pep Pharmacology Education Partnership

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Military pharmacology: It takes nerves

4

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

Module 4: Military pharmacology: It takes nerves

Description of the module

Exposure to nerve gas can lead to a very uncomfortable death. The lethal compound produces numerous actions in the body that result in pain and suffering and death is finally produced by paralysis of the respiratory muscles. How can one compound cause so many effects in the body? In this module, we explore the concept that some drugs and toxins have multiple targets throughout the body. The nervous system is a prime example of a system that has multiple targets for the actions of drugs. The unit focuses on several concepts including, 1) the characteristics of gaseous toxins that allow them to be absorbed into the body, 2) the routes that the toxin takes to be distributed throughout the body, 3) the organization of the nervous system and each of its subdivisions, 4) the role of specific enzymes to produce hydrolysis reactions in the nervous system and 5) how toxins can inhibit chemical reactions like hydrolysis.

Learning Objectives

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

1. How the chemical nature of drugs or poisons enable them to be absorbed from the air into the body
2. The basic structure of the nervous system
3. How drugs or poisons can affect multiple targets in the body at the same time
4. The chemical process of hydrolysis
5. The difference between reversible and irreversible chemical reactions
6. How the brain governs breathing

This module integrates information from the following areas:

chemistry, neurobiology, biochemistry, anatomy, physiology, history, political science, environmental science

Student Handout

One of the weapons developed during World War II was nerve gas. The idea was to develop a weapon that would not harm the land, only the people on it, since the victors would have no use for damaged or contaminated land. Fortunately, nerve gas was not actually used during World War II, but it has been used in more recent times. In the mid-1980s, Iraq used nerve gas in its war with Iran, killing thousands of people. More recently, a cult group in Japan, used nerve gas in a terrorist attack in a Tokyo subway, killing 12 people and wounding 5500 and US soldiers were exposed to nerve gas in Iraq during the clean-up after the Gulf War. Today, countries still store nerve gas and other chemical weapons, and they spend a great deal of money and time developing potential antidotes to nerve gas poisoning.

How toxic is nerve gas? For those unfortunate people that are exposed to high levels of nerve gas, they die a rapid (within minutes), horrible death. With lower levels of exposure, people may suffer over hours or up to a day before finally succumbing. And in the case of mild exposure, such as in the Tokyo subway or after the Gulf War, those who survive can suffer long-lasting neurological problems.

1. What is “nerve gas”?

2. Describe the chemical and physical characteristics of nerve gas.

3. Make a list of the things that nerve gas does to the body.

In order to become poisoned by nerve gas, it must enter the body and reach certain targets. Nerve gas can be breathed in through the lungs and it can be absorbed through the skin, the eyes and any other body surface. This occurs very rapidly. Once the nerve gas gets into the lungs or into the skin cells, it diffuses into the bloodstream capillaries. As the gas moves throughout the bloodstream, it reaches every cell in the body.

4. Explain how the nerve gas gets from the lungs into the bloodstream.

5. Describe how the nerve gas gets absorbed through the skin and through the eyes into the bloodstream.

6. Why is it so easy for the nerve gas to be absorbed through the skin?

7. Does the nerve gas stay in a gaseous form once in the blood? Explain your answer.

Nerve gas affects many parts of the body, yet it has only 1 action. Basically, it causes excessive information to flow between neurons and their target tissues all over the body, essentially causing the tissues to function in “overdrive”. To understand how this one chemical can have so many effects on the body, we must understand how the nervous system is constructed and how the nerve gas actually works.

The brain contains neurons that travel short distances within the brain and neurons that travel long distances, outside the brain. Neurons travel all over the body to provide information to target cells to perform some kind of work (depending on the target). Information travels along the axons of neurons in the form of electrical impulses. When electrical impulses reach the nerve terminal, special chemicals called neurotransmitters are released. One of the major neurotransmitters in the brain and in the peripheral neurons is acetylcholine.

8. Draw a neuron and label its parts.

9. What is the difference between the central nervous system and the peripheral nervous system? Draw a map showing the 2 nervous systems.

10. The peripheral nervous system can be divided into the autonomic and the somatic nervous systems. On your map, show where these nervous systems originate and which structures are targets of their axons.

11. The autonomic nervous system can be divided into 2 more nervous systems. They are called the sympathetic (SNS) and the parasympathetic nervous systems (PSNS). These 2 systems usually innervate the same structures, but the neurotransmitters within them differ. On your map, draw an example of the SNS and the PSNS. Place an arrow to show where the acetylcholine is released within these 2 systems. Where else is acetylcholine released (hint: there are 2 other major areas)?

Once released from the nerve terminal, acetylcholine binds to special proteins, called receptors, on neighboring nerves or on muscles (the neuromuscular junction). When acetylcholine binds to its receptors it causes an electrical current to spread across the cell membrane. Depending on the type of cell, the current has different functions. Acetylcholine plays a very important role in controlling everyday functions within the body. When acetylcholine binds to receptors on neurons, the electrical current causes a new electrical impulse to be generated. When acetylcholine binds to receptors on non-neuronal cells in organs such as the heart, stomach, bladder, glands and eyes, and in tissues such as skeletal muscle, they respond with specific functions.

12. Below is a list of organs or tissues that receive acetylcholine signals from various nerve pathways. To the right of each target are two functions. Indicate which function is produced by acetylcholine:

Intestines	contraction (diarrhea)	relaxation (constipation)
Heart	decreased heart rate	increased heart rate
Lungs (bronchii)	dilation	constriction
Sweat glands	no secretion (dry)	secretion (sweat)
Salivary glands	secretion (saliva)	no secretion (dry)
Tear ducts	secretion (tears)	no secretion (dry)
Eyes	pupil constriction (miosis)	pupil dilation
Muscles	relaxation	contraction
Brain (vomit center)	inhibit	stimulate (vomit)

Acetylcholine's actions must be terminated to prevent its effects from being too strong or too prolonged. The body synthesizes a special enzyme to do this. It is called acetylcholinesterase. It destroys acetylcholine by the process of hydrolysis. This is the process that is disrupted by nerve gas. Nerve gas prevents the ability of acetylcholinesterase to destroy acetycholine. When nerve gas is in the body, acetylcholine levels accumulate at the receptors, causing too much activation.

13. What kind of chemical reaction is hydrolysis? How does the acetylcholinesterase hydrolyze the acetylcholine?

14. When acetylcholinesterase hydrolyzes acetylcholine, what products are formed? How is the acetylcholine replaced?

15. Where is the acetylcholinesterase found?

16. How does nerve gas inactivate the acetylcholinesterase?

17. Now that you know what acetylcholine does, you can predict how nerve gas affects the body. Make a new list of the effects of nerve gas and compare it to the original list you made in question #3.

18. Which action of nerve gas actually causes death?

In our country, every day there are people exposed to other poisons that work in the same way that nerve gas works. The victims don't die from the exposure, but they do suffer neurological problems from long-term exposure to these compounds.

Chemistry of nerve gas

Nerve gas actually refers to a collection of different compounds that act in a similar manner to disrupt the nervous system. The "G" class of nerve gases are organophosphates and it is the phosphorous group that is so important in the poisonous activity of nerve gas. Originally produced during World War II but never used at that time, these compounds are a more contemporary threat since they have been used in modern times during wars and terrorist acts. The most common nerve gases in the "G" class are sarin, tabun and soman (**Figure 1**). These compounds are colorless and odorless gases and are extremely toxic; a small droplet can kill a person. They exist in both liquid and gaseous forms. Inside closed containers, the nerve gases are in liquid form, but since they have a very high vapor pressure at room temperature, they vaporize when exposed to air. The vapor is 4 times as dense as (heavier) air so it hovers close to the ground where it is more likely to come in contact with humans and animals.

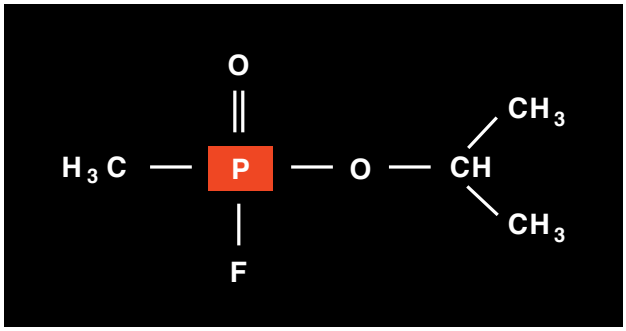

Figure 1. The chemical structure of sarin, a nerve gas. The phosphorus group is most important for toxicity.

How does nerve gas get into the body?

Once released into the air, the vapor can be breathed into the lungs, where it rapidly gains access to the bloodstream. The lungs have a very large surface area for absorption of drugs, toxins and other compounds 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. 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 other kinds of cell membranes. The fenestrae allow large molecules (up to molecular weights of 25,000 daltons) and charged molecules to pass through without difficulty (**Figure 2**). 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. In the case of nerve gas, the small size and lipophilic (lipid-loving) nature of the molecules allows them to pass through alveolar cell membranes (which are much like the capillary membranes) into the capillaries without any difficulty. In the capillaries, the nerve gas is dissolved in the blood (i.e. it is no longer in a gaseous form) because there is so little of it and it has high solubility in aqueous environments. The nerve gas 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.

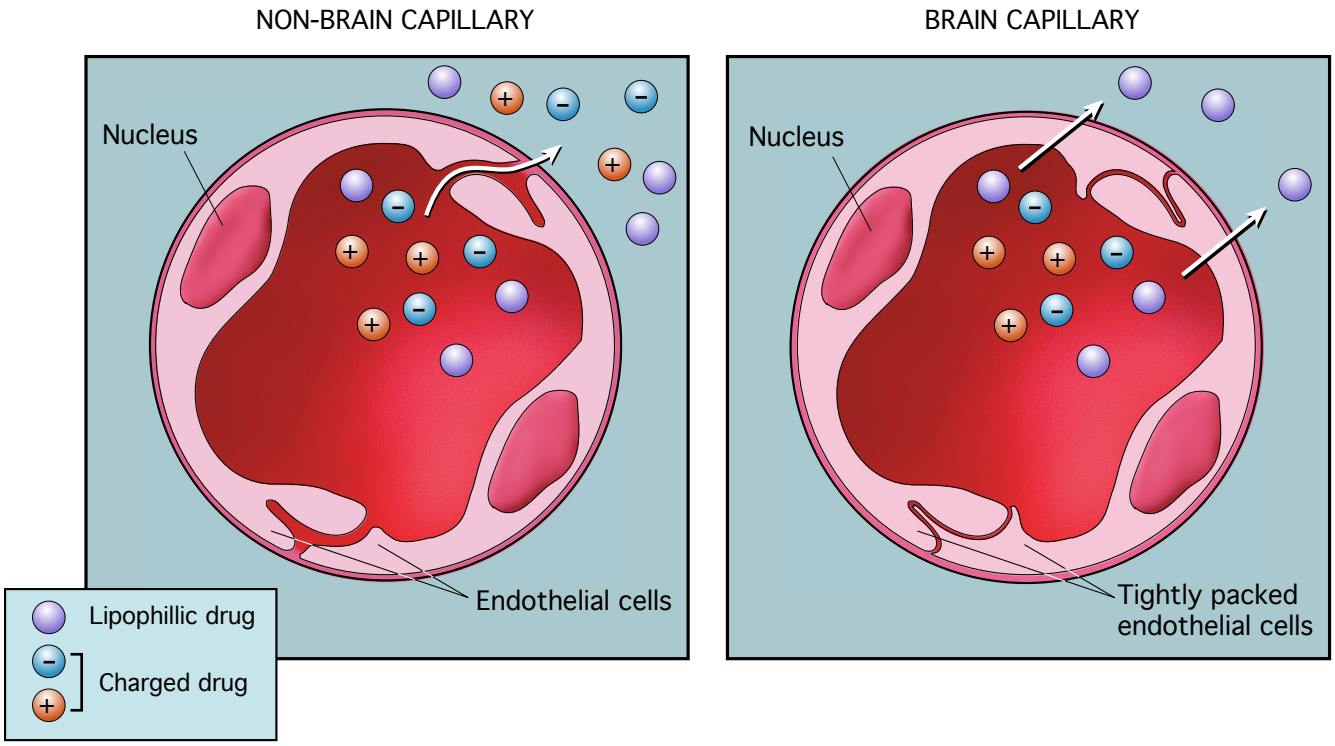

Figure 2. Cross section of capillary showing endothelial cells. In the non-brain capillary fenestrae are present. In brain capillaries the endothelial cells are tightly packed and no fenestrae are present.

Nerve gas can also be absorbed through the skin (epithelial) cells into the capillaries. It is fairly difficult for most drugs to gain access to the bloodstream from the skin because there are several layers of skin and the blood supply to the outermost layers is very sparse. However, in the case of nerve gas, these compounds are very lipophilic and can penetrate through the layers of skin cells easily. The cell 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 3**). Drugs that are hydrophobic (lipophilic or non-polar) or uncharged penetrate epithelial cell membranes easily because they dissolve in the hydrophobic core of the membrane. Hydrophilic (ionized or polar) compounds cannot penetrate the lipid interior of the membrane and they remain along the hydrophilic portions of the membrane. The lipophilic molecules (like nerve gas) are able to pass through the membrane along their concentration gradient (passive diffusion) from the side of higher concentration to the side of lower concentration, until an equilibrium is reached.

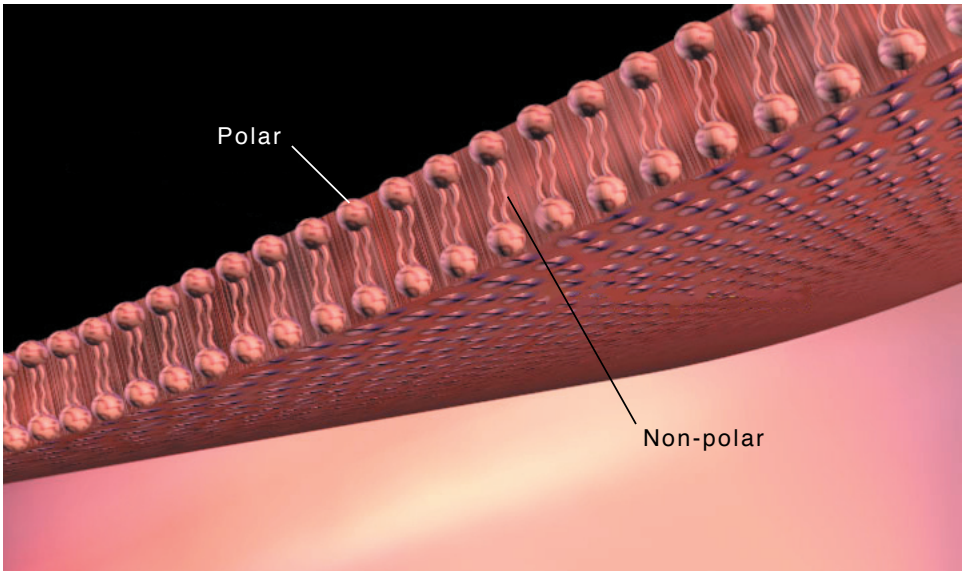

Figure 3. Schematic view of a cell membrane. Lipids are arranged with polar head-groups facing the outside and inside of the cell, while the fatty acid chains form the non-polar (hydrophobic) membrane interior.

Nerve gas penetrates the eyes as well. It can diffuse easily through the cornea, the schlera (white) and the conjunctiva (epithelial tissue near the corner). In addition, the gas can enter the capillaries embedded in the schlera. Thus, nerve gas has several effects on the eyes (see below).

Regardless of the method of exposure, nerve gas gets into the brain very easily. This is also due to its lipophilic nature. The brain permits the entry of certain kinds of drugs or poisons; only those compounds that are highly lipophilic (i.e. uncharged or unionized) 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 2**). Compounds that are highly lipophilic such as nerve gas penetrate most quickly. By restricting only certain molecules (and drugs) from reaching the brain, the brain can be protected from many (but not all!) dangerous compounds.

How does nerve gas affect the body?

If a person is exposed to a high dose of nerve gas, death ensues within minutes. Death is produced by respiratory arrest. With lower levels of exposure, fatalities can still occur within the first 24 hours. The victim will suffer many effects prior to succumbing by respiratory arrest. These include, intense constriction of the pupils (miosis) and severe eye pain, constriction of the bronchioles producing labored breathing, nausea and vomiting, lacrimation (tearing), salivation, sweating, urination, defecation, (basically everything oozes out!) and muscle twitching leading to muscle paralysis. Signs that the nerve gas gets into the brain include; anxiety, confusion, dizziness, nausea, vomiting, seizures and respiratory depression. Death is usually the result of respiratory failure. This occurs by 2 routes. The nerve gas acts directly on the diaphragm (smooth muscle) to paralyze it and it also inhibits the firing rate of neurons in an area of the brainstem that controls breathing. This area is called the respiratory center and it contains neurons that send their axons (see below) to the diaphragm to cause muscle contraction, and thus, breathing. After chronic exposure to low levels of nerve gas, victims suffer from a variety of neurological and mental disorders including; depression, insomnia, loss of memory, mental confusion and cognitive problems. This was typical in US soldiers exposed to nerve gas in Iraq during the dismantling of chemical weapons after the Gulf War.

How does nerve gas interfere with the nervous system?

To produce all of these effects in the body, a single compound must be able to affect targets all over the body. Nerve gas can do this. First, it has access to all cells in the body because it is distributed throughout the bloodstream to all cells. Second, it acts on specific parts of the nervous system that control almost all of our daily functions. To understand how nerve gas does this, it is helpful to review the organization of the nervous system and discuss its specific target, acetylcholinesterase, the enzyme that destroys the neurotransmitter acetylcholine.

Anatomy of a neuron

Neurons are the principal cells of the brain; they comprise a cell body (or soma), dendrites and an axon that ends at a terminal (**Figure 4**). The cell body contains the nucleus where DNA resides along with the nuclear machinery to direct the synthesis of proteins. The cell body is also the part of the cell in which an electrical impulse is generated. The dendrites form a branching structure off of the cell body and act as receivers. Neurotransmitters and drugs bind to receptors on dendrites that trigger membrane currents to promote or inhibit the electrical impulse generated in the cell body. The electrical impulse travels down the axon to the terminal where neurotransmitters are synthesized, stored and then released.

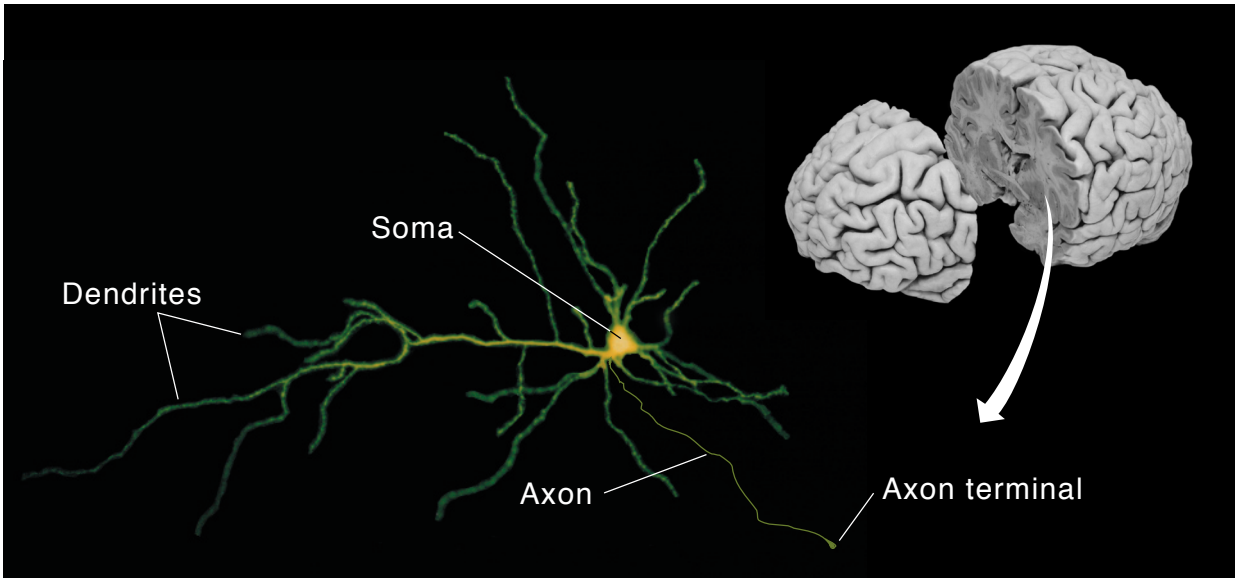

Figure 4. A real neuron filled with a yellow dye shows its structure.

Acetylcholine neurotransmission in the nervous system

Neurons synthesize and store specific chemicals called neurotransmitters which are released at the terminal following the arrival of an electrical impulse. For example, acetylcholine neurons synthesize acetylcholine by a series of enzymatic reactions that takes place in the neuron terminal. Acetylcholine is stored in the terminal in small sacs, or vesicles. When an electrical impulse originating in the cell body travels down the axon to the terminal, it triggers the release of acetylcholine from the vesicles into the space between neurons (the synapse) (**Figure 5**). Acetylcholine neurons also innervate tissues such as muscles and other organs. When acetylcholine is released from the axon terminals, it binds to

specific proteins called acetylcholine receptors on neighboring neurons or on other types of cells, like muscles. When acetylcholine binds to its receptor, it causes a change in the protein structure, opening a channel through which Na^+ ions move (with the concentration gradient) inside the cell (Figure 6). The influx of Na^+ generates a membrane current that triggers a new electrical impulse or some form of work. In the case of a muscle, it causes muscle contraction; this occurs in smooth muscle, like the intestines and the bronchioles of the lung, and in skeletal muscle. In sweat, salivary and tear glands, acetylcholine causes secretion. In the heart, acetylcholine slows conduction of electrical impulses and thus decreases the heart rate (it can also increase heart rate indirectly via the sympathetic nervous system—see below). In the brain, acetylcholine affects the firing rate of neurons and participates in memory and learning, motor control, and wakefulness. So depending on the location of the acetylcholine receptors, acetylcholine has many actions throughout the body.

To review, the effects of acetylcholine are listed below:

intestines	contraction (diarrhea, vomit)	tear ducts	secretion (lacrimation or tears)
heart	decreased heart rate	bladder	contraction (urination)
lungs (bronchii)	constriction	eyes	pupil constriction (miosis)
salivary glands	secretion (salivation)	muscles	contraction
sweat glands	secretion (sweat)	brain	stimulate (vomit)

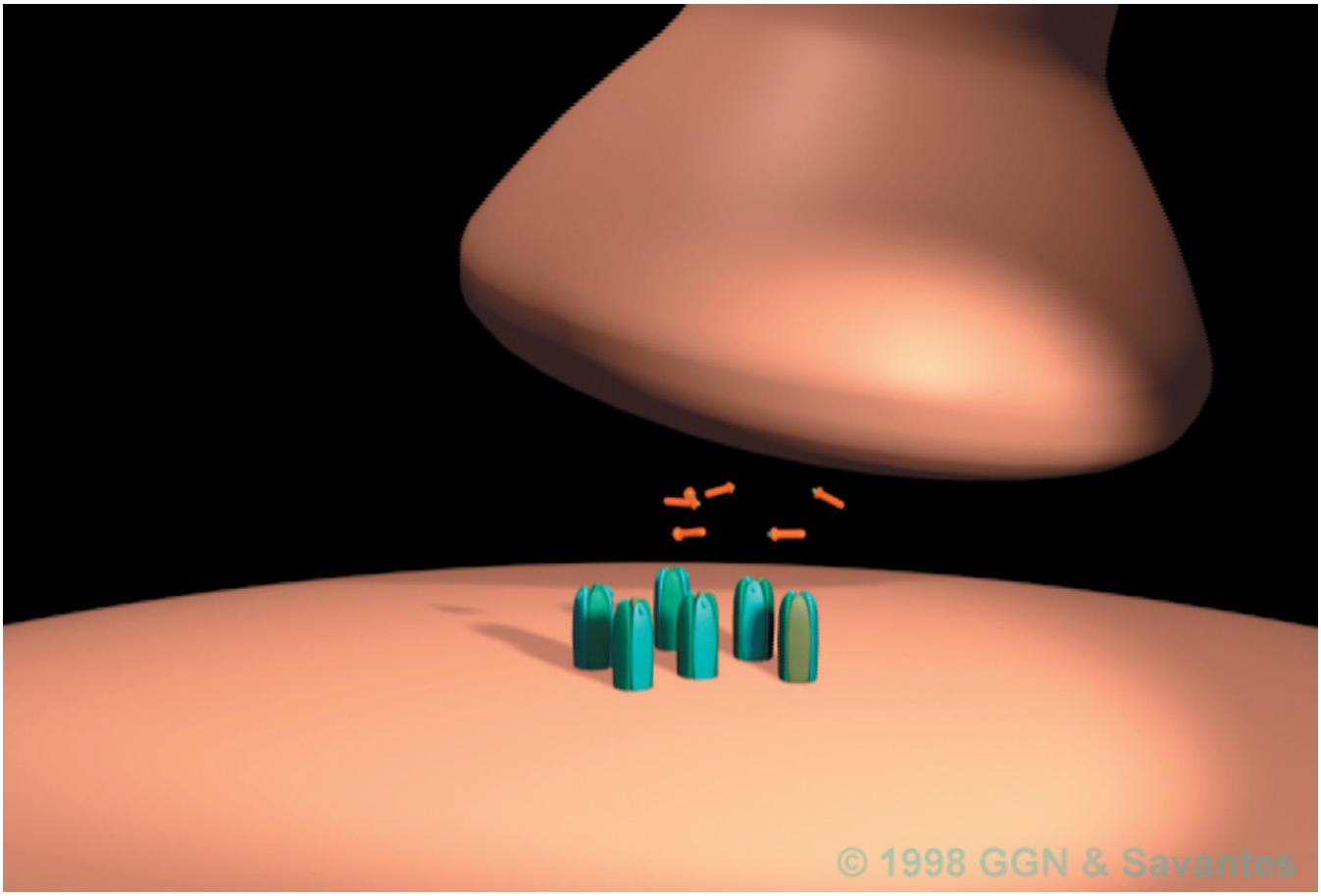

Figure 5. An acetylcholine synapse; the axon terminal releases acetylcholine, which binds to acetylcholine receptors

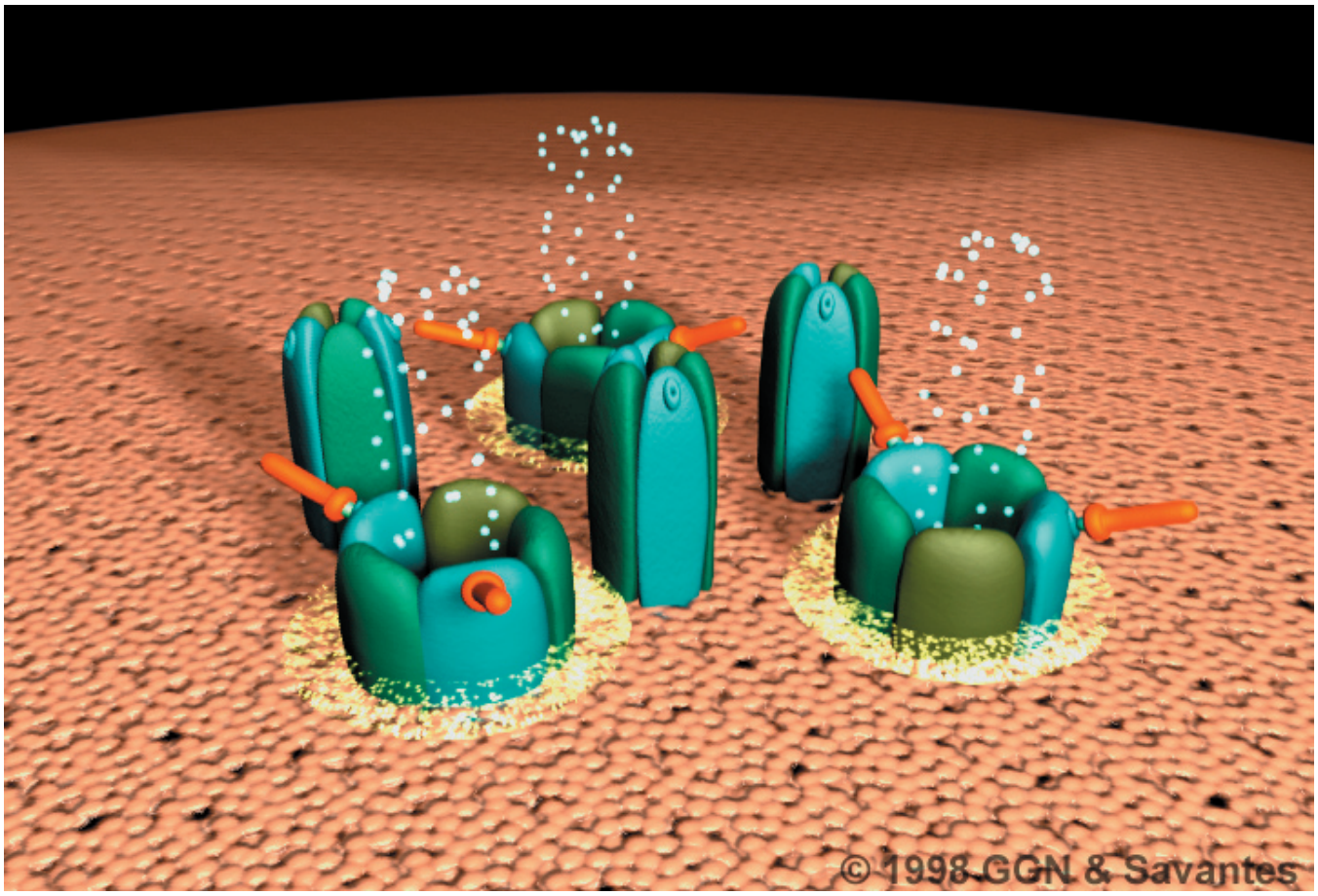

Figure 6. Acetylcholine binds to acetylcholine receptors and opens Na+ channels. The influx of Na+ generates an electrical current across the cell membrane that triggers some form of work (impulse conduction, contraction, secretion, etc.)

The location of acetylcholine neurons and receptors can be mapped with respect to the organization of the nervous system (**Figure 7**). Acetylcholine neurons are plentiful in the central nervous system, which includes the brain and the spinal cord. The peripheral nervous system includes neurons that connect the brain and spinal cord to muscles, organs and skin to send sensory and motor information. The peripheral nervous system is sub-divided into 1) the somatic motor system, in which skeletal muscles receive information from the spinal cord via motor nerves to cause movement (mostly voluntary) and 2) the autonomic nervous system, in which smooth muscles and other organs receive information from the brain and spinal cord to control organ function (mostly involuntary). Last, the autonomic nervous system is sub-divided into the parasympathetic nervous system (PSNS), which is active all of the time, and the sympathetic nervous system (SNS), which is active especially during times of stress, fear and emergencies. Acetylcholine neurons are present in all parts of the peripheral nervous system. In the somatic nervous system, motor nerves release acetylcholine onto skeletal muscle. In the autonomic nervous system, there are 2 types of neurons that contribute to the PSNS and the SNS. The first type of neuron leaves the spinal cord, en route to a cluster of neurons called a ganglion. In the ganglia, the acetylcholine neurons release acetylcholine onto the second type of neuron. This second type of neuron travels to its final destination (e.g., organs, glands, smooth muscle) and it either releases acetylcholine in the PSNS or it releases another neurotransmitter, norepinephrine in the SNS. These 2 nervous systems usually work in opposition to each other. For example, in the lungs, the PSNS causes bronchiole constriction and the SNS causes bronchiole dilation; the PSNS stimulates salivation and the SNS inhibits salivation. In each place where acetylcholine is released, acetylcholine receptors are present on the corresponding target (**Figure 7**).

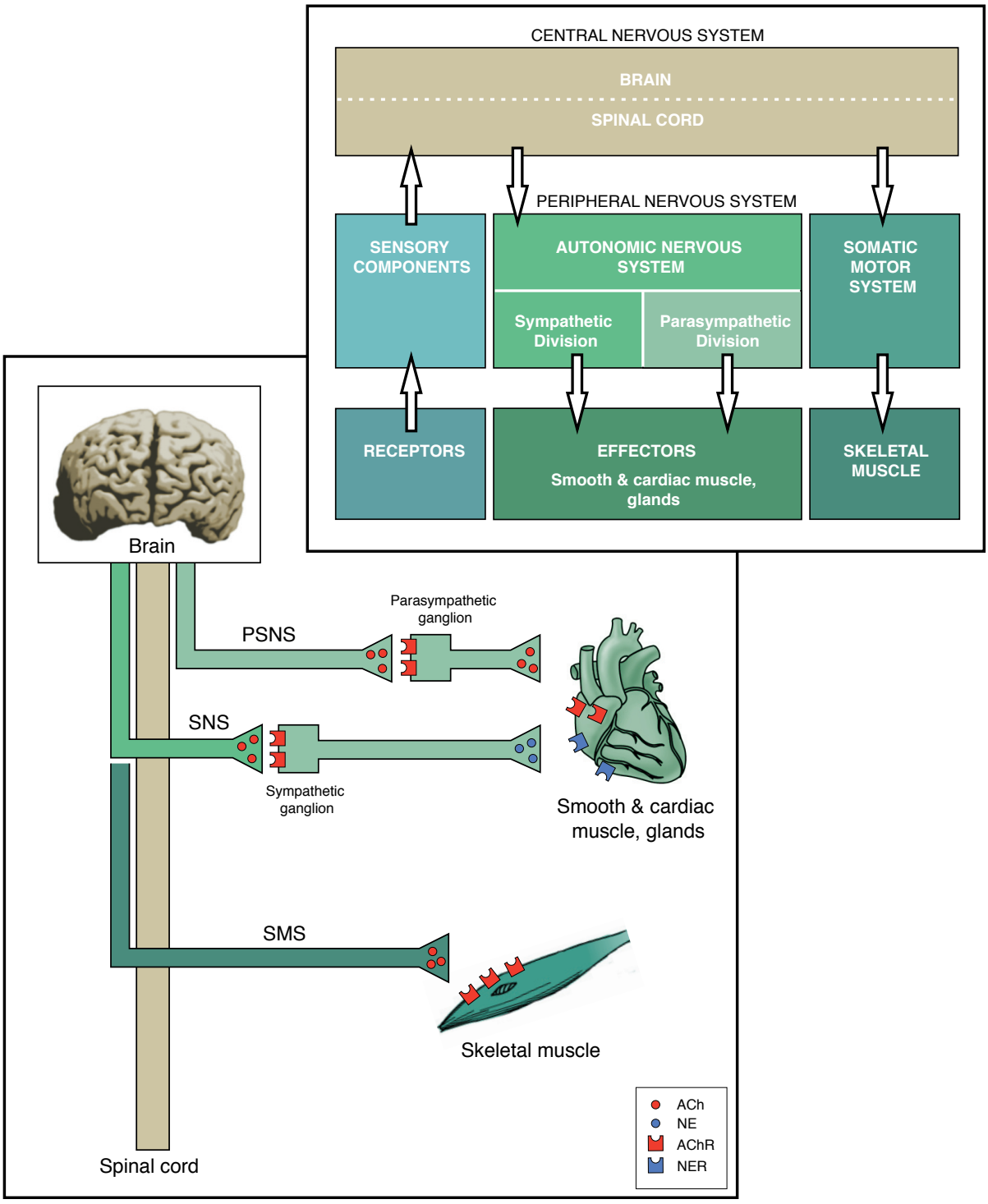

Figure 7. Organization of the nervous system including the central, autonomic (PSNS and SNS) and somatic subdivisions. Ach, acetylcholine; NE, norepinephrine; AChR, acetylcholine receptor; NER, norepinephrine receptor

Hydrolysis of acetylcholine

Normally, the actions of acetylcholine are terminated by a specific mechanism to keep the target cells from becoming overactivated. Acetylcholine is destroyed by an enzyme, acetylcholinesterase, that is located in every acetylcholine synapse. This enzyme hydrolyzes acetylcholine. Hydrolysis is a chemical reaction that involves water. Basically, a molecule is cleaved into two parts by reacting with water; part of the molecule binds to the H of water and the other part of the molecule binds to the OH of water, thus splitting the molecule and using up a molecule of water in the process. Compounds that are "esters" (they have an O atom sandwiched between a C chain and a C==O group) are easily hydrolyzed. When esters are hydrolyzed by water, the bond between the O atom and the C chain breaks. This forms an alcohol (a molecule containing an OH bound to the C chain) and an acid (a molecule containing a COOH group). Since acetylcholine has an ester group, it is especially vulnerable to hydrolysis by water (**Figure 8**). In this case, the ester bond which connects an acetyl group to the C chain, is hydrolyzed to give acetic acid (vinegar) and choline. These 2 compounds recombine inside the nerve terminal to synthesize new acetylcholine.

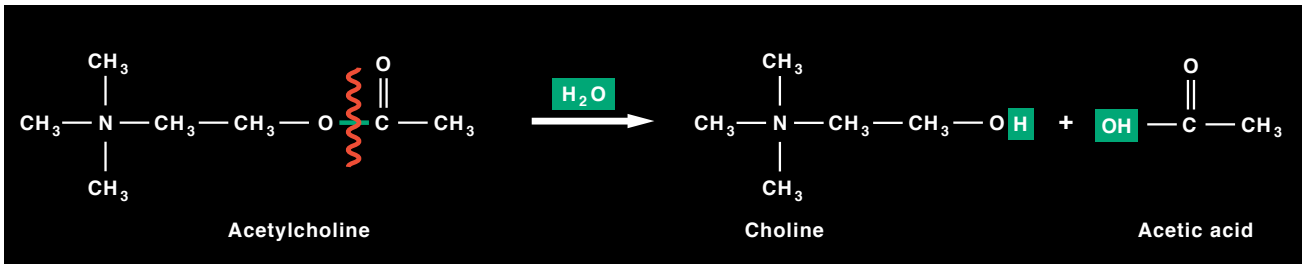

Figure 8. A typical hydrolysis reaction of ester compounds (acetylcholine) by water generates an alcohol (choline) and an acid (acetic acid). The red indicates where the ester bond is broken.

However, the hydrolysis of acetylcholine doesn't occur without the help of the enzyme, acetylcholinesterase. Acetylcholinesterase is the catalyst that makes this happen very quickly (**Figure 9**). First, acetylcholine binds to the enzyme at 2 different sites; its acetyl group (part of the ester) binds to a specific OH group (from the amino acid, serine) in one place on the enzyme and the other end of acetylcholine binds to the enzyme in another place. These bonds are ionic or electrostatic in nature; opposite charges on the acetylcholine and the enzyme attract each other. In the presence of water, the acetylcholine breaks its ester bond between the C chain and the O of the acetyl group. Water donates an OH group to the C chain end, forming choline, which separates from the enzyme. Water donates one of its H atoms to the acetyl group, forming acetic acid, which also separates from the enzyme. This reaction is extremely fast—it's one of the fastest enzyme reactions in the body. Thus, the enzyme is restored to its normal state, free to destroy another molecule of acetylcholine.

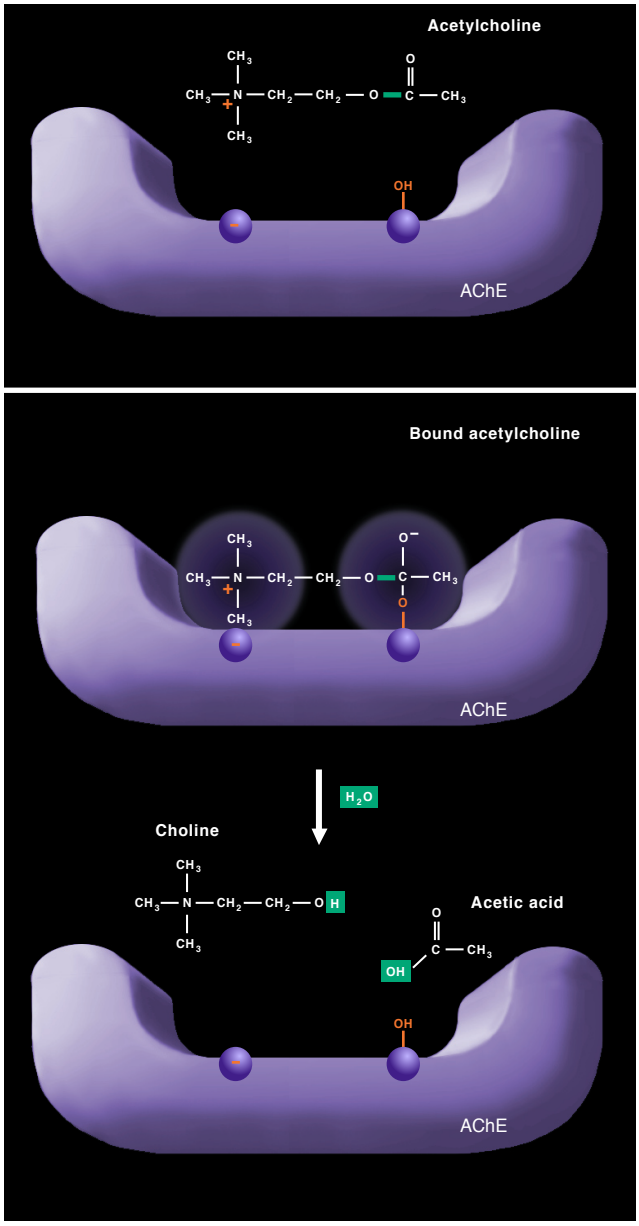

Figure 9. Hydrolysis of acetylcholine catalyzed by acetylcholinesterase generates choline and acetic acid

Inhibition of acetylcholinesterase by nerve gas

Nerve gas also binds to the acetylcholinesterase enzyme, but only at 1 site. Nerve gases have a phosphorus group that is extremely attracted to the same OH group on the enzyme that is bound by acetylcholine (**Figure 10**). The bond is so strong that, for most types of nerve gases, it can't be broken. This is called a covalent bond (see Module 5). Since the phosphorus atom of the nerve gas can't come off of the enzyme, the enzyme is no longer able to interact with acetylcholine. Thus, the enzyme is inhibited and acetylcholine builds up in the vicinity of its receptors. The body must synthesize new enzyme molecules to overcome the loss of acetylcholinesterase. Unfortunately, this doesn't happen fast enough and the person succumbs to the toxic actions of the nerve gas. [There are some antidotes (called oximes) that could work if given fast enough, before the nerve gas becomes irreversibly bound to the acetylcholinesterase. The oximes would have to be given within a few minutes of exposure to be effective.]

As discussed above, the accumulation of acetylcholine due to acetylcholinesterase inhibition by nerve gas causes overactivation of acetylcholine receptors all over the body. The knowledge of where acetylcholine receptors are and how they participate in bodily functions provides a basic understanding of the many actions of nerve gas on the body (see above). There are other examples of acetylcholinesterase inhibition that play a role in our lives. For example, insecticides are very good inhibitors of acetylcholinesterase. At the proper concentration, they kill insects not humans. However, humans who are chronically exposed to them (e.g. in the fields, etc.) do suffer neurological and mental disorders similar to those in people with chronic low-level exposure to nerve gas. In the case of the insecticides, they don't bind to the acetylcholinesterase as tightly as does nerve gas, so the enzyme can become regenerated with time.

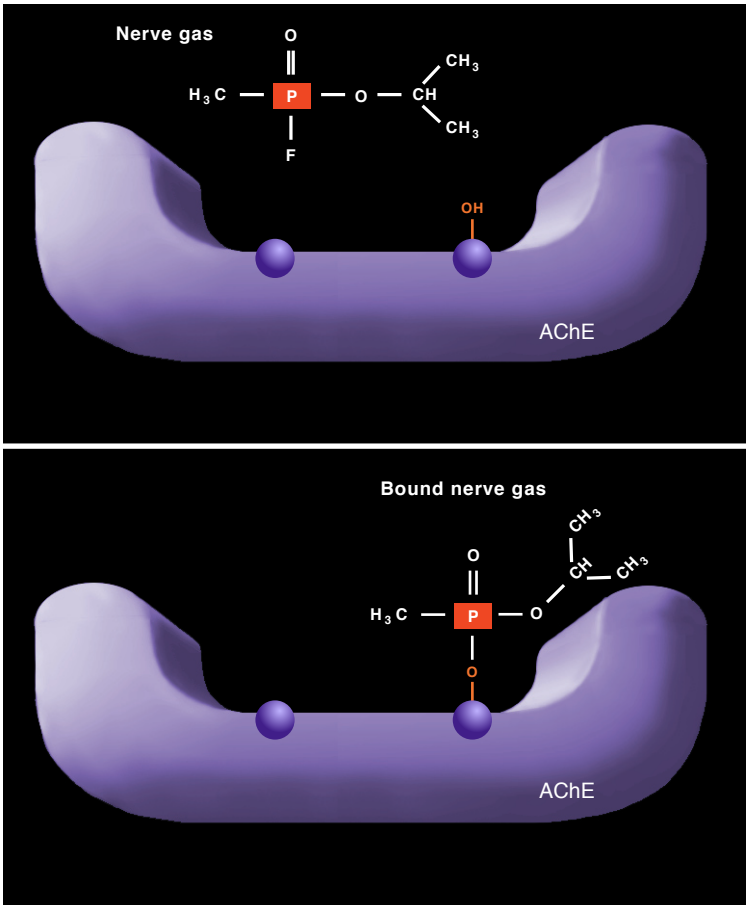

Figure 10. The phosphorus atom of the nerve gas binds covalently (irreversibly) to acetylcholinesterase to inactivate it.

Glossary

acetylcholine—a neurotransmitter stored in vesicles of nerve terminals; it is found in neurons within the central nervous system, the somatic nervous system, the parasympathetic nervous system and the sympathetic nervous system.

acetylcholinesterase—the enzyme that facilitates the hydrolysis (by water) of acetylcholine into choline and acetic acid. It is found near neurons that release acetylcholine.

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).

enzyme—a protein that catalyzes the rate at which a reaction occurs. It binds to one of the reactants (a substrate) to cause a change in the reactant's structure, facilitating the reaction.

ester—a part of a molecule that has an O atom bound to a chain of C and also to a C==O.

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.

ganglion—a bundle of nerve cell bodies, often referred to as the "post-ganglionic neuron". In the both the PSNS and SNS, the pre-ganglionic neurons release acetylcholine; the post-ganglionic neurons release either acetylcholine (PSNS) or norepinephrine (SNS).

hydrolysis—a chemical reaction that involves the cleavage of a molecule in the presence of water. Water donates a H atom to one side of the broken bond and an OH molecule to the other side of the broken bond, forming 2 products. In the case of an ester, hydrolysis produces an alcohol and an acid.

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

nerve gas—a group of very lipophilic compounds (e.g. sarin, tabun, soman) that can exist as a vapor at room temperature. They contain phosphorus groups and bind avidly to acetylcholinesterase to inhibit its activity. The inhibition of acetylcholinesterase causes the accumulation of acetylcholine in all areas of the nervous system, causing excessive muscle contraction followed by paralysis, secretions, seizures and death by respiratory failure.

oximes—compounds that bind to the phosphorus group on the nerve gas to pull it off of the acetylcholinesterase. This reactivates the enzyme to its normal activity and inactivates the nerve gas. This antidote must be given fast enough before the nerve gas irreversibly binds to the acetylcholinesterase.

parasympathetic nervous system—part of the autonomic nervous system which controls everyday functions of organs and tissues. It consists of 2 types of neurons, pre-ganglionic and post-ganglionic. Both types release acetylcholine.

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

somatic nervous system—part of the peripheral nervous system that controls movement. Motor nerves leave the spinal cord and innervate skeletal muscles. The motor nerves release acetylcholine to make muscles contract.

sympathetic nervous system—part of the autonomic nervous system which controls the functions of organs and tissues especially during times of stress, fear and emergencies. It consists of 2 types of neurons, pre-ganglionic and post-ganglionic. The pre-ganglionic neurons release acetylcholine and the post-ganglionic neurons release norepineprine.

synapse—the connection between two neurons; neurotransmitters are released from the terminal into

Module 4: Supplemental Classroom Activities

"A Fifty Minutes News Special: Nerve Gas"

Objective(s):
1. To understand the interaction of a chemical substance with biological targets such as enzymes
2. To understand how one compound has multiple actions throughout the body
3. To understand the basic structure of the circulatory and nervous systems

Standards and Skills:
AA1, AA2, AC2, AD2, AE2, CB3, CB4, CC1

Science Concepts:
Several areas of science are integrated into this activity. Concepts include 1) the behavior of a gas with a high vapor pressure in air and in the bloodstream, 2) the routes of entry of the gas into the body by absorption and inhalation, 3) the ability of the gas to get into the brain, 4) the covalent bonding of the nerve gas to an enzyme to irreversibly inhibit it, 5) the organization of the nervous system, the importance of the neurotransmitter acetylcholine, 6) the distribution of acetylcholine receptors as a basis for the production of multiple effects of nerve gas, and 7) the basis for antidotal therapy by other compounds.

Materials needed:
Video camera (optional)

Procedure:
This activity involves a presentation by the class in a "60 Minutes" television format. Divide the class into 4 groups. Each group is assigned a topic relating to nerve gas and its effects on the body.

Group 1: The history of nerve gas in warfare. The chemical properties of nerve gas.

Group 2: How nerve gas gets into the body and moves around to its targets (discuss absorption and distribution via the circulatory system, including crossing the blood brain barrier)

Group 3: How nerve gas produces its numerous effects on the body (discuss the nervous system, acetylcholine neurotransmission and role of the enzyme acetylcholinesterase)

Group 4: Why the effects of nerve gas are so difficult to reverse (discuss the chemical nature of the nerve gas-acetylcholinesterase bond and what kinds of antidotes are available)

Each group should research their topic prior to the presentation to the class. The presentation should be in the form of a "60 Mintues" show. For example, one of the students in the group could be the interviewer and the other students in the group could be various types of interviewees such as: an historian, chemist, military officer, neurologist, neuroscientist, pharmacologist, etc.. The interview should reveal all the necessary information associated with the group's topic. Encourage the students to include visual aids like posters to show some of the scientific principles. If a video camera is available, it should be used and copies of the tapes can be made for each of the students to keep.

Assessment strategies:
Have the students write "letters to the editor" asking specific questions about nerve gas and its effects on the body. They can hand in the questions at the end of the presentation. In the following weeks, read aloud 1 question at the end of a class period and invite an answer from the class. Keep track of number of right answers over the several weeks and then provide the class with a final printout of the questions with the correct answers.

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.

TC Marrs, RL Maynard and FR Sidell. *Chemical Warfare Agents: Toxicology and Treatment*, Wiley & Sons, New York, 1996. Chapters 3 and 4.

CP Holstege, M Kruk and FR Sidell. *Chemical warfare: Nerve agent poisoning*, Critical Care Clinics, 13:923-942, 1997.