pep Pharmacology Education Partnership

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Acids, bases and cocaine addicts

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A Project Funded by a NIDA Science Education Drug Abuse Partnership Award

Module 1: Acids, bases and cocaine addicts

Description of the module

Users of crack cocaine are more likely to become addicted than users of snorted cocaine. How can the same compound produce these differences in behavior? The answer lies in its pharmacokinetics, which describes the rate of distribution of drugs throughout the body. This module contains a combination of basic biology and chemistry principles to demonstrate several phenomena; 1) how the acid-base characteristics of cocaine enable it to be dissolved in aqueous solution or volatilized in smoke, 2) how the acid-base characteristics of cocaine enable it to pass through a biological membrane, 3) how the composition of a biological membrane affects the ability of a charged vs uncharged molecule to pass through, 4) how the connections between the circulatory system and the lungs govern the speed at which drugs are delivered to the brain, and 5) how the organism responds to psychoactive drugs that enter and leave the brain quickly vs. those that enter slowly and persist longer.

Learning objectives

After participating in this module, students should understand the following:

1. The properties of a drug that define it as a weak acid or a weak base.
2. What causes a weak acid to become charged or a weak base to become uncharged
3. The properties of a cell membrane and the drug that enable the drug to pass through the membrane
4. The basic anatomy of the circulatory system
5. How drugs distribute throughout the body
6. The relationship between the rate at which a psychoactive drug enters the brain and its abuse potential

This module integrates information from the following areas:

biology, chemistry, psychology, human behavior

Student Handout

Cocaine is a highly addictive drug. In recent years it has become well known that people who smoke cocaine (in the form of crack or the free base) may become more easily addicted and more readily abuse cocaine than people who snort cocaine. Why would people show different patterns of abuse of the same drug, when administered by different routes? To answer this question, one needs to understand the chemical nature of cocaine and how it gets from the site of administration to the brain, where it produces its psychoactive effects.

1. Most drugs are weak acids or weak bases. Is cocaine a weak acid or weak base?

2. A weak acid or base can exist in 2 forms—charged (ionized) or uncharged (unionized). What is the major factor that determines whether the weak acid or base is charged or uncharged?

3. In what chemical form (charged or uncharged) is cocaine snorted? Smoked? Why are they different?

Cocaine must pass through several barriers (cell membranes) to get from the nostrils or the lungs into the blood.

4. What kinds of molecules make a cell membrane? Are there charges present on cell membranes?

5. In what form (charged or uncharged) must molecules, such as drugs, be to pass through a cell membrane?

6. What forces play a role in helping a drug such as cocaine cross a cell membrane?

Once in the blood, cocaine travels throughout the body, including the brain, where there is a very special membrane barrier. The barrier consists of tightly packed cells that only allow certain compounds to cross from the blood into the brain.

7. How does the cocaine get from the blood vessels in the nose to the brain? How does the cocaine get from the blood vessels in the lungs to the brain? Which route is most direct to the brain?

8. In what form (charged or uncharged) must cocaine be to cross the barrier and enter the brain?

Scientists in the fields of pharmacology and drug abuse have found that there is a relationship between the speed at which a psychoactive drug reaches the brain and its potential to be abused. This is especially the case for drugs like cocaine that activate specific areas of the brain involved in addictive behavior.

9. Does cocaine reach the brain faster by smoking or snorting? Why? What about injecting it into a vein?

10. Is a user more likely to take more cocaine after smoking it or snorting it? Will this result in a greater addiction potential? Why?

Chemical characteristics of cocaine

Cocaine is a molecule made up of C, H, O and N atoms. It is a weak base (the N has 3 bonds) and, in solution, it exists in 2 forms in an equilibrium: the free base and the acid salt (see **Figure 1**). The predominant form in solution depends on the pH of the solution. In its free base form, the molecule is uncharged (unionized or non-polar) and is not readily dissolved in an aqueous medium (water). When the free base is reacted with hydrochloric acid (low pH), the N accepts a H^+ and forms the hydrochloride salt. In this form, cocaine is ionized and is water soluble. Because the hydrochloride salt dissolves in solution, it can be snorted or injected. However, the ionized form (salt) can not be smoked because it is so stable at high temperatures, it does not volatilize (vaporize) in the smoke (see Module 5). In contrast, the free base form of cocaine (unionized) is easily volatilized by high temperatures so that it can be breathed into the lungs. [By the way, this is true of other free bases including nicotine and morphine.] The free base is usually made by mixing the hydrochloride salt of cocaine with sodium bicarbonate (baking soda). When the liquid mixture is evaporated, the solid "lump" of cocaine can be crushed up and heated ("crack"). Free base heroin or amphetamine ("ice") are made the same way.

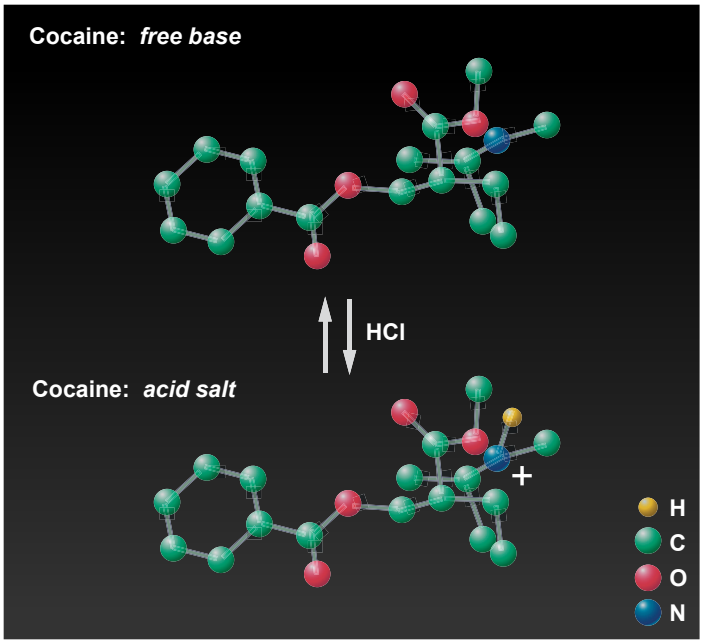

Figure 1. Treating the cocaine free base with HCl generates the charged form of cocaine, cocaine hydrochloride or the 'acid salt'. Conversely, treating the acid salt with a base such as sodium bicarbonate (baking soda) yields the free base form of cocaine. Note: only the extra H is drawn in.

How does cocaine pass through a cell membrane?

The ability of drugs or other molecules to pass through cell membranes is based on 1) the characteristics of the membrane and 2) the physiochemical characteristics of the drug. The membrane is a sandwich (bilayer) of lipids, with the polar or hydrophilic (water-loving) headgroups arranged at the surfaces of the membrane and the non-polar or hydrophobic (water-fearing) fatty acid carbon chains in the middle (see **Figure 2**). Drugs that are unionized and non-polar are able to pass through the membrane easily because they dissolve in the hydrophobic core of the membrane. They use the driving force of the concentration gradient to move from the side of higher concentration to the side of lower concentration, until an equilibrium is reached (passive diffusion). Thus, cocaine passes through mem-

branes readily by passive diffusion when it is in its unionized or free base form. Even if the ionized form is administered (i.e., by snorting or injecting) it is quickly converted to the unionized form at the normal physiological pH of 7.4 (in blood and tissues). Cocaine is a weak base, so it has less tendency to ionize at a neutral pH compared to a more acidic environment. [This is indicated by the high dissociation constant or pKa (~8.7) for cocaine listed in chemistry handbooks and other reference books.]. Although membranes are hydrophobic in nature, there are small gaps between cells of the membranes through which water passes. Any compound dissolved in water (this means it is charged) that is small enough, i.e. less than a molecular weight of 100 daltons, can pass through the gaps with the concentration gradient.

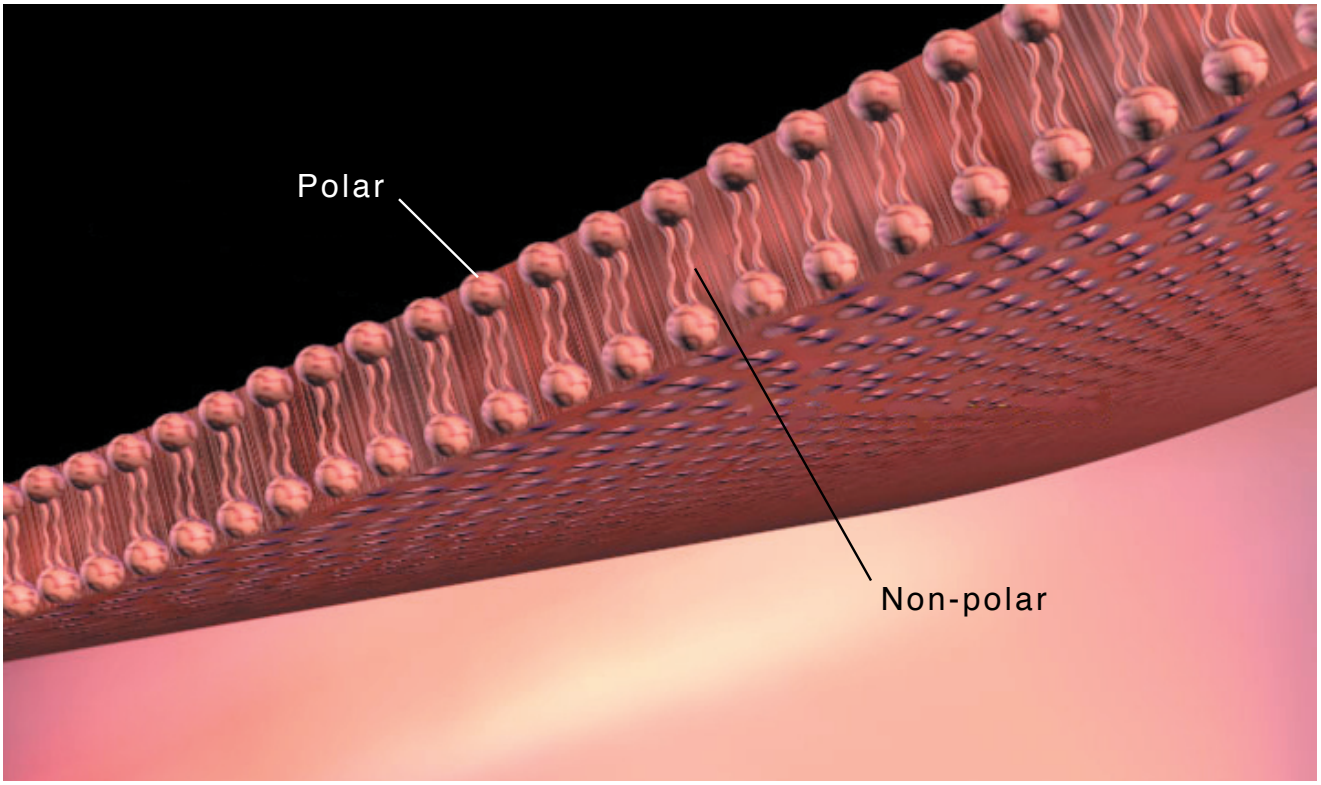

Figure 2. Schematic view of a cell membrane. Lipids are arranged with polar head-groups facing the outside and inside of the cell, while the fatty acid chains form the non-polar (hydrophobic) membrane interior.

Capillary membranes are a special case. Capillaries (made up of endothelial cells) have numerous pores ("fenestrae" – latin for windows). These pores are actually spaces between the endothelial cells and they are larger than the small pores found in non-capillary membranes. The fenestrae allow large molecules (up to molecular weights of 25,000 daltons) and charged molecules to pass through without difficulty (**Figure 3**). So capillaries are much less restrictive to the passage of solutes. This property allows large molecules such as proteins and water-soluble vitamins to be delivered to other cells throughout the body.

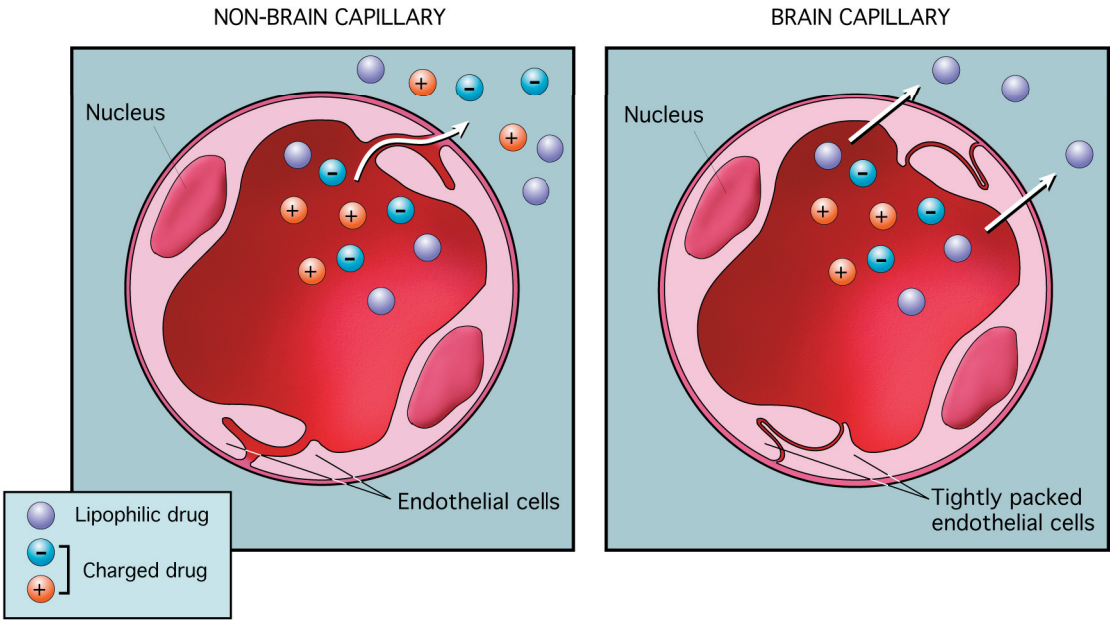

Figure 3. Cross section of capillary showing endothelial cells. In the non-brain capillary fenestrae are present. In brain capillaries the endothelial cells are tightly packed and no fenestrae are present.

How the route of cocaine administration affects its rate of entry into the brain

Cocaine, like many drugs can enter the body a variety of ways (**Figure 4**). The easiest way to get cocaine or any drug into the bloodstream is to inject it directly into a vein since there are no membranes to traverse in order to get there. In contrast, if cocaine is smoked, snorted or ingested by mouth, it must pass several membrane barriers before reaching the bloodstream, and some of these processes are slower than others. Smoking a drug such as cocaine, nicotine or heroin, enables its entry into the bloodstream almost as fast as injecting (also see **Figure 5**). The lungs have a very large surface area for absorption of the drug from the alveoli (very small sacs where gas is exchanged) into the capillaries. Capillaries are the smallest form of blood vessels and are very numerous. In fact they are able to deliver nutrients such as oxygen and glucose to every cell in the body. They also pick up waste such as carbon dioxide and metabolic products. Once in the capillaries, the drug travels in the oxygenated blood to the heart and then gets pumped throughout the body (organs such as brain, liver and kidneys that have a high blood flow receive blood first) to reach all cells.

However, the brain permits the entry of certain kinds of drugs; only those drugs that exist in their unionized form are able to penetrate the group of membranes that form the “blood brain barrier”. The blood brain barrier consists of tightly packed capillary endothelial cells, so there are no pores through which charged compounds can pass (**Figure 3**). Drugs that are highly lipophilic (lipid-loving) such as cocaine penetrate most quickly. Other drugs that cross the blood brain barrier easily include nicotine, marijuana and heroin. (Some drugs can be transported across the blood brain barrier by binding to transport proteins.) By restricting only certain molecules (and drugs) from reaching the brain, the brain can be protected from dangerous compounds.

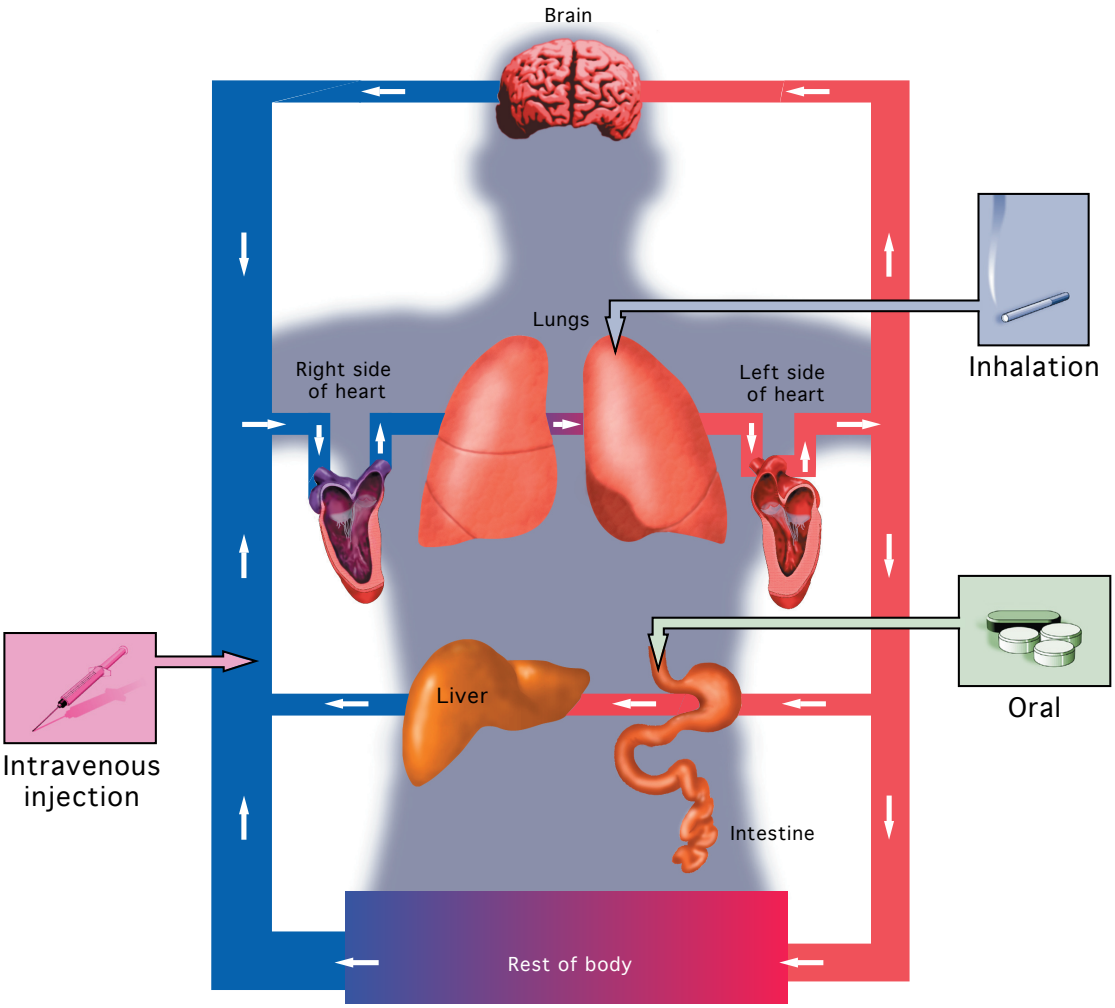

Figure 4. Modes of drug administration into the body. Red is the arterial side and blue is the venous side. Adapted from Ray O. and Ksir C. Drugs, Society, and Human Behavior, pg. 154. McGraw-Hill, New York, 2002.

If a drug such as cocaine is snorted, it takes a little longer to get to the brain where it produces its psychoactive effects. Cocaine diffuses through special epithelial cells (mucosal cells) lining the nasal passages into nearby capillaries. There is a very extensive capillary network in the nasal passages so drugs are absorbed into the bloodstream fairly quickly. Then, the cocaine travels within the venous system to the heart, then to the lungs, and back to the heart for distribution throughout the body (**Figure 4**).

The slowest way to get a drug into the bloodstream is by ingestion. When a drug is ingested by mouth, it travels first to the gut, where it must pass through mucosal cells lining the gut in order to get to the capillaries. Here in the gut, the pH is an important determinant of the drug's chemical charge, and thus its ability to pass through the mucosal cell membranes. Most drugs are weak acids or bases and their charge will be determined by the pH of the surrounding medium. The very acidic pH of the stomach will keep weak acids in their uncharged (non-polar or unionized) form. In contrast, weak bases, like cocaine, will be mostly charged or ionized (polar) at low pH. As discussed above, ionized compounds have difficulty passing through most membranes (other than capillaries), while unionized compounds are more lipophilic, and slide through the membrane easily. Another factor that slows the appearance of drugs taken by mouth into the brain is metabolism. The capillaries in the gut connect to blood vessels that go directly to the liver, so as drugs leave the gut they travel to the liver first (this is called the

portal circulation). There, some of the drug is metabolized and inactivated as it passes through. Metabolites are often more polar forms of the parent drug, allowing them to be excreted in the urine more easily. After the drug leaves the liver, it travels to the heart, then to the lungs and finally back to the heart to be distributed throughout the rest of the body (**Figure 4**). Thus, in this case, less cocaine (in its active form) reaches the brain. This is one reason why abusers do not take cocaine orally (see below).

Why is smoked cocaine (crack) more likely to be abused or addictive than snorted cocaine?

Research in the fields of drug abuse, pharmacology and psychology indicates that the period of time between the introduction of a drug into the body and its ability to produce euphoria or pleasure is important in the abuse potential of that drug. Cocaine produces its high within seconds when smoked as crack; but it takes several minutes to produce a high when snorted (see **Figure 5**). Furthermore, cocaine leaves the brain very quickly after smoking stops, so the cocaine high produced by smoking does not last very long. In fact, crack cocaine users often experience a depression or "crash", so they repeat the process. This can occur many times (binging). When snorted, the cocaine enters the brain more slowly since it must travel throughout the circulatory system first. The high lasts longer because the cocaine enters the brain over a longer period of time compared to when it is smoked. The user does not repeat the process as readily and the potential for abuse or addiction is not as strong compared to the user who smokes the free base. South American Indians obtain cocaine orally by chewing the coca leaf. As discussed above, relatively little cocaine reaches the brain and mild effects are produced slowly. The abuse liability of this form of cocaine is low.

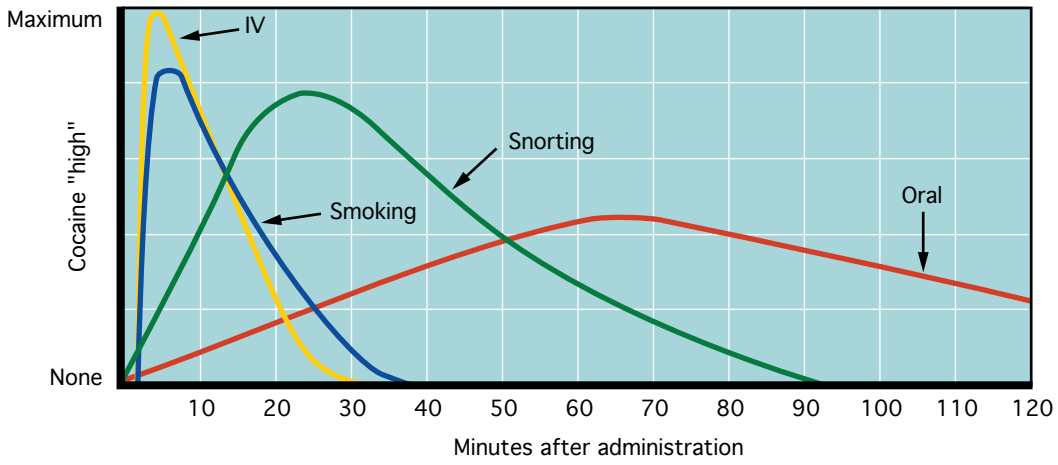

Figure 5. The relationship between the mode of cocaine intake and the intensity and duration of its euphoric effects

Glossary

addiction—the compulsive and habitual use of a drug, despite the experience of negative consequences.

blood brain barrier—a tightly joined layer of cells lining the capillaries in the brain. It restricts passage of drugs and other molecules across the cell layer into the brain to include only those that are lipophilic (uncharged).

cocaine hydrochloride—the stable and water soluble form of cocaine; usually snorted or injected

crack—the short term for a smokable form of cocaine (the free base)

drug—a substance that affects the structure or function of a cell or organism.

fenestrae—small spaces or pores between endothelial cells that form the capillary membrane. These pores allow charged drugs or larger drugs to pass through the capillaries.

free base—the unionized form of a weak base. With reference to cocaine, it is the smokable form.

hydrophilic ('water loving')— dissolves readily in water. Hydrophilic compounds exist in an ionized or polar form and have difficulty crossing biological membranes.

hydrophobic ('water fearing')—a compound that is soluble in fat but not water. This is typical of compounds with chains of C atoms.

lipophilic ('lipid loving')—high lipid solubility. Lipophilic compounds dissolve readily in oil or organic solvent. They exist in an uncharged or non-polar form and cross biological membranes very easily.

passive diffusion—The movement of a solute in its uncharged form to cross a membrane along a concentration gradient. No energy is required.

pharmacology—The study of the actions of drugs; a science that integrates biology and chemistry.

polar— a chemical property of a substance that indicates an uneven distribution of charge within the molecule. A polar substance or drug mixes well with water but not with organic solvents and lipids. Polar or charged compounds do not cross cell membranes (lipid) very easily.

psychoactive—Pertains to drugs that act in the brain to produce changes in mood, perceptions and behavior.

non-polar—a chemical property of a substance that indicates an even distribution of charge within the molecule. A non-polar or non-charged compound mixes well with organic solvents and lipids but not with water.

snort—To breath in a compound in solid form through the nostrils. With reference to cocaine, it is the hydrochloride salt.

stimulant—A compound that activates certain pathways in the brain to increase alertness and decrease fatigue.

weak acid—a compound that tends to give up a H+ when placed in an alkaline solution

Module 1: Supplemental Classroom Activities

"Why Does Aspirin Cross a Cell? To Get To The Other Side!"

Objective(s):
1. To understand the definition of a weak acid or base
2. To demonstrate the movement of ionized and unionized forms of aspirin between an aqueous phase (water loving) and organic phase (lipid loving) at different pHs.
3. To understand how aqueous and organic phases mimic the biological membrane and the intracellular extracellular space.

Standards and Skills:
AA1, AA2, AB1, AB2, AB3, AC1, AC2, AC4, CA1, CA2, CB3, CC1

Science Concepts:
Aspirin is a weak acid and it tends to ionize (give up a H atom) in an aqueous medium at high pH. Drugs do not cross biological membranes when they are ionized. In a low pH environment like the stomach (pH =2), aspirin is predominantly unionized and crosses membranes into the blood vessels readily. At higher pH, in the intestine (pH = 6), a greater proportion of aspirin is ionized, so it moves across membranes more slowly (however, due to the very large surface area for absorption in the intestine, all the aspirin does enter the bloodstream). The aqueous and organic phases can mimic the environment of the stomach or intestine and the cell membranes.

Materials needed:
4 separation flasks (125 ml) or 150 ml beakers with small stir bars, 100 ml graduated cylinders, water, ethyl acetate (or an oil such as peanut oil), 1 M NaOH, pH meter, 4 aspirin (not buffered or enteric-coated), micropipets, filter paper, hand-held UV lamp, graph paper.

Procedure:
Place 1 aspirin tablet (325 mg) in 4 different beakers containing 50 mls of water. The tablet will start to dissolve immediately, but the filler will not dissolve very well. Adjust the 4 beakers with several drops of 1 M NaOH to make the pH of the solutions approximately 3, 5, 7 and 9. The acidic aspirin will counteract the more basic solutions, so several drops must be added to get to a pH of 7 and 9. Record the pH of each solution. Shake or stir well. Include a 5^{th} beaker with no aspirin, just water, as a control.

This experiment can be performed with either peanut oil or an organic solvent such as ethyl acetate to mimic a biological membrane (a hydrophobic medium). A procedure using the ethyl acetate follows. Add ~50 ml of ethyl acetate to each beaker. Stir or shake vigorously for a few minutes. Let the solutions stand for several minutes to allow the phases to separate. The organic solvent is on the top and the water is on the bottom. Carefully insert a micropipet through the organic layer into the water layer and remove a small amount of the water phase. Apply it in a small spot on a piece of filter paper so that it spreads out to about the size of a penny. Allow the spot to dry a bit before adding more sample. The number of times the sample is spotted onto the filter paper must be the same for each of the different pH solutions. Write the pH of the aqueous phase next to the spot. Once the spots dry, the aspirin can be detected as a fluorescent spot by shining a UV lamp (short wavelength setting, 354 nm) over the paper.

Another way of detecting the presence of aspirin in the water phase is to use a UV spectrophotometer or a colorimeter. This is especially useful for quantitation (this would be a good exercise for an advanced chemistry class). Or, students might arrange to visit a scientist's lab equipped with a UV spectrophotometer to carry out the analysis. Instead of applying test or standard aliquots to filter paper,

aliquots can be added to cuvettes and placed in the instrument to obtain a reading of the absorbance of UV light (the absorbance wavelength should be around 275 nm). If quantitation is desired, a standard curve can be constructed and used to estimate the amount of aspirin in the different aqueous aliquots. To make the standards, first make a stock solution of 1 aspirin tablet in water adjusted to a pH of at least 7.0. Calculate the concentration of aspirin in the stock solution (325 mg in 25 ml or 13 mg/ml). After stirring with a stir bar for several minutes, filter the solution into a clean beaker to get rid of the undissolved filler at the bottom. Organic extraction is not necessary since all the aspirin will remain in the water phase at high pH. Make 3 standards by diluting the stock aspirin solution 1:1, 1:2 and 1:10 with water into clean beakers—calculate the new aspirin concentration for each dilution. Include a control beaker with no aspirin. Put an aliquot of each standard into a cuvette and scan the absorbance with the UV spectrophotometer from 200-400 nm.

Results:

If the filter paper method is used, the more fluorescent the spot, the more aspirin present in the sample. So, at the lower pH, the aspirin will become unionized and move into the organic phase. The pH 3 spot should not be fluorescent (the control spot should not fluoresce either). As the pH increases, more aspirin will be ionized and stay in the water phase. The pH 7 spot should be intensely fluorescent.

If a spectrophotometer is used to scan across a wavelength ranging from 200-400 nm, an absorbance peak will be present at approximately 275 nm. The absorbance level (peak height) is increased as the pH of the aqueous samples increases. (Note: at higher pH, the peak tends to move to higher wavelengths and it picks up a shoulder. This is probably due to contamination by the ethyl acetate which can become hydrolyzed at the more basic pH). For quantitation of the results, construct a graph of the absorbance area (or peak height) vs aspirin concentration in each of the standards. The amount of aspirin in each of the samples dissolved at different pHs can be estimated from this standard curve (i.e. for a given absorbance reading for each sample use the graph to find the aspirin concentration in the sample).

Discussion of Results:

Students can discuss how the effect of decreasing the pH caused the aspirin to move into the organic phase (it was unionized at low pH) while increasing the pH caused the aspirin to stay in the water phase (it became ionized). This is exactly how it happens in the body, where the cell membrane is the “organic” phase and the extracellular or intracellular space is the water phase. They can predict where the aspirin is more likely to be absorbed into the bloodstream (stomach better than small intestine). Students should be able to describe the properties of a biological membrane (i.e. lipophilic core) that allow drugs in their non-polar (unionized) form to move across, along the concentration gradient.

Assessment strategies:

Have students provide a definition of a weak acid in the context of the experiment. Determine if students can apply the concepts learned from the example with aspirin, a weak acid, to a drug that is a weak base, such as cocaine. The students should be able to hypothesize how the results would have differed if they had performed the experiment with cocaine. Without actually carrying out the experiment, they should be able to predict whether cocaine that is orally administered by chewing coca, is absorbed more readily through the stomach or the small intestine. If they quantitated their aspirin data, they should be able to plot hypothetical data for cocaine, with the expected results (with decreasing pH the cocaine should stay in the aqueous phase).

Resources

The following resources provide supplemental information that pertains to the topic in this module.

RR Levine, CA Walsh and RD Schwartz. *Pharmacology: Drug Actions and Reactions*, Parthenon Publishing Group, New York, 2000. Chapters 4-6, 15.

CM Kuhn, S Schwartzwelder and W Wilson. *Buzzed*, WW Norton & Co., New York, 1998. Chapters 12,13,14.

SH Snyder, *Drugs and the Brain* , WH Freeman and Co. New York, 1996. Chapters 1 and 5.

O Ray and C Ksir. *Drugs, Society, and Human Behavior*, Mosby, St. Louis, 1996. Chapters 6 and 7.

G Hanson and PJ Venturelli. *Drugs and Society*, Jones and Bartlett Publishers, Boston, 1995. Chapters 4 and 11.