

# REDISCOVERING BIOLOGY

Molecular to Global  
Perspectives

## Neurobiology

*“The human nervous system is probably the most intricately organized aggregate of matter on Earth. A single cubic centimeter of the human brain may contain well over 50 million nerve cells, each of which may communicate with thousands of other neurons in information-processing networks that make the most elaborate computer look primitive. These neural pathways control our every perception and movement and enable us to learn, think, and be conscious of ourselves and our surroundings.”*

CAMPBELL AND REECE<sup>1</sup>

The most striking differences between humans and other animals are in the size and the complexity of our brains. With our big brains we have acquired a rich culture, which far exceeds that of any other species in scope and complexity. We have developed science to understand how and why an immensity of things and processes work, including those of our own brain. At the start of the twenty-first century neuroscientists are increasingly able to explain the functions of brain in molecular terms.

To understand how the brain works we first must consider what the brain does. This can be broken down into three basic functions: (1) take in sensory information, (2) process information between neurons, and (3) make outputs. The neurons that take in information from the environment are called sensory neurons. These are specialized to respond to a particular stimulus, such as light, heat, chemicals, or vibration — anything you might encounter from outside, or even inside, the body. The processing within the brain can range from a knee-jerk reaction — which takes place entirely in the spinal cord — to the strategy adopted by a master chess player. In humans, we usually call this “thinking.” The output is most often a body movement, which results from the action of motor neurons. The brain is the link between the outside world and behavior, and is thus crucial for survival. These three basic functions are shared by organisms from humans down to invertebrates like *Caenorhabditis elegans*, a nematode that doesn’t even have a true “brain” but a collection of about three hundred neurons. (See the *Genes and Development* unit.)

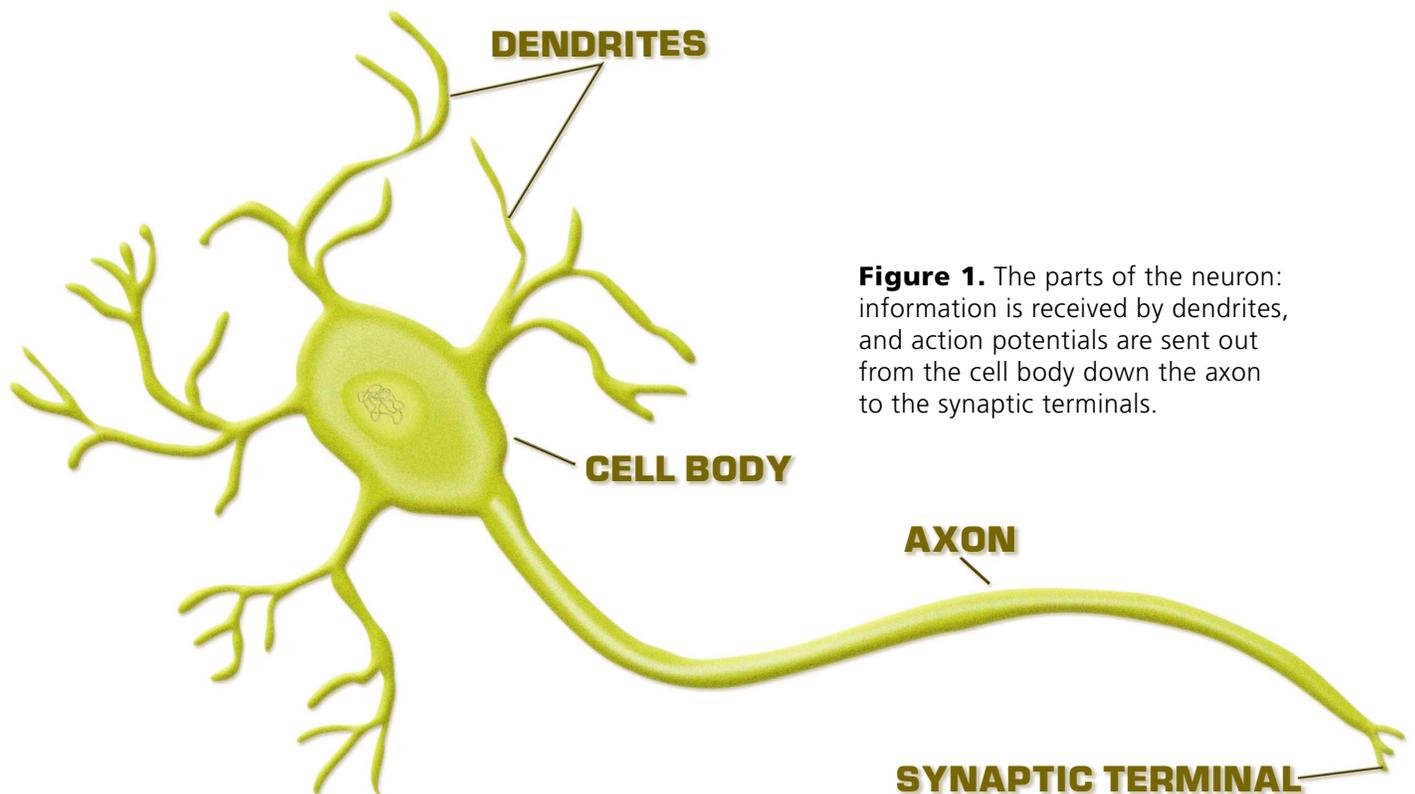
But how does the individual neuron work to carry out these tasks? Neurons’ unique systems capabilities arise from their cellular ability to communicate with one another very rapidly, using both electrical and chemical communication. Keep in mind, however, that the neuron is not the only type of cell in the brain. The neuron may be the star of the show but there are other supporting players. Indeed, neurons

constitute only a small fraction of cells in the brain. For every neuron there are about ten to fifty supporting cells, called glial cells, in the brain. The word “glial” means glue, and these cells are the “glue” of the nervous system. They perform many vital tasks, including removing dead neurons and debris, releasing critical growth factors to neurons, and acting as insulating material for the neurons.

The incredibly complex ways in which brains function exemplify the importance of cell-cell interactions. Below we discuss the chemical and electrical means by which neurons communicate, and describe how various therapeutic and recreational drugs alter these processes at the molecular level. We then turn to the molecular nature of memory and learning. Finally, we describe recent studies that demonstrate that new neurons are being produced continuously in us.

## The Neuron as a Battery

The neuron is an extraordinarily specialized cell. Most neurons are referred to as “bipolar”; they have a cell body and many small extensions, called dendrites, at one end which receive information. **(Fig. 1)** At the other end is its most striking feature: a long axon that ends in “synaptic terminals,” which send signals to the dendrites of an adjacent neuron. The longest axon in the human body, the one that goes from the base of the spinal cord to the big toe, is about one meter long. Early studies on the physiology of neurons examined those from the giant axon of the squid, which is so big that it is visible with the naked eye. Note that the neuron, in addition to its specialized functions, carries out nearly all of the functions of a normal cell, except for division.



**Figure 1.** The parts of the neuron: information is received by dendrites, and action potentials are sent out from the cell body down the axon to the synaptic terminals.

Photo-illustration — Bergmann Graphics

The neuron is an electric battery and works by changes in its voltage. Compared with its surroundings, the inside of a “resting neuron” has a lower concentration of sodium ions and a higher concentration of potassium ions. Because of this imbalance of positively charged ions across the membrane, the inside of the resting neuron is negative relative to the outside. This difference in voltage is called the membrane potential. A typical **membrane potential** for a neuron at rest, the **resting potential**, is -0.07 volts, or -70 mV. Although this is a rather modest voltage (about five percent of that of an AA battery), consider that this voltage occurs across a miniscule length — that of the cell membrane. If this were an electric field, the charge separation would be about 100,000 volts per centimeter.

Note that the term “resting neuron” refers only to its electrical state. The cell is really not at rest because, in addition to carrying out all of the normal functions of the cell, the neuron has to maintain this ionic imbalance. This is achieved by the sodium-potassium pump, which actively transports potassium in and sodium out. The pump maintains a negative voltage because it actually pumps three sodium ions out for every two potassium ions it pumps in. The membrane potential of a neuron at any given time is the product of many variables, including the imbalance of ions across the membrane and the membrane’s permeability to each ion. In addition to sodium and potassium, chloride is an important ion in “setting” a neuron’s rest potential because negatively charged chloride ions can pass through open “leak channels” at rest. Another ion crucial for neural communication is calcium, which acts as a powerful intracellular signaling molecule once it enters through its ion channels.

## Voltage-Gated Channels

The neuron, like all cells, possesses a cell membrane that is mostly lipid. Ions like sodium and potassium cannot cross the lipid membrane on their own. In all cells transport of ions, as well as some small molecules, is carried out by channels, which are very tiny openings in the membrane formed by protein pores. These channels are often gated — that is, opened or closed — depending on the conditions of the cell. When open, the ions can enter and pass through channels by diffusion. Ions will always travel down their electrochemical gradient. For example, sodium is much more plentiful outside the cell than inside. It is also positively charged, while the inside of the cell is typically negatively charged relative to outside. Thus, both the chemical and electrical components of the gradient will drive sodium ions into the cell when sodium channels open. **Voltage-gated channels** are those in which the membrane potential of the cell determines whether they are opened or closed. Other channels can be opened or closed by various chemicals, such as neurotransmitters.

Channel proteins that span the cell membrane form the ion channels. To determine the structure of proteins, scientists have often used **X-ray crystallography**. (See the *Proteins and Proteomics* unit.) In 2003 Roderick MacKinnon and his colleagues used this technique to examine the structure of a voltage-gated potassium channel from a unicellular archaea. Previous studies have shown that ion channels have a central ion-conduction pore. Like all proteins, ion channel proteins are made up of amino acids, some of which are charged. When voltage changes occur, these charged components of the protein

make very small movements. This can result in more dramatic conformational changes, causing the channels to open and close. MacKinnon's group found that "voltage-sensor paddles" surround this pore. It appears that with voltage changes in the membrane, these paddles will move and thus permit potassium ions across the membrane.<sup>2</sup> Further study of the structure of the different classes of ion channels from other species will help elucidate the mechanisms by which they allow ion transport.

## The Action Potential

What is a nerve impulse? A nerve impulse, or an **action potential**, is a series of electrical responses that occur in the cell. (Fig. 2) With the appropriate stimulation, the voltage in the dendrite of the neuron will become somewhat less negative. This change in the membrane potential, called **depolarization**, will cause the voltage-gated sodium channels to open. Sodium ions will rush in, resulting in a rapid change in the charge. At the peak of the action potential, that area of the neuron is about 40 mV positive. As the voltage becomes positive, the sodium channels close, or inactivate, and the voltage-gated potassium channels open. These potassium channels let potassium ions rush out of the cell, causing the voltage to become negative again. The potassium channels remain open until the membrane potential becomes at least as negative as the resting potential. In many cases, the membrane potential becomes even more negative than the resting potential; this is called **hyperpolarization**. An action potential typically lasts a few milliseconds.

**Figure 2.** A cross-section of an axon, with an action potential (AP) moving from left to right. The AP has not yet reached point 4; the membrane there is still at rest. At point 3, positive sodium ions are moving in from the adjacent region, depolarizing the region; the sodium channels are about to open. Point 2 is at the peak of the AP; the sodium channels are open and ions are flowing into the axon. The AP has passed by point 1; the sodium channels are inactivated, and the membrane is hyperpolarized.

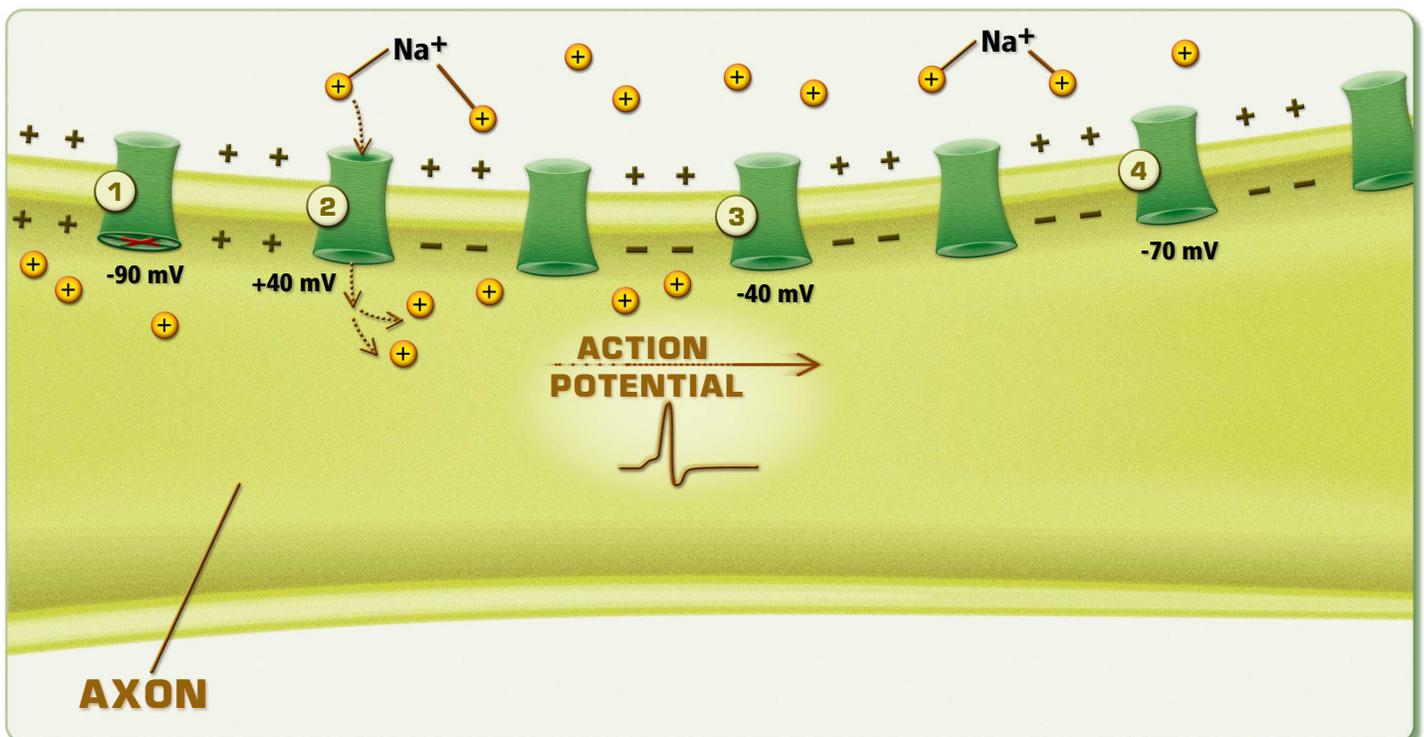


Photo-illustration — Bergmann Graphics

How can this action potential be propagated along the neuron? When the sodium channels are opened, sodium ions rush in; once inside they cause nearby regions of the neuron to become depolarized by moving laterally through the axon. This, in turn, causes the opening of more voltage-gated sodium channels in those regions. Thus, the sodium channel activation moves in a wave-like fashion: the action potential is propagated down the length of the neuron, from its input source at the dendrites, to the cell body, and then down the axon to the synaptic terminals. How does the action potential maintain this directional flow that is key to information processing? The sodium channels have a mechanism that avoids “back propagation” of the action potential, which would result in a confused signal. After opening, the sodium channels become inactivated as the potential becomes more positive, and they cannot open again until they are “reset” by hyperpolarization at the end of an action potential. This brief period of sodium channel inactivation, called a refractory period, prevents bidirectional propagation of the action potential, constraining it to go in only one direction.

## Myelin Speeds Up Thought

Most neurons have a fatty outer layer called myelin, which insulates and protects the axons of neurons. In this way, myelin is like the plastic that surrounds electric wires. Myelin is actually made up of two special classes of glial cells, called the oligodendroglia and Schwann cells, which wrap themselves around the axon much like a jellyroll. Between these cells there are small gaps in the myelin sheath called the Nodes of Ranvier. Action potentials are able to jump from one node to the next one down the neuron incredibly rapidly. For this reason, impulses will travel down a myelinated neuron faster than they will across an unmyelinated neuron. In myelinated neurons, action potentials usually travel at over 100 meters per second, which is about half the speed of sound. In about one-hundredth of a second, an action potential can travel from the brain to the base of the spinal cord of an adult. Though seemingly instantaneous, this rate is still on the order of a million times slower than electricity.

Several degenerative diseases are due to the loss of myelin in certain neurons. The loss of muscle coordination that people with multiple sclerosis face is due to the degeneration of the myelin sheath in classes of neurons that are involved in the movement of muscles. The disease is suspected to be an autoimmune disorder — the immune system attacks the myelin sheaths. While MS is usually strikes first in early adulthood, many other diseases that are due to myelin degeneration occur in infancy or early childhood.

## Across the Synapse

How is information transferred from one neuron to the next? Neurons communicate at their meeting points, called **synapses**; the small gaps separating the neurons are referred to as the synaptic space. These synapses are not merely gaps but are functional links between the two neurons. Signals are transferred in only one direction across the synapse. The neuron that transmits information when it fires is called the **presynaptic neuron**. The synaptic terminals of the presynaptic neuron are on one side of the synapse; the dendrites of the other neuron, the **postsynaptic neuron**, are on

the other side. Presynaptic and postsynaptic are relative adjectives; a postsynaptic neuron at one synaptic connection can be a presynaptic neuron at another synapse.

Synapses can be either chemical or electrical. An electrical synapse is what is often called a “gap junction,” in which the membranes of two neurons are continuous at tiny spots, making the cells electrically contiguous. Gap junctions, which are not unique to neurons, allow for even more rapid communication. No chemical intermediary is involved in an electrical synapse. In the case of chemical synapses, however, chemicals called **neurotransmitters** are released from a presynaptic neuron, and dock with receptor proteins on the postsynaptic neuron. Such binding causes the shape of the protein to change and ion channels to open, much like the voltage-gated channels open in response to membrane potential changes (**Fig. 3**). We will discuss neurotransmitters in more detail below. Neurons are typically separated by about twenty to thirty nanometers in chemical synapses. Electrical synapses are more rapid than chemical ones but chemical synapses are easier to modulate. In vertebrates and many invertebrates, chemical synapses are more common than are electrical ones.

The action of the presynaptic neuron is referred to as an “all or none” response. A neuron can only fire or not fire; there is no “slightly activated” signal from a neuron. Whether or not a neuron will fire an action potential — that is, send a signal down its axon to be received by other neurons — depends on how many inputs it is receiving. It also depends on the nature of each input signal — excitatory or inhibitory — at each synapse. The sort of “net total” result of those signals determines whether the neuron will become excited, or depolarized, enough to fire an action potential and release neurotransmitter from its axon terminals.

Also recall that a signal traveling through the brain often involves many neurons, each making so many connections. This interconnectedness gives rise to the extraordinary complexity of the brain. The activation of a single sensory neuron could quickly lead to the activation or inhibition of thousands of neurons.

## Neurotransmitters and Receptors

Neurotransmitters are usually small molecules, such as amino acids (e.g., glutamate and aspartate) and amines (e.g., dopamine, serotonin, and histamine). Some neurotransmitters stimulate neurons to fire, while others inhibit firing. The effect of the neurotransmitter comes about by its binding with receptor proteins on the membrane of the postsynaptic neuron. Each neurotransmitter binds specifically in a lock-and-key mechanism to its type of receptor. Neurons in different pathways will often have different types of receptors in a given family. For example, dopamine binds to dopamine receptors, but there are about a dozen subtly different dopamine receptors. Neurobiologists think that the human nervous system uses at least fifty neurotransmitters, but about ten carry out most neurotransmission. Many of these neurotransmitters are highly conserved in other organisms. Most neurons release only one type of neurotransmitter.

Neurotransmitters are released in a process called **exocytosis**. When the action potential reaches the end of an axon the depolarization causes calcium channels to open. The calcium causes **synaptic vesicles**

**Figure 3.** Synaptic vesicles fuse with the presynaptic membrane to release neurotransmitter into the synaptic space. Here, they bind with neurotransmitter receptors in the postsynaptic membrane.

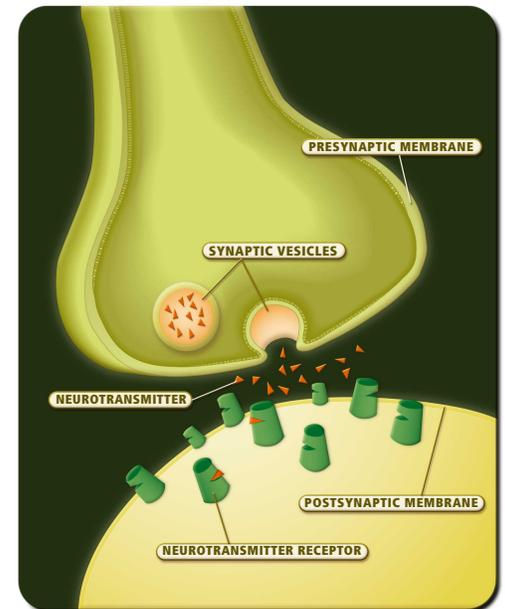


Photo-illustration — Bergmann Graphics

that carry the neurotransmitter to fuse with the cell membrane. This fusion allows the neurotransmitter to be released into the synapse. Although exocytosis occurs in many cell types, neurons use a specialized form in which calcium causes a chain of events that culminates in fusion of the vesicles.

There are two general categories of receptor proteins: **ionotropic** and **metabotropic**. Activation of ionotropic receptors causes membrane ion channels to open or close. In contrast, activation of metabotropic receptors involves an intracellular biochemical cascade. Such a cascade may end with the opening or closing of ion channels or other intracellular effects.

As long as the neurotransmitter remains in the synapse, it will continue to bind its receptors and stimulate the postsynaptic neuron. At some point the signal is no longer needed. Moreover, continual stimulation can injure some neurons. So, halting the stimulus is just as important as the appropriate starting of the stimulus. How does the neurotransmitter leave the synapse? There are several ways, such as diffusion away from the synapse or breakdown of the neurotransmitter by specific enzymes. Another common mode, called **reuptake**, involves specialized molecules present on the membrane of the presynaptic neuron. These molecules, called **neurotransmitter transporters**, have receptor sites that will bind to the neurotransmitter and actively transport it out of the synapse, back to the presynaptic neuron. That neuron can then reuse the neurotransmitter. The action of several drugs takes place at the reuptake stage.

## Neurotransmitters, Psychoactive Drugs, and the Reward Pathway

Drugs that have effects on the central nervous system are known as psychoactive drugs. The mode of actions of both therapeutic drugs (e.g., Ritalin, Prozac, and Paxil) and recreational drugs (e.g., alcohol, cannabis, cocaine, and nicotine) affect the firing of certain neurons by changes in various neurotransmitters or receptors. Not all drugs have specific modes of action; alcohol, for example, has many and varied effects. We will focus, however, on a few examples of those drugs that have specific effects.

Humans and many other animals engage in many activities from which they derive pleasure. Researchers working with various animals have shown that there are regions of the brain, such as the ventral tegmental area, that are more active when animals engage in pleasurable acts. When researchers stimulate these areas experimentally, the animals will perform various tasks in order to receive further stimulation. Hence, the neural pathway comprises those regions has been called the **reward pathway**.

Like many drugs, nicotine from tobacco products acts on the reward pathway. This drug, however, is unusual in that it directly affects the dopamine receptor in the reward pathway's neurons. Unlike the action of most drugs, no intermediary steps are involved: nicotine binds to the receptor and stimulates the postsynaptic neuron. The overstimulation of the postsynaptic cell, however, also has effects at the cellular level. Over time, it leads to a decrease in the number of dopamine receptors being expressed and inserted to the membrane, as well as a change in the shape of the cell. The reduction of receptors is

referred to as desensitization. When the nicotine is removed, because there are fewer receptors on the postsynaptic cell, more dopamine than normal is required for proper stimulation of postsynaptic neuron. Addiction can result because nicotine becomes needed just to maintain the normal stimulation of the postsynaptic cells.

Allelic variation at the dopamine receptor gene appears to affect one's likelihood of becoming addicted to nicotine. Individuals who have the A1 allele have fewer dopamine receptors than those that do not have the allele. These individuals also have more difficulty in quitting smoking and are more likely to exhibit other addictive and compulsive behaviors. The genetic components of many types of addiction are the topic of intensive research — and often heated debate.

Cocaine also works on dopamine and the reward pathway but does so in a different way. Recall that some neurotransmitters are normally taken up by the presynaptic neuron by reuptake receptors, or transporters, in the presynaptic membrane. (Fig. 4) The molecular structure of cocaine is such that it can block the binding site for dopamine on its reuptake receptor. Because this cell is now impaired in the reuptake of dopamine, an excess of dopamine builds up in the synapse. This excess leads to overstimulation of the postsynaptic neuron. Because the action is occurring in the reward pathway, overstimulation leads to euphoria. The effects of overstimulation of the postsynaptic cell by cocaine are much the same as those of nicotine: the reduction of the number of receptors leads to desensitization and the possibility of addiction.

**Figure 4.** Left: Dopamine in the synaptic space binds to dopamine receptors on the postsynaptic cell. Dopamine transporters in the presynaptic membrane take up the dopamine molecules from the synaptic cleft and return them to the presynaptic cell. Right: Cocaine blocks the reuptake of dopamine, leading to molecular changes that contribute to addiction.

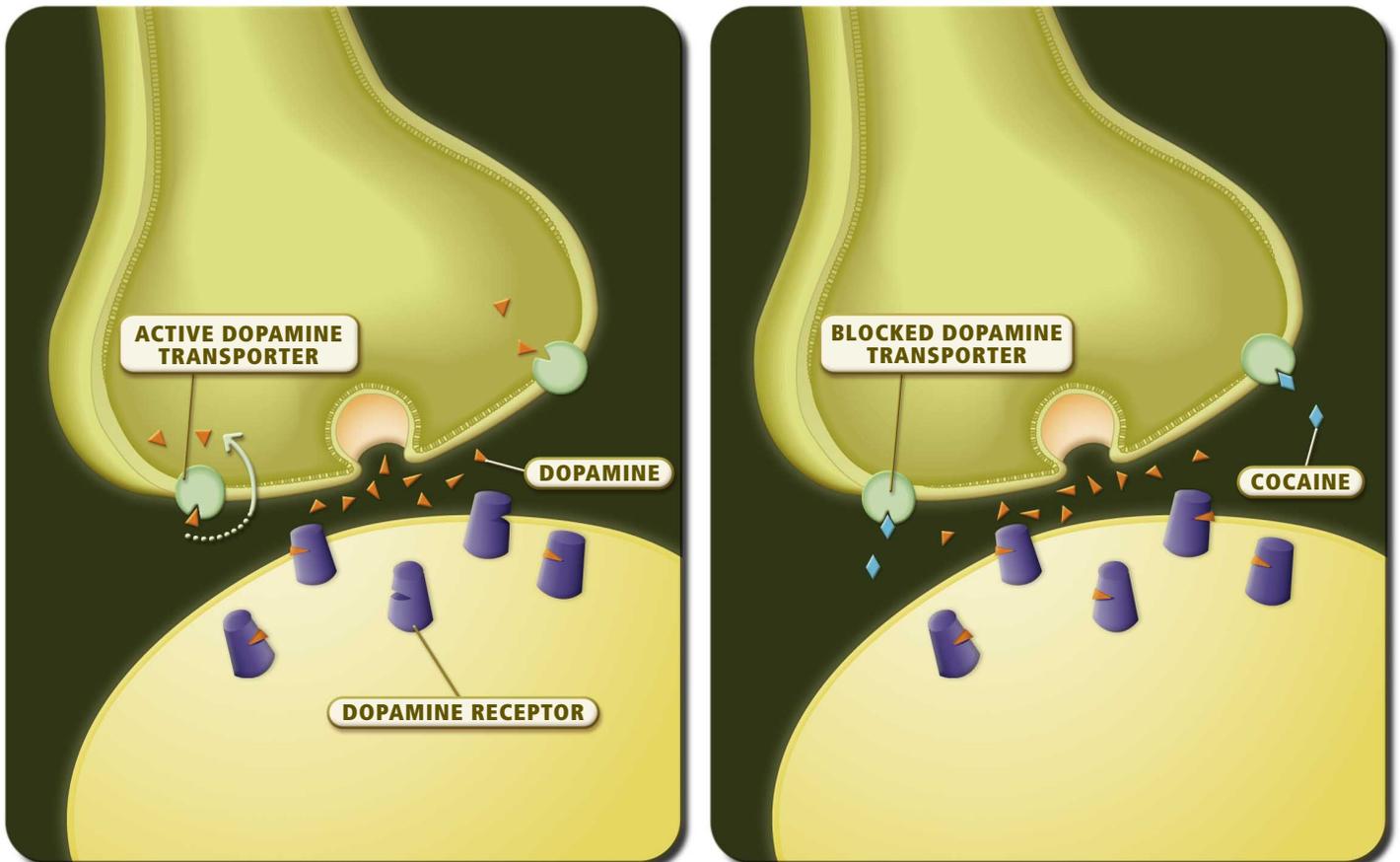


Photo-illustration — Bergmann Graphics

There have been concerns that Ritalin (methylphenidate), used for treatment of attention deficit and hyperactivity disorder (ADHD), is chemically similar to cocaine. Indeed, Ritalin increases dopamine levels by interfering with reuptake. Moreover, Ritalin and cocaine compete for the same receptor site. One crucial difference between these two drugs is that Ritalin acts much more slowly than cocaine. While cocaine's effects on dopamine levels occur within seconds, the response from Ritalin (when administered in pill form) takes about an hour. Some studies suggest that, far from leading to addiction, Ritalin treatment in childhood may be associated with decreased risk of drug and alcohol use later on. Other studies, however, suggest that Ritalin may be a gateway drug: by using it, teens may be more willing to experiment with other drugs. As of 2003 the consequences of Ritalin treatment remain unresolved. (**Fig. 5**)

**Figure 5.** The chemical structures of dopamine, Ritalin, and cocaine are structurally similar: they all bind at the dopamine transporter, affecting reuptake of dopamine.

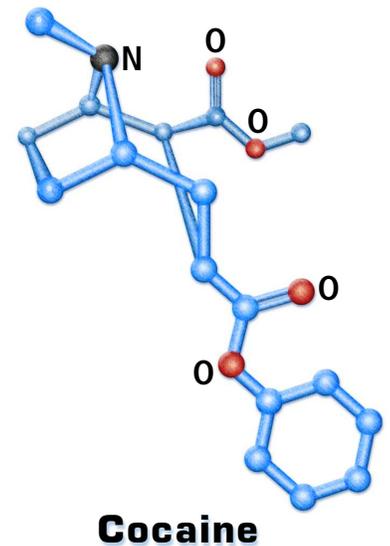
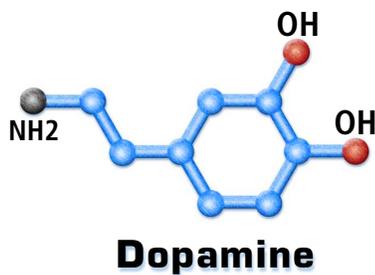


Illustration — Bergmann Graphics

## Prozac and Serotonin Reuptake

Soon after it was released to the market in 1988, Prozac (fluoxetine hydrochloride) became the most prescribed drug to treat depression. It and several other antidepressants inhibit the reuptake of serotonin, a neurotransmitter that affects mood, sleep, and appetite. These drugs are called selective serotonin reuptake inhibitors (SSRIs) because, unlike older antidepressants, they have little effect outside of serotonin reuptake. By inhibiting the reuptake of serotonin, Prozac and SSRIs increase the level of serotonin in the synapses. The increased levels of this neurotransmitter generally result in an improved mood. Depressed patients often had lower than normal levels of serotonin.

## Cannabis, the Cannabinoid Receptors, and Endocannabinoids

The active ingredient of marijuana, from the cannabis plant, is THC (delta-9-tetrahydrocannabinol). This chemical exerts its effects on the brain by binding to receptors called the cannabinoid receptors. Scientists have identified two cannabinoid receptors (CB1 and CB2), and evidence suggests that there may be others. Although CB1 is found in many regions of the brain, CB2 is present only in certain cells

of the immune system. Because the receptor is present in several brain regions, THC can have manifold effects. For instance, THC may affect memory formation. CB1 is prevalent in the hippocampus, a region of the brain strongly associated with memory. By binding to and activating CB1, THC decreases activity of neurons in the **hippocampus** and interferes with the proper function of that region, which may translate to an interference with memory formation.

The human body does not produce THC, so why would there be receptors that can bind it? During the 1990s researchers discovered that the body makes chemicals, such as anandamide, that can bind to the cannabinoid receptors. The function of these chemicals, called endocannabinoids, and their receptors is still unknown. To investigate the role of the CB1 receptor, scientists have studied mutant mice that lack the receptor. Compared with normal mice, these mice have a decreased appetite, are less active, and have a reduced lifespan; however, the mice have an enhanced memory.

The CB receptors have recently been associated with some beneficial actions, such as pain relief and extinguishing some fear behaviors. THC has even been prescribed as medication in some states for pain relief for various diseases, including glaucoma, AIDS, and cancer.<sup>3</sup>

## The Molecular Basis of Learning and Memory

It is clear that an understanding of mechanisms at the level of the synapse explains changes in our behaviors, like movements. But what about longer-term changes associated with learning and memory? Can they be understood in molecular terms, too? Memory, and thus learning, involves molecular changes in the brain. During the last few decades, researchers have started to map the molecular processes involved in memory formation. They have been increasingly able to link the ability to remember with physical changes in the structure of neurons.

One important change that occurs in memory formation is **long-term potentiation (LTP)**. This phenomenon involves the long-term modification of the synaptic communication. Under normal circumstances the rate at which a postsynaptic neuron fires depends on how much stimulation it receives from presynaptic neurons. Once the increased stimulation has stopped, the postsynaptic neuron will return to its normal rate of firing. In LTP, however, the postsynaptic neuron will continue to fire at an elevated rate, even after the increased stimulation has subsided. It seems to become more sensitive — or gives a bigger reaction by firing more action potentials — to a given stimulus. How does this happen?

Glutamate is the neurotransmitter involved in LTP. Glutamate can bind to several different types of ionotropic receptors, including the NMDA- (N-methyl-D-aspartate) and AMPA- (amino-3-hydroxy-5-methyl-4-isoxazolepropionate) type glutamate receptors, each of which opens a specific type of channel within the receptor proteins. Both channels are involved in memory formation. The NMDA channel requires both glutamate and depolarization from another source to open. Why? The molecular mechanism is as follows. Normally, at negative potentials, positively-charged magnesium ions plug the pore of the NMDA channel. While glutamate may “open” the pore, the ions cannot travel

through the channel due to the magnesium block. When the membrane is depolarized, however, the inside of the cell becomes more positive, and the magnesium ions are no longer driven into the channel. Thus, the block is relieved, allowing sodium and calcium ions to flow in.

So, this mechanism allows the NMDA-type glutamate receptor to act as a “coincidence detector.” When the neuron receives input from only one source — another neuron — glutamate binds to and opens both NMDA- and AMPA-type receptors. (**Fig. 6**) Because the neurotransmitter arrives at a resting, negatively charged, postsynaptic membrane, magnesium ions prevent flow through NMDA channels. When, however, stimulation of a neuron occurs simultaneously from more than one source — say several other neurons — some glutamate will bind NMDA receptors in parts of the neuron that are already depolarized, or less negatively charged.

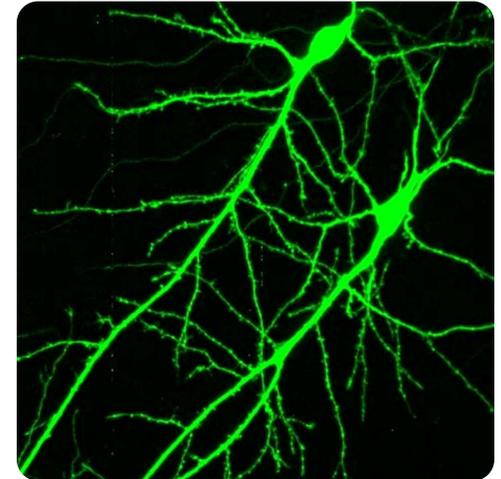
Where does this voltage change come from? Recall that once an action potential has started, it spreads from its source throughout the entire membrane of the neuron in a wave-like fashion; thus, other dendrites may be “pre-depolarized” before glutamate binds. In this case, the block by magnesium is relieved and the NMDA channel also passes ions. While AMPA channels can pass only sodium ions in, NMDA channels also pass calcium. This calcium permeability gives the NMDA channel its ability to trigger LTP.

Now that we have examined the requirements for LTP, what is the effect? When calcium ions rush in, they set off an intracellular signaling cascade that can involve dozens of molecules. Speculation about the identity and functions of these molecules has been the subject of intense scientific inquiry since the early 1990s — it was perhaps the most studied aspect of neuroscience during that “decade of the brain.”

So how could this intricate electrical mechanism act to form new memories? LTP, like learning, is not just dependent on increased stimulation from one particular neuron but on a repeated stimulus from several sources. It is thought that when a particular stimulus is repeatedly presented, so is a particular circuit of neurons. With repetition the activation of that circuit results in learning. Recall that the brain is intricately complicated. Rather than a one-to-one line of stimulating neurons, it involves a very complex web of interacting neurons. But it is the molecular changes occurring between these neurons that appear to have global effects. LTP can lead to strengthened synapses in a variety of ways. One such way, as discussed in the video, is by the **phosphorylation** of glutamate receptor channels, which is accomplished by a calcium-triggered signaling cascade. This results in those channels passing more ions with subsequent stimulation, strengthening the signal to and from the neuron.

But more permanent changes — long-term memory — require the synthesis of new proteins. In a variety of organisms, including flies (*Drosophila*) and humans, one enzyme, CREB (cyclic-AMP response element binding protein), seems to be involved in the steps that facilitate this new protein expression. When calcium flows in through NMDA channels, one of the molecules it activates is CREB. In turn, activated CREB acts as a **transcription factor** (see the *Genes and Development* unit) that activates the expression of other genes. This

**Figure 6.** Two hippocampal neurons, labeled with green fluorescent protein, viewed with confocal microscopy. Such neurons release and sense glutamate, and engage in long-term potentiation (LTP). Note the synaptic connections between the lateral processes of the two neurons.



Courtesy of Rick Huganir, PhD.

gene expression can lead to the production of more ion channel receptors, as well as structural proteins like actin, which cement the synaptic connection between two repeatedly communicating neurons.

Mutant mice lacking the NMDA receptors show severe deficiencies in memory tasks. On the other hand, researchers have genetically engineered (see the GMOS unit) mice that have more of the NMDA receptors. These mice, dubbed “smart mice” by the popular press, are substantially better at several memory tasks than are normal mice.

## Memory and the Hippocampus

Psychologists have long argued that there are many different types of memory. These can be classified by many criteria, based on decades of experimental research and the different memory defects seen in people who have suffered brain damage. Scientists have agreed that memory can be viewed in temporal terms; that is, there is a short-term memory, with a limited capacity for about a dozen items, and a long-term memory, to which these items are presumably transferred for “storage.” Short-term memory seems to be much more vulnerable to loss due to trauma than does long-term memory: people may even lose the ability to form new memories, while their ability to remember their entire lives before an accident remains intact. This memory defect is exemplified in the movie *Memento* (2000), in which a widower avenges his wife’s murder — during which he suffered brain damage — over and over again. Such individuals with this condition of “anterograde amnesia” usually have severe damage to their hippocampus. As Kempermann points out, the hippocampus is not the equivalent of the brain’s hard drive but rather a gateway, “a structure, through which all information must pass, before it can be memorized.”<sup>4</sup>

It is widely agreed that while the hippocampus is undeniably important for memory, the “recording” of information into long-term memory involves plasticity, or physical changes, in multiple regions throughout the entire nervous system. Another interesting distinction that scientists have made in types of memory is between declarative memory, which allows you to remember facts and is extremely complex, and reflexive memory, which usually consists of learning by repetition and often involves motor learning. While declarative memory can be reported, reflexive memory is exhibited by performance of a task and cannot be expressed verbally. It is now thought that the two types of memory may involve two entirely different neuronal circuits.

The hippocampus plays a major role in spatial learning and memory in a number of animals. Research with black-capped chickadees and other species of birds has shown that when the hippocampus is removed, the birds still store food but cannot recall where they stored it. Moreover, bird species that rely heavily on stored food as a winter resource in general have larger hippocampi than those species that don’t.

Studies of cab drivers in London have provided fascinating information about the role that the hippocampus plays in spatial memory. London cab drivers are known for their navigational skills and knowledge of the streets of London. To learn how to navigate the streets of the city, would-be cab drivers undergo “the Knowledge,” a rigorous training that can take two years to complete. Recent studies using magnetic resonance imaging (MRI) demonstrate that the hippocampi of the

London cab drivers are somewhat different. Specifically, the posterior region is significantly larger and the anterior region is significantly smaller in the cabbies when compared with control subjects. Other studies have found that the posterior region is active during tasks involving spatial memory. It is possible that the cabbies come disproportionately from those individuals with excellent spatial memories and corresponding larger posterior regions of the hippocampus. There is further evidence, however, that suggests that the memory work of the cabbies has altered their hippocampi. Those cab drivers that have been working the longest tend to have larger posterior hippocampi than more recently hired cabbies. Furthermore, other imaging studies show that the right hippocampus is activated in the cab drivers when they are asked to remember complex travel routes but not when they are asked to provide information about famous landmarks.<sup>5</sup>

## Neuronal Stem Cells

What neuronal processes have led to the changes in the hippocampi of London taxi drivers? Perhaps this is achieved by neurons migrating from one region to the posterior hippocampus? Another intriguing possibility is that the changes are the result of new neurons going to the region.

New neurons? Don't we have our complete store of neurons by early childhood? That previous dominant paradigm had been found incorrect. In the past two decades, researchers have shown that neurons are continually produced in a variety of animals, including humans. It isn't that neurons divide. They don't. Instead, the brain maintains a reservoir of stem cells that are capable of generating new neurons (neurogenesis). One area of the brain where stem cells have been found is the hippocampus.

The discovery of stem cells and neurogenesis began with basic research with songbirds. During each breeding season male songbirds need to recall their mating song. Starting in the 1980s researchers noted that the number of neurons in certain areas of the brain (especially the hippocampus) would increase in male birds around the start of the breeding season. The number of neurons in these areas would decrease after the mating season. This striking evidence led other researchers to look for neurogenesis in the brains of mammals. Studies on rats found substantial neurogenesis. In one part of the hippocampus alone nearly 10,000 new neurons are generated each day in adult rats. Starting in the 1990s Elizabeth Gould of Princeton University found that the adult brains of several species of monkeys also undergo considerable neurogenesis.

Following these animal studies researchers examined whether humans have the capacity for neurogenesis. They studied postmortem brain tissue from humans, using various stains to determine whether new neurons were being generated from dividing progenitor cells. They were able to find such new neurons in the hippocampus, showing that neurogenesis proceeds throughout life in at least some regions of the human brain.

Engaging in mental and physical activity is one important way elderly people can maintain their mental acuity. This aspect of conventional wisdom has been vindicated by medical research. Mental and physical activity reduces the risk of neurodegenerative disorders and improves

the prognosis of stroke patients. Yet, we know little about the molecular mechanisms behind this effect. Studies in mice of neurogenesis in the hippocampus, however, point to one possible reason for why activity keeps the mind sharp. Mice who were exposed to an enriched environment for the second half of their lives showed a dramatic increase in neurogenesis in the hippocampus as compared with control subjects. The hippocampi from the mice that received the enriched treatment also appeared like those of younger animals. These results strongly suggest that activity maintains the proper function of the brain by increasing neurogenesis in the hippocampus.

Elizabeth Gould and other researchers studying neurogenesis think that the new neurons generated in the hippocampus are involved in modulation of the stress response as well as learning. There are some complications, however. Learning enhances neurogenesis but only under certain conditions. Moreover, experimental blockage of neurogenesis interferes with some types of learning but not others.

Our understanding of neurogenesis remains far from complete. Yet, tremendous progress has been made during the last two decades and further progress is expected. In addition to what these studies tell us about how the brain works, they may also pave the way toward treatment of degenerative diseases like Alzheimer's and Parkinson's as well as brain trauma.

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## Further Reading

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### Books

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*Building from case examples, a neurobiologist and a neurosurgeon describe the workings of the brain.*

Drickamer, L. C., S. H. Vessy, and E. M. Jakob. 2002. *Animal behavior: Mechanisms, ecology, and evolution*. 5th ed. McGraw-Hill.

*A university-level textbook on animal behavior that has an excellent section on the neurobiology of behavior.*

Timmons, C. R., and L. W. Hamilton. *Drugs, brains & behavior*.  
[www.rci.rutgers.edu/~lwh/drugs/](http://www.rci.rutgers.edu/~lwh/drugs/)

*A short e-book detailing the neuropharmacological effects of drugs.*

### Article

Sullivan, J. M. 2002. Cannabinoid receptors. *Curr. Biol.* 12:R681.

*A short guide to recent research on cannabinoids and their receptors.*

## Glossary

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**Action potential.** The nerve impulse, or “firing,” of a neuron. A traveling wave of depolarized voltage that is propagated along a neuron. Results in the release of neurotransmitter and the movement of information to another neuron.

**Depolarization.** The state in which the inside of a neuron becomes more positive in voltage than it is at rest.

**Hippocampus.** A region of the brain associated with memory formation.

**Hyperpolarization.** A state in which the membrane potential is more negative than is the resting potential; occurs transiently at the end of an action potential.

**Ionotropic receptors.** Receptors for which neurotransmitter binding results directly in an ion channel opening or closing.

**Long-term potentiation.** An enduring increase in the strength of the connection between two neurons, which results from repeated stimulation of a given input pathway.

**Membrane potential.** The difference in voltage between the inside and the outside of a neuron; the outside is always zero.

**Neurogenesis.** The formation of new neurons from precursor stem cells.

**Neurotransmitter.** A molecule that travels across the synapse and binds to its receptor on the postsynaptic neuron, influencing its probability of firing.

**Phosphorylation.** The addition of a phosphate group to a molecule, such as a protein.

**Postsynaptic neuron.** At a given synapse, the postsynaptic neuron is the receiving neuron at its dendritic end.

**Presynaptic neuron.** At a given synapse, the presynaptic neuron is the transmitting neuron, its axonal synaptic terminal forms the synapse.

**Resting potential.** The resting membrane potential of a neuron; it is about -70 mV.

**Reuptake.** The recapture of neurotransmitters from the synapse back into the presynaptic neuron; accomplished by transporters.

**Reward pathway.** A pathway in the brain that is stimulated when an animal is engaged in pleasurable activities.

**Synapse.** A functional connection between two neurons where information can be exchanged in the form of electrical or chemical energy.

**Transcription factor.** A protein that influences transcription of another gene by binding to DNA.

**Voltage-gated channels.** Ion channels in the cell membrane that open or close in response to changes in the membrane voltage.

**X-ray crystallography.** A method for determining the structure of a molecule, such as a protein, based on the diffraction pattern resulting from focused X-ray radiation onto pure crystals of the molecule.