy for events lasting more than 30 minutes. Therefore, resulting in burning of fat storage in the body and aiding in weight loss).
- Notice that ketone bodies are produced in the liver. They are utilized by all tissues except the liver itself because it is deficient in the enzyme thiophorase.

✓ Protein oxidation:

- Starts in the following sequence: amino acid oxidation → Krebs cycle → electron transport system.
- Which amino acids are used in direct muscle oxidation? → branched-chain amino acids (leucine, isoleucine and valine). Remember that amino acids can also be used for gluconeogenesis which is occurring in the liver during fasting-state. Notice that branched-chain amino acids are transported via the same carrier system as tryptophan. Therefore, ingestion of branched-chain amino acids increases their concentration in plasma and reducing the uptake of tryptophan by the brain resulting in reduction of serotonin synthesis in the brain and delaying fatigue of muscles.
- There is a limited total energy capacity (not really important) but it might be a significant source of energy during long-endurance events.



- **There are two types of shuttles:**
  - **Glycerophosphate shuttle**: it allows reducing equivalents to be transferred to DHAP to form glycerol 3-phosphate which can be translocated across the mitochondrial membrane. Once inside the mitochondrial matrix, the reaction is reversed with regeneration of DHAP that can leave the mitochondria in exchange for glycerol 3-phosphate.
  - **Malate-aspartate shuttle:**
    - ✓ Oxaloacetate accepting reducing equivalents → converted to malate → which will cross into the mitochondria in exchange with aspartate.
    - ✓ In mitochondrial matrix, malate can be oxidized using mitochondrial NAD to generate NADH (which is used to generate 3 ATP molecules in oxidative phosphrylation).
- **Glucose-CO_2-lipids:**
  - Glycolysis converts one glucose (6-carbon molecule) to two pyruvate (3-carbon molecule).
  - Pyruvate is converted to acetyl CoA through the action of the enzyme pyruvate dehydrogenase complex. Then, acetyl CoA can either enter Krebs cycle in mitochondria or can be used in the synthesis of fatty acids.
  - Notice that pyruvate dehydrogenase complex is an irreversible step (which means that there will be no conversion of lipids back into carbohydrates).
  - The enzyme pyruvate dehydrogenase complex is:
    - ✓ Stimulated by: insulin (through stimulation of pyruvate dehydrogenase phosphatase).
    - ✓ Inhibited by: glucagon (through stimulation of pyruvate dehydrogenase kinase). This enzyme is also inhibited by:
      - ❖ High ATP.
      - ❖ High NADH.
      - ❖ Acetyl CoA.
- **Anaplerotic reactions from amino acids:**
  - **Anaplerosis**: it is the act of replenishing TCA cycle intermediates that have been extracted for biosynthesis (in what are called cataplerotic reactions).
  - **Notice that all amino acids are glucogenic except for: leucine and lysine.**
- **Pentose phosphate pathway:**
  - **It is divided into two reactions:**
    - ✓ Two oxidative –removing hydrogen- irreversible reactions:
      - ❖ *1st oxidative reaction*: catalyzed by glucose 6-phosphate dehydrogenase.

❖ *2nd oxidative reaction*: catalyzed by 6-phosphogluconate dehydrogenase which will generate ribulose 5-phosphate.
Notes:
- ➢ Both of these oxidative reactions will generate NADPH which is used for detoxification of reactive oxygen species (ROS) and synthesis of fatty acids.
- ➢ Ribulose 5-phosphate can be:
  - Isomerized to ribose-5-phosphate: which is used in nucleotides biosynthesis or enters glycolysis to generate energy.
  - Epimerized to xylulose-5-phosphate.

✓ Several non-oxidative reversible reactions.

- **Gluconeogenesis:**
  - **Definition**: it is the synthesis of glucose/ glycogen from non-carbohydrate precursors (lactate, glycerol and amino acids).
  - It occurs during fasting in the cytosol of liver (90%) and kidneys (10%). Notice that with prolonged starvation more gluconeogenesis will be carried out in kidneys.
  - Fructose 1,6 bisphosphatase is the rate limiting enzyme in gluconeogenesis. It converts fructose 1,6 bisphosphate to fructose-6-phosphate. This enzyme is:
    - ✓ Stimulated by: citrate, glucagon and cortisol.
    - ✓ Inhibited by: AMP and fructose 2,6 bisphosphate.
- **Ketone bodies (ketogenesis):**
  - When β-oxidation of fatty acids generate huge amounts of acetyl CoA → these will be used in production of ketone bodies in the liver.
  - Why is it important?
    - ✓ Serving as a major source of energy during times of glucose insufficiency.
    - ✓ Spare the use of amino acids.
- **Compartmentalization of the major pathway of metabolism (see the image below):**