AN INTRODUCTION TO METABOLISM
Part 1: Overview [*]

Summary: In this class you will learn what metabolism is and how we can attempt to measure it. You shall see that every method of measurement of metabolism is limited to some degree and that no fully satisfactory means exists to measure it.

I. METABOLISM AND ITS MEASUREMENT:

A. Defined as the sum of all reactions, i.e.,

METABOLISM = CATABOLISM + ANABOLISM

B. Metabolism is indicative of the magnitude of at least three very important physiological factors:

1. **GROWTH AND REPRODUCTIVE RATE** (i.e., rates of synthesis)
2. **ACTIVITY** -- energy needed to operate the various biochemical pathways needed directly and indirectly in mechanical locomotion.
3. **COMPLEXITY**, since presumably the more complex the organism, the greater the metabolism required to maintain that complexity. This idea is difficult to actually substantiate with measurements since more complex organisms may have lower rates of growth and reproduction or they may be less active. Also, how do you measure complexity? Structurally? Biochemically? By size?

C. HOW DO WE MEASURE METABOLISM?

1. We commonly think about metabolism as energy or power with units such as Joules, calories, watts or calories per time. Why?

a. **Energy: Metabolic Cost**: Nearly all chemical reactions involve changes in stored energy (**potential energy, PE**) such as the release or absorption of heat or some other type of energy. Since heat is a by-product of most of the chemical reactions in an organism and since metabolism is the sum of all processes, we can use the total heat released by an organism as an estimate of an organism's metabolism; that is, as an estimate of the cost of existence for this organism. If we measured metabolic cost as heat production, we would symbolize the cost as Q with units either of calories or Joules.

b. **Power: Metabolic Rate**: If we calculate the rate of the metabolic processes -- *i.e.*, if we divide the energy cost by the time over which the cost was incurred, we have the metabolic rate which has units of power. In physiology it is common practice to indicate something is a rate by using a dot over a symbol for the process. For instance, $\dot{Q}$ is the rate of heat production and is one way of expressing metabolic rate. It has units of power -- usually watts or calories per time.

2. METHODS USED TO DETERMINE METABOLIC RATE or METABOLISM:

a. The "WHAT COMES IN MUST GO OUT" method

1. We sum all of the PE contained in materials that go in and out of an organism:

1. ***I*** = ***G*** + ***E*** + ***M***

where ***G*** is growth and reproduction
E is egested and all other wastes
M is respiration, this represents the actual chemical work done by the system and therefore is the metabolism.
Thus:

2. ***M = I - E - G***

2. By converting all *I, E* and *G* to energy values by **BOMB CALORIMETRY**, *M* can be obtained as energy. If we then divide M by time, we have the metabolic rate.

3. Problems with this method:

a. difficulty in monitoring all inputs and outputs

b. destruction of the organism -- its hard to get student volunteers.

b. **HEAT PRODUCTION -- Direct Calorimetry** (*Q and* $\dot{Q}$):

1. <u>Method</u>: Encase the organism in a calorimeter and measure the heat production. As stated previously, the heat production is proportional to the total metabolic rate since the doing of chemical work results in heat production as a by-product.

2. Problems:

a. the organism must be enclosed in a rather unnatural state.

b. the calorimeters are very expensive.

c. free-ranging measurements are impossible.

d. this method ignores external work done by the organism, but that is usually small compared to energy released within the organism.

c. THE MEASUREMENT OF METABOLISM AND METABOLIC RATE USING OXYGEN CONSUMPTION (V_{O2} **and** $\dot{V}_{O_2}$ **) AND CARBON DIOXIDE PRODUCTION (** V_{CO_2} **and** $\dot{V}_{CO_2}$ **)**

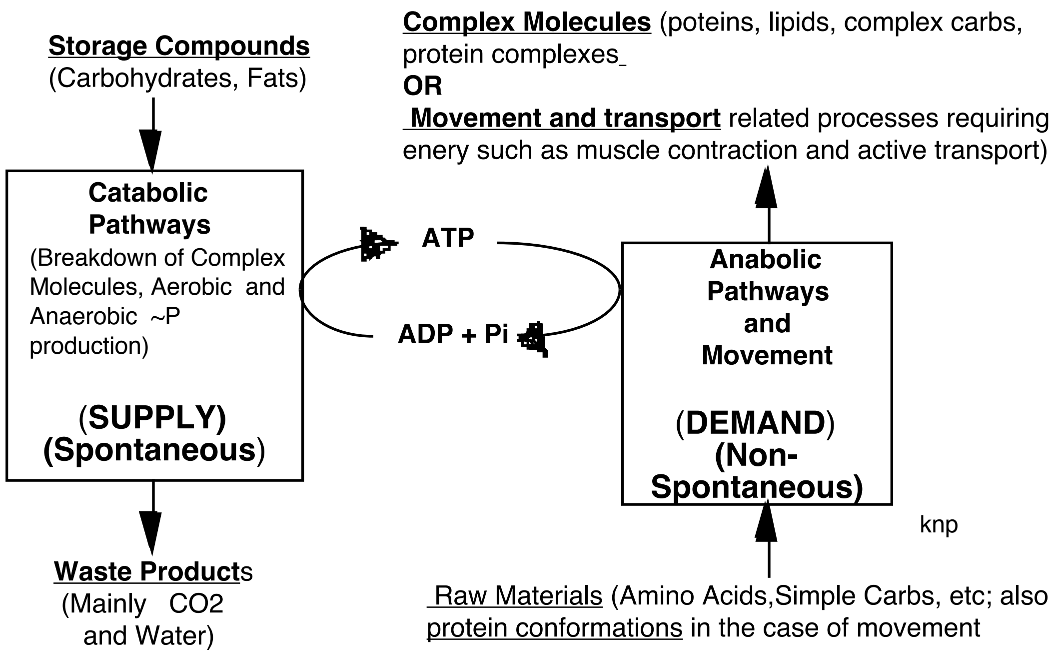
1. Metabolism can be measured in <u>**aerobic**</u> organisms by recording O_2 consumption and CO_2 production. This requires that the organism must, as a whole be acting aerobically when the measurements are taken. Thus, if any anaerobic metabolism is occurring in some tissues, its effects must be reversed elsewhere in the organism. For most animals this will mean that if any anaerobic by product is being produced (for example, lactic acid) it must be used up (not eliminated) by some other part of the body. If anaerobic products build up (increase) or if they are eliminated from the body, then the entire energy demand cannot be estimated just from anaerobic processes and so measurements of $\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$ would both be underestimates of metabolism.

2. When using $\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$ **the assumption must be made that virtually all reactions are driven directly or indirectly by use of ˜P taken from ATP or similar compounds.** (This is essentially true, but there are some exceptions). Since the production of ˜P is largely tied to the use of oxygen and evolution of CO_2, then

measurement of these should allow estimation of total energy flux. Let's look at this in a bit more detail:

a. The ATP cycle. Anabolic reactions and movement (muscle action, active transport, exocytosis, *etc*.) are non-spontaneous processes. Thus, they all require some sort of energy source and that source is usually ATP. We can refer to these processes that need energy from ATP as "**DEMAND**" reactions. I use the term demand because their rates are turned up or down and the processes that make new ATP must adjust their rates to keep the [ATP] at normal values. We will call the reactions that take energy from complex, energy storage molecules such as carbohydrates or fats and transfer some of that energy to the formation of ATP (or more simply ~P) the "**SUPPLY"** reactions: (NEXT PAGE)

The Central Role of ATP in Cellular Energetics



The rate of the demand reactions is set by some factor (for instance the need to grow or move) and the supply must meet it. ATP is used to shuttle energy from the energy-rich compounds degraded in the supply reactions to those needing energy in the demand side. The supply reactions must be adjusted to keep the level of ATP roughly constant. Thus, we will need to learn not only the nature of the supply reactions (principally they are glycolysis, the Krebs cycle, β-oxidation of fatty acids, and the Electron Transport System) but we will also need to understand how they are regulated.

! Be sure to keep in mind that **the most important factor being regulated by metabolism is the ratio of ATP to ADP and Pi**.

TEMPORARY STORES OF ~P

In tissues that experience very high transient demands for ~P, it may not be possible to synthesize new ~P at the rate that it is being used -- at least not in the short term.

1. The most common reason for this is the supply reactions were regulated to a certain level of demand. This happens both at the cellular and organismal level.

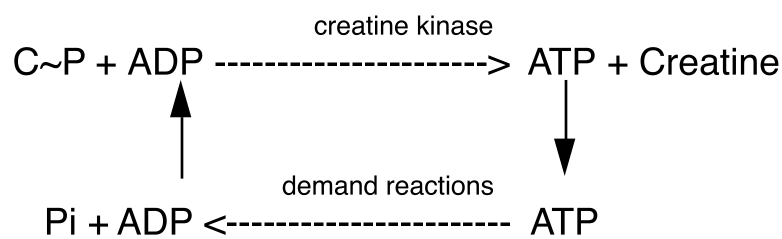
(a) At the cellular level, key enzymes (rate-limiting regulated enzymes) are activated/inhibited to achieve a rate of ~P production consistent with demand (see illustration above). We will look at this in more detail in a couple of classes.

(b) At the system level, the circulation and respiratory rates are set to supply O_2 and remove CO_2 to keep it relatively constant. They are also adjusted to a certain demand and if the demand changes, it takes time for their delivery/removal rates to change.

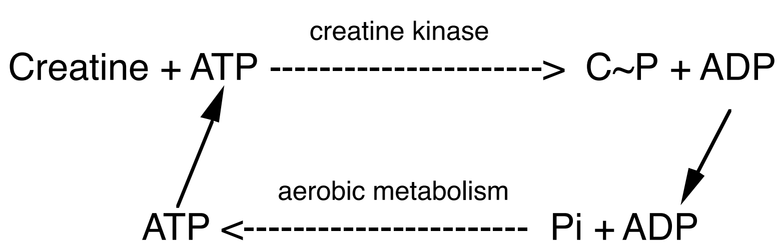
2. A less common problem is that the system is working at full capacity and even more ~P is demanded than can be made.

3. In either case, some of the shortfall can be made up by getting ~P from storage molecules called **phosphagens**. The two most important ones in animals are **creatine phosphate** and **arginine phosphate**. Both are chemically very similar. In both cases, the structure of the "carrier" (creatine or arginine) means that the phosphate group is strongly repelled electrically. This gives it a very high transfer potential -- it is easily removed and that is what makes this a high-energy bond. Here is the typical process using creatine phosphate, C~P -- it is the same with arginine phosphate, A~P.

Here is the reaction that shows what happens when demand increases: As ATP is converted into ADP when its terminal phosphate is transferred to compounds in demand reactions, the ADP can receive a new ~P that was stored on C~P; the reaction is catalyzed by creatine kinase (or arginine kinase if A~P is used):



The opposite happens with C~P is depleted and if there is excess capacity (compared to demand) to synthesize ~P:



In this case an excess of ATP (and capacity for ~P systnesis) and creatine help drive the reaction towards the production of C~P.

Notice that the phosphagen can be thought of as part of the supply and demand systems. I like the analogy of it as a bank account, ATP as pocket cash, aerobic and anaerobic metabolism as "jobs" that produce income and demand as whatever you want to spend the money on!