Physiological Chemistry Laboratory
CHEM 1106

Biochemistry & Drug Action

Living organisms are made up of cells, the basic unit of life, which can be divided up into specific compartments along with their contents. Simply put, biochemistry is the study of how living organisms operate at the molecular level. The exterior boundary of a human cell is known as the plasma membrane. It is comprised of *lipids* (figure 1), hydrocarbons that contain *hydrophilic* ("water loving") functional groups, such as *hydroxyl* (-OH), *carboxylate* (-COOH) or *phosphate* (-PO_4). The hydrocarbon portion of the lipid is *hydrophobic* ("water fearing") and comprised of repeating *methylene* (-CH_2-) or *methyl* (-CH_3) groups. The hydrocarbon portion has chemical characteristics similar to oil, and does not mix well with water. When lipids are mixed with water, they form structures known as *micelles*. Micelles form small ball-like structures which have the hydrophilic functional groups on the outside and the hydrophobic functional groups on the inside. Lipids can also form *sheets* which are comprised of two layers of lipids. This double layer will have the hydrophilic groups on the outside of the "sandwich" and contain the hydrophobic groups on the sandwich interior. This sandwich structure represents the structure of the plasma membrane as well as the membrane for most other subcellular *organelles* such as the nucleus, mitochondria and endoplasmic reticulum.

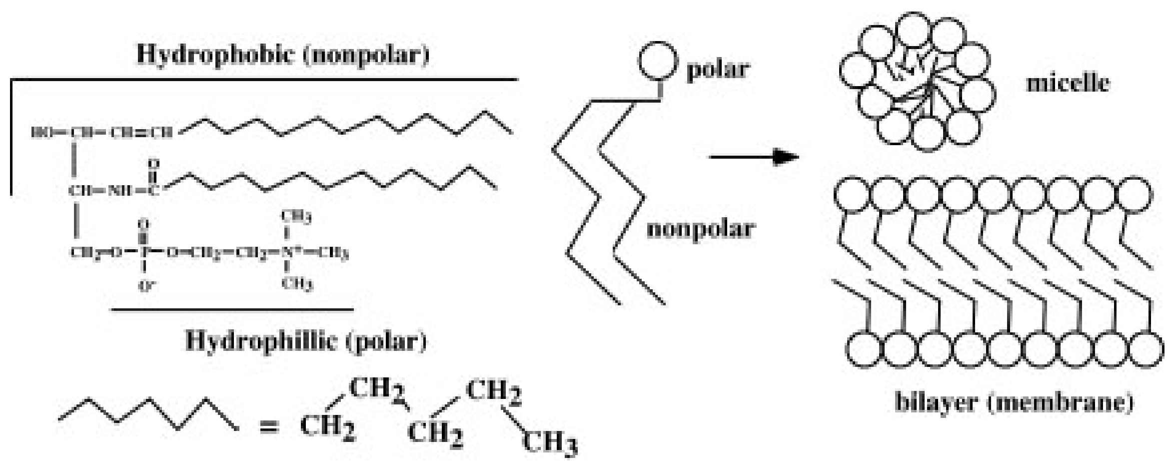

Figure 1. Lipid molecule and schematic structure of micelles and bilayer membranes

Cells contain all the machinery for life, including membrane bound organelles such as the nucleus, which contains our genetic material (DNA and RNA), mitochondria , which convert food molecules such as carbohydrates (*sugars,* figure 2) and fats (lipids) to energy the cell can use and lysosomes, which serve as cellular "recycling centers" for the degradation and reuse of molecules protein, DNA and RNA synthesis). A large part of the volume of most cells is comprised of a gel-like substance known as the *cytoplasm*. The cytoplasm consists of proteins, RNA molecules, sugars, amino acids, vitamins and a host of other biomolecules. Proteins are long strings of *amino acids* (figure 3). There are 20 different amino acids that make up most of the proteins found in nature. Many of the proteins are *enzymes*, biological catalysts that speed up the rates of chemical reactions. Enzymes are necessary because most chemical reactions required for life do not occur at an appreciable rate under physiological conditions of temperature (37^{o}C), pH (7.0), pressure (1 atmosphere) or for the concentrations of reactants found in a typical cell. Examples of such chemical reactions include the degradation or synthesis of sugars, lipids, amino acids, proteins, DNA or RNA, among others. We refer to the synthetic reactions that occur in a cell as *anabolism* and the degradative reactions as *catabolism*. The combined process of anabolism and catabolism is knows as *metabolism*.

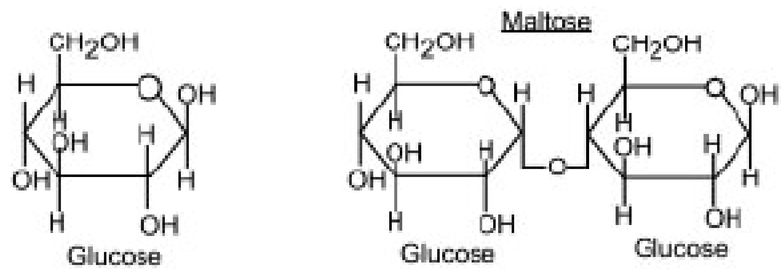

Figure 2. Example of carbohydrates *glucose* and *maltose*

Drugs (and toxins!) target several different cellular structures or metabolic pathways. Drugs which target non-human cellular pathogens or cancerous tumors are often referred to as *antibiotics*. Antibiotics can be classified along several lines, including those that target bacterial cells, viruses, fungi, protists, helminths (worms) or cancerous tumors. Various antibiotic drugs have their affect by their action on the different types of cellular structures and biomolecules. Let’s look at a few examples:

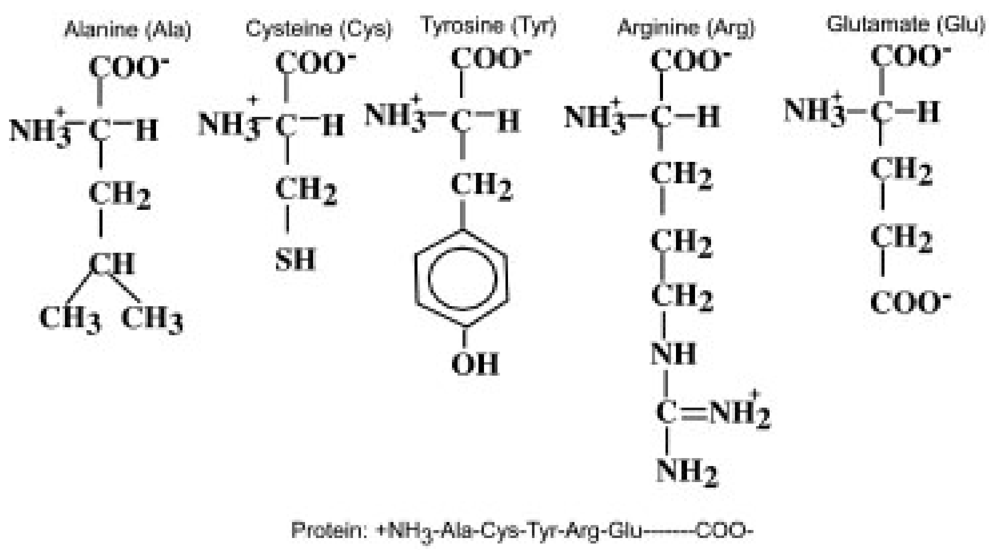

Figure 3. Representative amino acids and schematic protein structure

Antibacterial drugs

Bacteria have cellular structures and metabolism quite different from our own. For example, because bacteria are free-living, unicellular organisms they must have a way to protect themselves against changes in their environment (temperature, salt concentration, etc.). One way they have adapted to life on their own is by having an rigid, outer cell wall. This cell wall is quite different from the plasma membrane, which lies beneath the cell wall. It is comprised not of lipid, but of a cross-linked structure of sugar and amino acid fibers. These fibers contribute tensile strength to the wall, which helps prevent the bacterial cell from swelling and the membrane from being broken down too readily when environmental conditions are less than ideal.

Bacteria must also synthesize all their own biochemical building blocks, such as amino acids for proteins, lipids for membranes, and various vitamins which are required for particular enzymes to become active. Humans obtain many of these compounds in their diet, so they do not have many of the metabolic pathways found in bacterial cells.

Antibacterial drugs act by targeting four general areas: bacterial metabolism, cell wall synthesis, the plasma membrane, protein synthesis and DNA/RNA synthesis.

I. Bacterial metabolism inhibitors

Drugs such as the *sulfonamides* attack bacterial cell metabolism. The sulfonamides, in particular, block the synthesis of folic acid, an important vitamin required for the synthesis of amino acids and nucleotides. These were one of the earliest antibiotics discovered and are still in use today, though many bacterial strains have mutated to become resistant to their action. They are still one of the best drugs for the treatment of leprosy.

II. Cell Wall Synthesis Inhibitors

Another popular class of antibiotics act by inhibiting cell wall synthesis. The *penicillins* and *cephalosporins* are the best known members of this class, although others such as *cycloserine, vancomycin* and *bacitracin* also act in this manner. If bacteria are not able to synthesize their cell wall, water moves into the bacterial cell under the influence of a difference in osmotic potential (solute concentration) between the interior and exterior of the cell. Movement of water into the cell causes it to swell. Without the rigid cell wall, the bacterial cell will swell so much that it eventually bursts and dies. Penicillin was also one of the first antibiotics discovered and is still a very powerful and safe drug, though again, many strains of bacteria have become resistant to its action.

III. Plasma Membrane Disruption

Plasma membranes, as noted earlier, serve as the barrier between the interior of the cell and the exterior. The interior of the cell has the consistency of a gel, due to the high concentration of proteins, sugars (carbohydrate), amino acids, vitamins, metabolic intermediates, nucleotides, minerals (Na^+, K^+, Mg^{2+}, Ca^{2+}) and other small biomolecules. Some antibiotic drugs, such as *polymxin*, act by creating pores in the plasma membrane. This allows the contents of the cell to leak out, which quickly kills the cell.

IV. Protein Synthesis Inhibitors

Protein synthesis is essential to the life of the cell. Without protein synthesis, essential proteins such as enzymes cannot be produced. Several antibiotic compounds act by preventing protein synthesis in bacterial cells. Some of these include the *rifamycins* (rifampicin), *aminoglycosides* (streptomycin), *tetracyclines* (chlorotetracycline), *chloramphenicol* and the *macrolides* (erythromycin).

V. DNA/RNA synthesis inhibitors

DNA is the molecule which contains our genetic “blueprint”. All instructions for the synthesis of our proteins, and by default the carbohydrates, lipids, nucleotides, vitamins, etc. synthesized by proteins (enzymes), are contained in our DNA molecules (chromosomes). Certain antibiotic drugs act by attacking bacterial DNA and RNA, the intermediate between the DNA “blueprint” and final protein product. These drugs either prevent DNA from being copied into new “daughter” DNA strands or into RNA intermediates. Some of these drugs include the *quinolones* and *fluoroquinolones*, of which the best known example is probably *ciproflaxin* (“cipro”). Ciproflaxin has received a lot of attention recently due to its activity against *anthrax*, the deadly bacterial strain used in the terrorist attacks against members of congress and employees of the tabloid publication based in Florida.

Antiviral Drugs

Viruses, technically speaking, are not true living organisms. Outside of a living cell, the are rather static objects, without the capacity to reproduce, self-assemble, or perform metabolic reactions. Once inside a host cell, however, they become active, and cause a number of pathological conditions such as *polio*, *smallpox, herpes* and AIDS (*Acquired Immune Deficiency Syndrome*). Viruses come in a variety of shapes and structures, but they all contain some type of genetic material, either DNA or RNA. Many antiviral compounds act by attacking the viral genome. Compounds such as the AIDS drug (AZT), acyclovir (herpes) or famciclovir all act by mimicking *nucleotides*, the normal constituents of DNA and RNA molecules (figure 4). The drugs, however, lack a crucial chemical structure, which prevents the DNA or RNA molecules from being copied into “daughter” molecules. This prevents replication of the viral particles and slows or stops the infection.

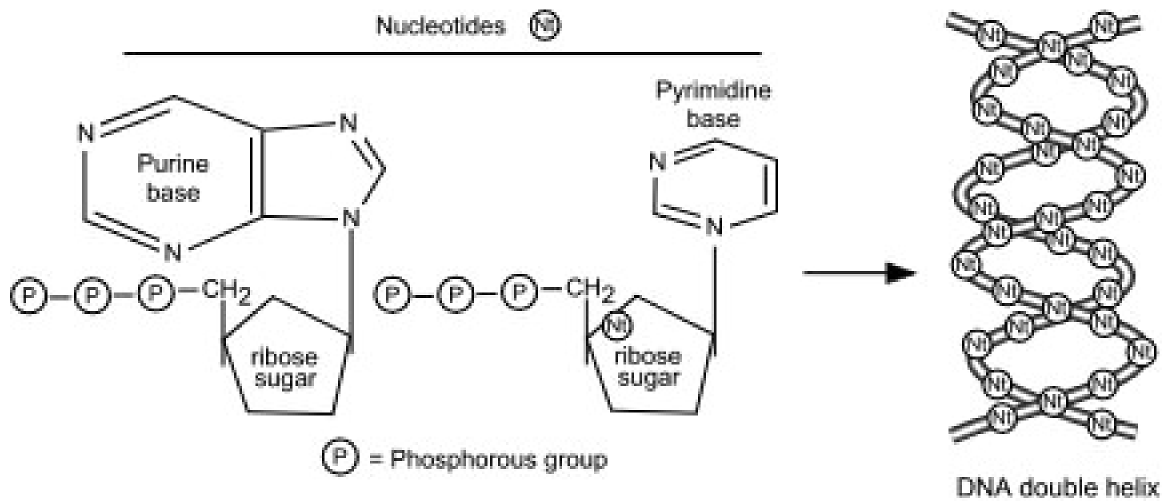

Figure 4. Nucleotide and DNA structure

Anticancer Drugs

Cancer is caused by normal cells which have somehow lost their ability to regulate their own growth and replication. Unregulated cell growth and division results in tumors which damage the ability of organs (liver, brain, thyroid, etc.) to perform their normal functions. In many cases this can result in a life-threatening situation. Anticancer drugs seek to target only those cells which are growing and reproducing rapidly. They attack these cells by way of a number of mechanisms which are similar in some respects to the way antibacterial antibiotics work; inhibiting metabolic pathways, attacking DNA, preventing cell division, etc. For example, the anticancer agents *methotrexate* and *5-fluorouracil* act by inhibiting the synthesis of compound necessary for the synthesis of amino acids and nucleotides, respectively. The compounds *actinomycin D*, the *anthrocyclines* and the alkylating agents *mechloroethamine*, *cyclophosphamide* and *cisplatin* act act by binding to DNA and preventing their replication. The compounds *vincristine, vinblastine* and the new anticancer drug *taxol* (paclitaxel) act by preventing mitosis (cell division) in cancer cells, so tumor growth stops and (hopefully) declines.

This lab has only been a brief preview on the relationship between chemistry and disease. Many more relationships could be examined, including the details of metabolism, nerve transmission, cell growth or aging. Hopefully this preview will initiate further interest, and motivate you to pursue further understanding of the chemistry of life.