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BRAIN BASICS

NOTHING CHANGES THE way we feel or the way we perceive the world unless it interacts with our central nervous system (CNS). Whether we take a sip of wine, snort a line of cocaine, or see an attractive person, our CNS is the place where the action occurs. To understand how any drug works, we need to understand some very basic principles governing brain function.

THE PRINCIPLES

1. The brain is not only the organ that tells us who we are, what we are doing, and what we have done, but it is with our brains that we sense the world, control our actions, and maintain basic body functions such as heart rate, blood pressure, and breathing. Drugs can strongly affect all of these functions.

2. The brain is an extraordinarily complex structure, with thousands of different sites for drug action on thousands of different kinds of nerve cells. This complexity can cause different people to have very different experiences with the same drug.

3. The CNS, especially in children and young adults, has a remarkable capacity to change in response to experience; this is called plasticity. We see it happen every day as learning and remembering, but the

CNS, in response to a variety of influences, can undergo changes that occur without our awareness of them.

4. The ability of the CNS to undergo plasticity can be modified by chemicals, whether taken for medical benefit or for recreational purposes.

CHAPTER CONTENTS

SINGLE NERVE CELLS

It is laughable to think that anyone completely understands how the brain functions. Every time neuroscientists make a discovery that explains some property of the nervous system, that discovery opens new doors and raises new questions. For example, no one knows exactly how the CNS stores memories, but we do know a lot about how to alter the storage process.

Often the brain is compared to a computer. That analogy is overworked, but in one way, it is not such a bad one. Most people know how to use a computer, but they do not know precisely how the circuits inside the computer do the job. However, not knowing just how the circuits work does not prevent the user from knowing what to type on the keyboard, how to access the internet, and how to run a program. Likewise, there is a lot to know about the nervous system, and a little knowledge can help you keep yours healthy.

The first step is to appreciate what an amazing structure the brain is.

One of the most amazing things is that such a complex structure can function so well even under some of the terribly difficult conditions that we impose on it. It has an ingenious balance of excitatory and inhibitory influences coursing through it. It's like a sports car moving along a winding country road with just the right amount of pressure on the accelerator (excitation) and the brakes (inhibition). In the brain, the brakes are the release of inhibitory chemicals. They suppress the firing of nerve cells by opening channels in the cells' membranes, letting ions flow in a direction that causes the cells' electrical potential to move away from the point at which it would fire a signal (an action potential). Without action potentials, there is no action, so we say that that cell or network of cells is inhibited. An inhibited network cannot carry out its function, so that function is lost. The lost function might be thinking, feeling anxiety, staying awake, having reflexes to pain, adjusting the circulatory system, or breathing. An overly excited network is like a pot of boiling water, or like that sports car out of control at high speed. There is a chaos of discharges that randomly fire in many parts of the brain, leading to all sorts of feelings and movements. Yet in most of us, for most of the time, the brain maintains the delicate balance of excitation and inhibition that permits a normal life.

The first step to understanding that delicate balance, and how drugs disrupt it, is to understand the building blocks of the CNS—the nerve cells, or neurons. There are many other CNS cells that support the neurons, but the neurons are where the information is stored, where feelings are sensed, and where actions are initiated.

Neurons look a little like trees. There's the trunk and the top with many branches and the leaves that receive the sunlight. Then there is the root system that is equally branched, with a large taproot going off into the earth. Under the microscope, many neurons look the same way. They have a "top" receiving area called the dendrites, where connections from other neurons make contact. Then they have a "trunk" area, where the body of the nerve cell is located, containing the genetic information for that cell. Finally, out of the cell body emerges the axon of the cell (like the root of a tree), which goes off and branches to make contact with other nerve cells or muscle cells and transmit signals to them.

Like all cells, a nerve cell is held together by its cell membrane, which is a mixture of lipids (fats) and proteins. Many nonneuronal cells (for example, blood cells, muscle cells) have cell membranes that are more or less the same all over. The cell membranes of neurons, however, are vastly dif-

ferent in different parts of the cell. These differences allow a cell to receive different types of signals from many other cells, integrate these signals, and then send out signals of its own. Even a single neuron is a very complicated bit of biochemical machinery, but this complexity is what allows the enormous information storage and processing capacity of the human brain to exist in such a compact form.

CONNECTIONS BETWEEN NERVE CELLS

The dendritic, or receiving, area of neurons is where axons (transmitting fibers) from other nerve cells make contact. These points of contact are called synapses. A single synapse is, in itself, a complex structure, consisting of the presynaptic and the postsynaptic regions. The presynaptic region is the termination point of the axon of the transmitting cell, and at that point the axon balloons from a very small fiber to a group of bulblike endings called the presynaptic terminals. These terminals contain chemicals—neurotransmitters—that are released into the space between the presynaptic terminal and the dendrite of the postsynaptic (receiving) cell. The neurotransmitter molecules react with special receptors that are sensitive only to that neurotransmitter on the postsynaptic cell, and, in just thousandths of a second, these receptors cause electrical and/or biochemical signals within the receiving cell.

A single neuron can have a large number of synapses on its dendrites, and it is the job of the neuron cell body to take in signals from all of those synapses and make a decision. That decision is whether to fire electrical signals itself down its transmitting fiber—its axon. The signals that are transmitted down the axon are called action potentials because they can cause action somewhere else. If they come from a nerve cell synapsing onto a muscle cell, they can cause the muscle cell to contract. If they come from a nerve cell connecting to another nerve cell, they can cause that follower nerve cell to either fire or stop firing, depending on what kind of signal it gets from the neurotransmitter molecules.

The input to a neuron is from synaptic connections from other neurons, while the output is a series of action potentials firing down its axon. The action potentials are all the same, just quick (about one-thousandth of a second) discharges of electrical activity. The information is carried at the rate by which these discharges occur. So, if a neuron fires lots of action potentials in a brief period (up to four hundred in one second), it can have a large influence on its follower cells, while slow firing would have less influence.

Some drugs may affect the generation and spread of action potentials down the axon, but that is not a common site of drug action. These drugs usually produce drastic and often toxic changes because they can completely stop a neuron from firing. One such toxin that does this is the chemical present in the ovaries of puffer fish, which are delicacies in Japan. This chemical, called tetrodotoxin, is so toxic that eating just part of a fish can paralyze the muscles responsible for breathing and lead to death. Japanese restaurants have chefs who are specially trained and licensed to remove the ovaries before the fish is served. This same class of toxin is also thought to be used in Haitian voodoo rituals to induce zombie-like behavior.

Most drugs act either at the presynaptic terminal, where the neurotransmitter is released, or at the postsynaptic membrane on the neurotransmitter receptor. The synapse is the primary site of action of the majority of drugs that affect human brain functions. So to understand how drugs affect our CNS, we must understand the synapse.

The presynaptic terminal is the place where neurotransmitters are synthesized, packaged, and released. When action potentials travel from the cell body of the transmitting neuron down to the terminal area, the electrical signals cause changes in the shape of protein molecules that reside in the terminal area. These molecules sense the electrical signals and, within thousandths of a second, reconfigure themselves to form pores, or channels, in the terminal membrane. Calcium ions flow into the terminal through these pores, and the calcium initiates a chain of biochemical reactions. The result of this biochemical sequence is that packets of neurotransmitter molecules break through the terminal membrane and move toward the postsynaptic area of the receiving cell.

What happens to the neurotransmitter molecules after they are released? After all, if they stayed around forever, the postsynaptic neuron, or muscle fiber, would constantly be under their influence and further signaling would be impossible. Removal of neurotransmitters is accomplished in three ways. First, the molecules just diffuse away into other areas where there are no receptors and are removed by the general circulation of fluids in the brain. Second, there can be specific chemicals that break the neurotransmitters into inactive parts that are returned to the cells. Finally, there are specific sites on the presynaptic terminal that attach to the active neurotransmitter molecules and transport them back into the terminal for release again. These transport sites are often places where drugs act to prolong the presence of the transmitter in the postsynaptic area, therefore increasing its effect. Cocaine is an excellent example

of such a drug, because it suppresses the uptake of the transmitter dopamine, which is important in the reward center of the brain.

This entire neurotransmitter-release process can be controlled by neurochemicals active at the presynaptic terminal. In some cases there are receptors for the transmitter being released that serve to suppress further release of the transmitter and thus limit the action at that synapse. In other cases there are receptors for different neurotransmitters that can regulate release. Any of these sites could be important places for drugs to act.

THE ROLE OF RECEPTORS

Next, consider the postsynaptic region of the cell, where the neurotransmitter receptors are located. The postsynaptic region contains the proteins bound in the lipid cell membrane that react with the neurotransmitter molecules. These proteins are, in themselves, very complex structures. They are three-dimensional molecules that have sites into which the neurotransmitter molecules can fit. In fact, this arrangement is just like a lock-and-key mechanism. The neurotransmitter molecules from the presynaptic cell are the keys and the postsynaptic receptors are the locks. When the key "enters" the lock by binding to the receptor molecule, the lock operates and the bioelectrical activity is initiated.

The lock-and-key analogy is good to a point, but it's certainly too simplistic. Unlike a lock, which usually has only one action (to throw a bolt into a door), a receptor can have numerous actions, and each one of these steps can be changed by drugs. The first two actions that occur at a receptor are electrical and biochemical.

The fastest signal is the electrical process. Once the neurotransmitter binds, the receptor molecule can change its shape and open channels (pores) into the cell on which it is located. These channels allow the flow of charged molecules (ions) into or out of the cell, and this movement of electrical charge causes an electrical signal to develop across the cell membrane.

Normally neurons have an electrical charge so that the inside of the cell is negative (about 0.1 volt) compared to the outside. This is called the resting potential, and when a neuron is at rest, it fires no action potentials. When the inside of the cell at the point of the cell body becomes considerably less negative (about 0.04 volts), then action potentials begin to fire and the cell is then transmitting to its follower cells.

Neurotransmitters released at the synapse change the charge across the membrane near the postsynaptic receptors, and so control whether a cell starts to fire action potentials. If a receptor opens a channel that lets in ions that make the cell less negative, then the electrical potential of the cell moves in the direction of firing action potentials. If the receptor opens a channel that causes the cell to become more negative inside, then the cell becomes less able to fire. Every cell has many synapses, and when all of this electrical activity together adds up, the sum of it determines whether a cell fires its own action potential. This addition of pro- and anti-firing (excitatory and inhibitory) currents occurs in and around the cell body of the neuron, in a place where action potentials originate. Thus, all of the synaptic activity of the cell converges to the cell body, where the cell makes the decision to fire or not to fire, depending on the voltage across its cell membrane.

The two most common neurotransmitters in the CNS are the amino acids GABA (gamma-aminobutyric acid) and glutamate. These are referred to as inhibitory (GABA) and excitatory (glutamate) amino acid neurotransmitters. These neurotransmitters are responsible for much of the second-to-second processing in the CNS. If either of these is significantly blocked, the proper functioning of the CNS is dramatically disrupted. There are many subtypes of these receptors, and each of these subtypes has different characteristics. Some of the most interesting drug effects come from activating just a particular subtype of a receptor rather than the whole class of receptors.

Receptors can initiate a cascade of biochemical events within neurons. Either by letting calcium ions into cells or by activating intracellular enzymes directly, activated receptors can profoundly change the biochemical environment of a cell. These biochemical signals can alter the numbers of receptors for different transmitters, change the degree to which they recognize their transmitters, or even change the systems that regulate the function of the cell—literally, thousands of different processes. It is no wonder that drugs that interact with receptors can be so specific and so powerful.

This diversity of receptors and biochemical signaling pathways is what makes the brain infinitely more complex than a computer. There may be as many as one hundred neurotransmitters in the human brain. Instead of just a single plus or negative signal, there is an almost infinite variety of signals, each generated by a different neurotransmitter—from a tiny, fast excitation as described above, to a prolonged, slow, and powerful inhibition.

This diversity also allows humans to devise drugs that have quite specific effects. Throughout this book there are references to actions of a drug at a specific receptor, receptor regulation site, or biochemical-signaling pathway. Although we know much about the way these chemicals operate, it is important to remember the mantra of every pharmacologist: "Every drug has two effects—the one I know about and the one I don't know about."

COLLECTIONS OF NEURONS FORM SPECIALIZED BRAIN AREAS

While neurons are the basic components of the brain, the ways in which they are connected determine what functions will occur. An old cartoon shows a neurosurgeon in the operating room saying, "Well, there go the piano lessons." Like most humor, it's somewhat based on fact. The brain is organized into specialized areas that control speech, hearing, vision, fine movements, gross movements, learning, anger, fear, and much more.

It would be very useful to know which neurotransmitters and receptors carry the information for all of these functions, because then we could design specific drugs to modulate them with great precision. However, we are far from having that information, and even if we did have it, there is another complication—the pattern of connections between neurons. While neurochemistry is important, the patterns in which neurons connect are equally important. This is where the computer analogy holds up: in fact, neuroscientists call the web of connections that mediate specific brain functions "neural circuits."

Behaviors, even simple ones, are possible because neuronal connections are very specific and complex. Even the simplest reaction, such as blinking when a dust particle gets in your eye, involves several nerves connected to each other. So, when a drug alters one process, the effect it has depends on how that process participates in the function of the network. Thus, our ignorance of nerve-cell connections accounts for some of the uncertainty in knowing the effects of drugs.

THE CENTRAL NERVOUS SYSTEM CONTROLS MANY FUNCTIONS

In the following section, we will talk about some of the most exciting parts of brain function, learning, and memory. But it is crucial to understand that the central nervous system controls almost everything about us: how we perceive the world through our senses (vision, hearing, smell, taste, touch); how we organize movement from the moment we are motivated to do something to the completion of the act; our motivation and emotional states (are we sad, excited, depressed, anxious, elated, bewildered, and so on); and how we organize these functions. For example, when you smell a doughnut, your mouth waters, you feel hungry, and perhaps cheery at the prospect of eating. You become motivated to find the doughnut, use your other senses to do so, and activate your motor systems to get there. The brain also controls some very important body functions that sustain life. These are boring functions until they fail, and then they get attention right away. The three most vital functions that the CNS controls are the circulatory system (heart and blood vessels), the respiratory system (breathing), and the reflex system (which instantly, and without thinking, causes you to respond to a threat).

The circulatory system is maintained in a stable condition by its own built-in control system. However, the brain can easily modify this set point. For example, during periods of anger or excitement, the heart beats rapidly and blood pressure rises. The CNS also stimulates the respiratory system and causes breathing to increase. The brain has decided that the "normal" status is incorrect and that the body needs to be prepared for fight or flight. In contrast, when the mind is at peace, and perhaps meditative, the heart rate falls, blood pressure falls, and breathing is slowed.

The CNS reflex system is equally important but often forgotten. People who think about drugs and safety often mention hearts and breathing, but they don't put as much emphasis on how reflexes keep us safe. Take, for example, how we jerk our hand back from a hot surface. This is a pure reflex action that is signaled in the spinal cord. The sensing nerves in the fingers and hand send a powerful signal to the spinal cord. This signal excites neurons that cause movement and withdrawal of the hand. This all happens before the pain signals are even interpreted by the conscious brain.

A more important example is the reflex to clear the airway for breathing. Notice how fast and how strongly the body responds when something touches the airway in the back of the throat. This is a critical reflex to sustain life. If this reflex were suppressed by a drug, then something (such as vomit) could easily block the airway and it would not be cleared. The person would die of asphyxiation. The list of basic body functions

that can be impaired by drugs goes on and on. This is not a particularly glamorous or fascinating area of drug effects, but it is one that everyone must understand.

PLASTICITY IN THE CNS— LEARNING FROM EXPERIENCE

The third principle of this chapter stated that the CNS responds to experience by learning—that is, it reorganizes some of its neurochemistry and connections so that the experience is remembered. It is very important to understand that this plasticity is a broad concept. Not only does the CNS remember events that are consciously experienced, but it also changes in response to all sorts of signals, such as the constant presence of drugs.

The most familiar plasticity in the CNS is the simple remembering of experiences—faces, odors, names, classroom lectures, and lots more. The neurobiological mechanisms through which this kind of learning happens are not completely understood, but we have some clues. One important site of learning appears to be the synapse.

As discussed, synapses of nerve cells are quite complex, and there is extensive biochemical machinery in both the presynaptic and the postsynaptic areas. We think memory is built one synapse at a time: some synapses that are stimulated repeatedly change how they function (learn) and maintain that change for a long time. There is an electrical manifestation of this learning that scientists call long-term potentiation (LTP). It is a long-lasting strengthening (potentiation) of the electrical signal between two neurons that occurs when the synapse between them is stimulated.

We're not sure how this happens, but it is likely through a series of biochemical changes in how the first neuron releases its neurotransmitter and how the second neuron responds to the neurotransmitter. On the presynaptic side, a synapse could be strengthened by increasing the number of presynaptic terminals, by releasing more transmitters from the same number of terminals, or by a reduction in transmitter removal. On the postsynaptic side, strengthening could occur with an increase in the number of receptors, a change in the functional properties of the receptors, a change in how well the postsynaptic site is coupled to the remainder of the neuron, or a change in the biochemistry of the postsynaptic neuron. There is scientific controversy about the true mechanisms of LTP, and the issue may not be clear for a number of years.

Almost every neuron can modify many aspects of its function to adapt to new conditions—by making more or less neurotransmitter, by changing the number of receptors on the surface of its cells, by changing the number of molecules responsible for the passage of the electrical stimulus down the axon, and so forth. If a neural circuit is being overstimulated, it can reduce the stimulation by removing some of the receptors for the neurotransmitter stimulating it. Therefore, even if the neural circuit is being sent lots of signals, they don't get through. Alternatively, if a neural circuit is receiving much less stimulation than usual, it can adapt by becoming more sensitive to each stimulus. This is how the brain stays in balance.

This type of biochemical plasticity goes on all the time and is part of normal brain function. However, these same changes can cause abnormal brain function. For example, we think that the tremendous mood changes in depression might result from changing numbers of neurotransmitter receptors following changing stimulation of specific neurons in the brain.

If neurons and synapses learn, do they also forget? The answer appears to be yes. We just described how stimulating a neural pathway in a certain way can cause it to "learn" to respond to stimulation differently. Stimulating it in another way (slowly, and for a long time) can cause a process called depotentiation, which appears to be the opposite of long-term potentiation. Why is this interesting? Depotentiation could be quite important because it may represent the synaptic equivalent of amnesia. Depotentiation can be produced by prolonged slow activity or by very strong high-frequency activity, like that which occurs in seizures. It may be a protective mechanism by which the CNS prevents a seizure or brain trauma from encoding new information into the circuits. Again, it is almost certainly under the control of cell-signaling pathways and thus could be manipulated by drugs.

This gradual change in the electrical strength of a connection seems subtle, but it makes intuitive sense that memories could form in this way. Can the brain actually change physically? We used to think that once a person was mature, the brain didn't change anymore. However, more and more research shows that actual changes in the shapes of neurons also can happen in response to earlier experiences. We know that the shape of certain neurons in the brain changes when different hormones become available. For example, at least in animal studies, treatment with hormones can stimulate the production of little protuberances, or

"spines," on the dendrites of neurons. Other research has shown that synapses actually remodel themselves over time after different levels of activity. So, connections actually get lost or remade. For example, prolonged stress seems to actually shrink the dendrite on neurons, perhaps explaining the cognitive difficulties people encounter during prolonged stressful periods.

It has been known for a long time that this happened in lower animals. For example, as songbirds learn new songs, the structure of certain parts of their brains changes. It was once thought that the brains of mammals did not have this type of structural plasticity. However, more recent studies have shown similar changes in rats, and scientists think that they probably occur in all mammals.

One of the most exciting findings about neuronal plasticity is that the brain can actually make new neurons. This process, called neurogenesis, was long thought to occur mostly during prenatal development, but now we find that it is happening in adult mammals. Neurogenesis results from the conversion of neural stem cells into functional neurons. The rate of conversion seems to increase in response to injury or other pathologies and decrease in response to chronic stress. As with most neuroscience research, the data come primarily from animal experiments, usually rats, and as always, relevance to humans needs to be established.

There have been some intriguing findings regarding the effects of drugs on neurogenesis in animals. It appears that depression reduces neurogenesis and subsequent treatment with antidepressants restores it. More relevant to this book, the laboratory of Fulton Crews at the University of North Carolina has made the startling discovery that binge exposure to alcohol dramatically suppresses rat neurogenesis, particularly in the adolescent forebrain, which is a brain area in rapid development. The potential implications of this are enormous, because adolescents tend to be binge drinkers. Is this behavior impairing their brain development? What other drugs affect these processes? Does this really happen in humans? These questions should and will be answered by future research, but for now they alert us to the possibility that drug abuse could have profound effects on teenage brain development.

DO ALL PARTS OF THE BRAIN LEARN?

The processes that we just described do not happen in just one part of the brain. There are indeed specialized neural networks, especially in a part

of the brain called the hippocampus, where learning occurs and memories are created. (People who have had damage to this part of the brain have great difficulty learning new things, although they can readily remember things that happened before.) However, most forms of plasticity can occur all over the brain and affect all brain function.

For us to be able to function normally, all brain processes need to proceed unimpaired. All of the neurotransmitter systems need to be working. The brain needs to change with time to reflect previous experience—that is, learn—to restore balance if it is over- or understimulated.

THE DEVELOPING BRAIN

While the brains of adults change all the time, what goes on in adults is trivial compared to the phenomenal changes that occur while the brain is developing. The brain assembles itself carefully through the process of neurons growing out, and through chemical signals around them, gradually finding their way to the correct destination, where they make the connections that they then maintain. During this time of life, the physical changes in the brain are dramatic. New synaptic connections are being made at a high rate every day. The growing brain also has its own way of "forgetting." Many of the neurons growing out never reach their destination and die in the process. Others reshape their connections until they are correct. Through all of this furious growth, neurons must remain active or they can fail to make their appropriate connections. Therefore, changes in neuronal function that in an adult would simply shut down a pathway for a while can have more drastic consequences in a developing brain.

Growing neurons are affected by processes that don't affect the neurons of adult brains. Exposure to substances that inhibit cell growth has some impact on an adult brain but a devastating impact on the developing brain. The neurotoxic element mercury provides a good example. Mercury affects the function of the adult brain and can lead to serious, but largely reversible, disruption of brain function. However, exposure of the brain of the developing fetus to mercury disrupts brain development so totally that severe mental retardation results. For example, an industrial spill of mercury into the water near a small, coastal Japanese town called Minamata contaminated the fish that were the local food source. While many adults experienced diseases that eventually resolved, many children born during this time frame had terrible dis-

ruption of normal brain development and remained mentally retarded throughout their lives.

Recently, medical imaging techniques have made it possible to study the development of the human brain at various points from birth to adulthood. Some of the most interesting studies use magnetic resonance imaging (MRI) with the machine set to reveal the white matter of the brain, the myelin insulation on the nerve cell axons. As the brain matures, the connections between cells become permanent, and then they are insulated with myelin. So, imaging for the myelin tells the scientist just how much development has occurred in a brain area. The big news is that the human brain is not fully developed until early in adulthood. And among the last parts to develop are the frontal lobe areas that give us the capability of inhibiting inappropriate behavior, handling complex tasks, and planning ahead. When we lecture about this, we often make the point that from the standpoint of the brain, adolescents are not "young adults," but rather, "big kids."

We believe it is very important to teach kids that their brains are still developing through adolescence. This means that they have the opportunity to take some control of the final development of some of the most critical areas of their brains.

There are an increasing number of studies examining the effects of drugs on the adolescent brain from our laboratories and others. Most of these studies have focused on the acute effects of alcohol and other drugs, but some epidemiological studies have examined the associations between drug use and brain pathology. We have discussed these issues in the appropriate chapters, primarily those dealing with alcohol and marijuana.

DRUGS AND PLASTICITY

Whatever the exact mechanisms are that underlie learning, there is strong evidence that supports the correlation between synaptic changes, neuroplasticity, and learning. The best of this evidence comes from drug studies. Chemicals that block the development of LTP tend to block other manifestations of neuroplasticity and, in particular, can block learning.

For example, a drug called AP-5 (D-2-amino-5-phosphonopentanoate) blocks a certain subtype of the excitatory neurotransmitter glutamate. This particular subtype, the NMDA (the N-methyl-D-aspartate) receptor, has the very special property of letting calcium into the cell

only when the cell is receiving excitatory signals through other synapses. The calcium causes LTP to occur at those synapses. Thus, the NMDA receptor is like a memory switch. When the cell is receiving a signal and the NMDA receptor is activated, the cell "remembers" the signal by strengthening that synapse.

We were fortunate to find the NMDA receptor, because it appears to be one of the most important receptors for learning and other forms of neuroplasticity. It may teach us much about how memory occurs and how some drugs disrupt it. For example, in laboratory experiments, if we chemically block the NMDA receptor so that glutamate cannot bind there, LTP does not occur, rats do not learn mazes, and the CNS does not reorganize its neuronal connections following injury. There is increasing evidence that such learning and neuroplasticity can be suppressed in humans.

Alcohol in rats blocks NMDA receptors, suppresses LTP, and suppresses maze learning. So, now we may know why we forget what we did when we were drunk (see the Alcohol chapter for more information).

Many drugs affect the ability of the brain to learn—there is no question about it. But which drugs have which effects, and for how long? One of the best stories about the effects of drugs on learning was told to one of us by a drug company representative during an airplane trip. It seems that some of the professional staff from his company were making a quick trip overseas to a meeting, and they needed to sleep during the plane ride because their lectures were scheduled almost as soon as they were to arrive. So, this group had a few alcoholic drinks and then took one of their newly marketed sedatives (a benzodiazepine) to get to sleep. Everything went well, including the lectures, and the scientists returned home in a couple of days. The only problem was that when they returned, they remembered nothing of the meeting—not their lectures or those of anyone else. They did not know that the drug they chose, in the dose they chose, would have powerful amnesiac effects, especially when mixed with alcohol.

This story is legend in the pharmaceutical industry, and whether it is exactly true does not make any difference. It illustrates the point that even the people who develop and manufacture drugs by the highest standards may not know every effect they can have and how long these effects can last.

There are basically three ways in which drugs can affect learning: they can impair the ability of the brain to store information (amnesia), they can distort reality, or in some cases, they can stimulate the brain to increase learning.

By far the most common effect of drugs is to suppress learning. Almost all of the drugs that have sedative or anxiety-reducing properties impair the retention of information. Although we do not know exactly how this happens, there are three mechanisms that have been proposed at the synaptic level.

The first of these is increased inhibition. We know that many sedative drugs increase GABA-mediated synaptic activity, which inhibits the firing of neurons. The experimental data suggest that this increase in inhibition can reduce the effects of the type of neuronal firing that is usually necessary for LTP, and thus prevent neuroplasticity.

The second of these mechanisms is reduced excitation. Some drugs, such as alcohol, not only increase GABA function (and thus inhibition) but also suppress the glutamate-mediated excitatory channels (the NMDA receptor channels) that let calcium ions into the neurons. This reduction in calcium entry prevents the signaling mechanisms within the neurons that lead to long-term synaptic changes.

Finally, there are drugs, such as the THC in marijuana, that act through their own receptors to change cell biochemistry so that learning is impaired. From what we know of their biochemistry, they may directly regulate the signal-processing pathways within the cell that govern the strength of synaptic activity, perhaps by suppressing the signals that mediate LTP or, alternatively, by enhancing the processes underlying LTD and/or depotentiation.

Now that we know about LTD and depotentiation, it is easy to imagine that there would be reasons for the CNS to reduce activity in some pathways and thus "forget" some neuroplastic changes. Therefore, it is completely reasonable that some drugs could enhance this type of signaling, reducing the ability to learn.

On a brighter note, neurobiologists are exploring ways to use drug therapy to enhance learning. This research is particularly important for the many people who suffer from Alzheimer's disease or other brain disorders that impair learning. Most of the rest of us would also relish the ability to learn more or faster. There are some tantalizing clues that this may be possible.

One of the most interesting clues comes from an experience that almost all of us have had. It's the "Do you remember what you were doing when . . . ?" question. Every generation has at least one of these questions. For older people, it's what they were doing when they heard that JFK was assassinated. Nearly everyone recalls the fateful morning of 9/11. Think

of an example: the first time you had a very important and emotional experience, either positive or negative.

Why is it that we remember some experiences so well, and not only the event but maybe what clothes we wore, what the room looked like, what we ate? Ongoing experiments shed a lot of light on this phenomenon. Dr. James McGaugh (of the University of California at Irvine) took two similar groups of people and placed them in separate but similar rooms with all sorts of cues, or decorations. The goal was to subject the groups to an emotional story and to see how well they remembered the story and the environment (the room) in which they experienced the event.

What makes this experiment interesting is that one group was given a drug (propranolol) that blocks a subtype of the adrenaline receptor—the beta-adrenaline receptor. This receptor is the one responsible for the increase in heart rate and blood pressure that occurs under physical or emotional stress; the blocker, propranolol, is used to control blood pressure and heart problems in some patients. So, one group was completely normal, while the other group had their excitatory adrenaline activity blocked.

The experimental subjects were then told a heartbreaking story about an injured child. After a period of time the two groups were removed from their rooms and then asked to recall the story and the details of their environment in the room. Both groups remembered the story. However, only the normal (undrugged) group remembered the details of the room. The treated group remembered very little of their environment.

What does this teach us? We all know that we tend to learn what interests us, and we know that we remember emotional events. Now we know why. The brain interprets an event as important and activates circuits that facilitate learning and remembering the environment associated with an emotionally powerful event. This is probably a critical characteristic for both humans and other animals to have, because it tends to help us remember events and places that were either wonderful or threatening, and thus adjust our future behavior accordingly. So, now it is clear why a smell or a face or a place might make you feel good or bad, even if you cannot immediately recall why: your brain is recalling an emotional experience.

This insight into learning is useful in several ways. First, it illustrates how important it is to be alert and interested in what we are trying to learn. When we are sleepy or depressed we are poor learners, in part

because we are not so sensitive to stimuli. To really learn or teach something, we must include an emotional component.

In addition, this experiment suggests that there may be ways to facilitate learning through manipulating brain chemistry. Neuroscientists already know that learning is controlled by multiple neurotransmitters and neural circuits. However, increasing the function of any of these systems has proven difficult to achieve without producing unacceptable side effects.

At this point, no drug has yet been approved to increase learning. Until then, readers, you'll have to "trick" your brain by studying what is exciting and by getting excited about what you must study!

What about other kinds of learning and memory besides what you learned in school or "where was I when . . ."? Multiple neurotransmitters and circuits participate in the neuroplasticity of the brain, and the outcomes are not always helpful.

Posttraumatic stress disorder (PTSD) is a prime example of pathological neuroplasticity. When a person experiences extremely frightening or distressing events repeatedly, the fear system of the brain becomes hyperreactive. People with PTSD then find themselves extremely vigilant and quick to react to stimuli that would not normally disturb a person. It could be sensory stimuli or psychological stimuli. Unfortunate examples are members of the military who have experienced the horrors of war, or children who have been repeatedly abused. At the time of this writing, there is no known way of reversing this plasticity, any more than one can reverse a pleasant memory. But there are significant research efforts under way to find solutions to PTSD that will offer relief to the individuals.

Another example of neuroplasticity and "learning" by the brain is epilepsy. In many cases, epileptic seizures begin with a lesion at one site in which the neurons fire in a hyperexcited, coordinated pattern. This neuronal excitability is transmitted to other, normal areas of the brain that, in turn, "learn" to fire in the same way. Eventually enough of the brain "learns" to fire in this way, and generalized seizures develop. Drugs called anticonvulsants can suppress the hyperexcitability, but we have no drugs that can erase the "learned" tendency to generate the seizure activity.

In the Addiction chapter we talk about another type of pathological neuroplasticity—how the reward system learns to crave a drug or a pleasurable behavior. All of these forms of neuroplasticity involve basic alterations of neuronal behavior, and all of them depend on a number of different neurotransmitters besides GABA and glutamate. Recreational drugs can alter the function of different neurotransmitters, often in subtle

but damaging ways. While the details of all of the possibilities are beyond the scope of this book, it is important to understand that if a drug is altering your perception of the world or your reactions to your environment, there is a good chance that drug has the capacity to enable the brain to change in a permanent way that is likely not to be good in the long run.

THE LATEST BRAIN IMAGING

It's hard to find a media story about the brain that doesn't refer to the latest technology for imaging the activity of the brain, most often using functional magnetic resonance imaging (fMRI). This is a powerful tool for imaging ongoing brain activity in humans as well as animals. As with structural MRI that yields "still" images of the brain, fMRI uses magnetic fields rather than radiation to image the tissue. So, as far as we know, there is no safety issue about long or repeated exposures (unless you have something in your body that can be magnetized).

fMRI depends on a particularly useful property of hemoglobin, the molecule in red blood cells that carries oxygen to all tissues, including those in the brain. As you may have learned in biology class, oxygen is bound to hemoglobin in the blood and is released from hemoglobin as blood perfuses tissues that need oxygen for producing energy. The magnetic properties of hemoglobin change as the hemoglobin releases oxygen to tissues. Thus, the fMRI system looks for changes in magnetic signals as tissues consume oxygen. The signal is called the blood oxygen level dependent (BOLD) signal.

When neural circuits are active, blood flow increases in those areas and oxygen is stripped from hemoglobin in the blood. Thus the BOLD signal changes to reflect that shift in the amount of hemoglobin that has oxygen bound to it. So literally, a person can lie in an fMRI machine and decide to wiggle a thumb and watch the brain activity associated with that movement. What is being displayed is blood flow and oxygen-consumption changes in the brain areas that control that movement—not the electrical activity of the brain. The BOLD signal lags the neuronal activity for one to two seconds, and there is still controversy about what exactly triggers the increased blood flow and oxygen delivery. But it is safe to say that fMRI is at least measuring a correlate of brain activity.

fMRI has its limits. First, there is the time issue we just mentioned, because the signal lags the neural activity for a long time compared to the

firing rate of neurons. Then there is the issue of spatial resolution. The very best fMRI resolution (at this writing) is a cube that's about 0.9 millimeter on each side—and that requires a machine with a very strong and expensive magnet. That small cube contains many neurons and synapses between them. So, using an fMRI to examine brain circuits is a bit like looking at a low-resolution TV—there is information there, but not as much as one would like. Another problem is that it is not possible to determine whether a BOLD signal in a brain area is a result of that area *transmitting* information or *receiving* information. All we can say is that the area is active. Furthermore, we don't know the result of that activity—it may be stimulating or shutting down its neighbor by activating neurons that normally slow down cells they contact.

Finally, the BOLD signals are very small compared to the background activity. This requires that the fMRI system average the images to reveal the relevant activity of an area. To further emphasize the active area, colors are used and the contrast is enhanced. Those techniques are very helpful to scientists but can produce images that are misleading to nonscientists. One of us was consulted by a major television network talk show about the effects of Ecstasy as shown by brain images (not fMRI, but it doesn't matter) of individuals who had used the drug. The images had very high contrast, and it appeared that the Ecstasy users had "holes" in their brains. In fact, there was just a small percentage difference in the true signals, but the images had been enhanced to emphasize those differences. Nevertheless, they talked about Ecstasy producing holes in the brains of users.

fMRI has been used to monitor brain activity in a vast array of studies, ranging from epilepsy to lie detection. It has also been used to image the response of the brain to various drugs as scientists try and determine where in the brain a drug acts to produce a change in behavior. To some extent this works. For example, one can show pictures of cocaine to nonusers and compare their response to the response of cocaine addicts. The BOLD images can vary remarkably between brain areas. But it is hard to know exactly what these changes mean.

First, individual variations make it hard to draw conclusions about a particular individual's responses. Doing studies with groups of people and averaging the group results produces reliable images, but we are not yet at the point of being able to image one individual and draw firm conclusions. Second, even if a brain area is reliably activated in some circumstance, we don't know enough about the brain to know exactly what each area does. Probably most important, brain activities are executed by coordinated signaling between a variety of areas, and fMRI may not be able to tell us the direction of signal flow or what role an area is playing. Finally, variations in signal strength may obscure proper interpretations. This could easily happen if a very small collection of neurons exerted powerful effects on a much larger circuit. The BOLD signal from the small number of neurons initiating the activity might not even be visible, while the larger circuit would dominate and appear to be the source of the activity.

All of this is not to say that fMRI and other brain imaging tools should be ignored. They are truly fantastic tools to begin to understand the relationship between behaviors and brain activities. As they become more refined, they may be able to reveal individual differences that have diagnostic meaning. But our advice at this moment is to view the nonscientific media with a degree of caution and to not be seduced by pretty pictures.

WHY SHOULD ANYONE CARE ABOUT ALL OF THIS?

We hope that this chapter offers some good reasons to develop a respect for the brain and the body that supports it, as well as some insight into why drugs do what they do. This is especially important for teenagers, because as every teenager knows, they are different from adults.

What adults may not know is that the teenagers are right. For some time we have known that the very immature brain, as in babies, has a number of characteristics that are different from the adult brain. Now we are finding that the adolescent brain may be different also. It may respond differently to drugs, and it may learn differently.

A psychologist at Duke University, Dr. David Rubin, carried out a fascinating series of experiments showing just how different young people may be. The basic experiment was to take adults at various ages and ask them questions about events that occurred in every ten-year period of their lives, including a lot of trivia. Of course, recent events were remembered fairly well, but other than those, the events best recalled were those that occurred during young adulthood (from age eleven to age thirty). This means that a senior citizen recalled his life events and what was going on in the world during his adolescence even better than those events that had occurred just a few years earlier.

If our conclusions from this research are correct, then there is something very special about either our brain biochemistry or our psychological state during adolescence that enables us to store our experiences for life. Whatever the explanation, the implications are clear—the experiences, good or bad, that we have during our youth are very well stored in our "sober" memory systems and can be recalled for the rest of our lives. Thus, when teenagers say they are different, they are right, and when adults say that these are formative years, they, too, are right.