

Brain Facts

THE NEURON

A SPECIALIZED CELL designed to transmit information to other nerve cells, muscle, or gland cells, the neuron is the basic working unit of the brain. The brain is what it is because of the structural and functional properties of interconnected neurons. The brain contains between 1 billion and 100 billion neurons, depending on the species.

The neuron consists of a *cell body*, *dendrites*, and an *axon*. The cell body contains the nucleus and cytoplasm. The electrically excitable axon extends from the cell body and often gives rise to many smaller branches before ending at *nerve terminals*. *Dendrites* extend from the neuron cell body and receive messages from other neurons. *Synapses* are the contact points where one neuron communicates with another. The dendrites and cell body are covered with synapses formed by the ends of axons from other neurons.

Neurons signal by transmitting electrical impulses along their axons, which can range in length from a tiny fraction of an inch to three feet or more. Many axons are covered with a layered *myelin* sheath, which speeds the transmission of electrical signals along the axon. This sheath is made of specialized cells called oligodendrocytes in the brain and Schwann cells in the peripheral nervous system.

Nerve impulses involve the opening and closing of *ion channels*, which are selectively permeable, water-filled molecular tunnels that pass through the cell membrane and allow ions — electrically charged atoms — or small molecules to enter or leave the cell. The flow of these ions creates an electrical current that produces tiny voltage changes across the neuron's cell membrane.

The ability of a neuron to generate an electrical impulse depends on a difference in charge between the inside and outside of the cell. When a nerve impulse begins, a dramatic reversal in the electrical potential occurs at one point on the cell's membrane, when the neuron switches from an internal negative charge to a positive charge state. The change, called an *action potential*, then passes along the membrane of the axon at speeds up to several hundred miles per hour. In this way, a neuron may be able to fire impulses multiple times every second.

Upon reaching the end of an axon, these voltage changes trigger the release of *neurotransmitters*, the brain's chemical messengers. Neurotransmitters are released at nerve terminals, diffuse across the intrasynaptic space, and bind to receptors on the surface of the target cell (often another neuron but also possibly a muscle or gland cell).

These receptors act as on-and-off switches for the next cell. Each receptor has a distinctly shaped region that selectively recog-

nizes a particular chemical messenger. A neurotransmitter fits into this region in much the same way that a key fits into a lock. And when the transmitter is in place, this interaction alters the target cell's membrane potential and triggers a response, such as the generation of an action potential, contraction of a muscle, stimulation of enzyme activity, or inhibition of neurotransmitter release from the target cell.

Increased understanding of neurotransmitters in the brain and of the action of drugs on these chemicals — gained largely through animal research — guides one of the largest fields in neuroscience. Armed with this information, scientists hope to understand the circuits responsible for disorders such as Alzheimer's disease and Parkinson's disease. Sorting out the various chemical circuits is vital to understanding how the brain stores memories, why sex is such a powerful motivation, and what makes up the biological basis of mental illness.

Neurotransmitters and neuromodulators

Acetylcholine The first neurotransmitter, identified about 75 years ago, was acetylcholine (ACh). This chemical is released by neurons connected to voluntary muscles (causing them to contract) and by neurons that control the heartbeat. ACh also serves as a transmitter in many regions of the brain.

ACh is formed at the axon terminals. When an action potential arrives at the nerve terminal, the electrically charged calcium ion rushes in, and ACh is released into the synapse, where it attaches to ACh receptors on the target cells. On voluntary muscles, this opens sodium channels and causes the muscle to contract. ACh is then broken down by the enzyme acetylcholinesterase and resynthesized in the nerve terminal. Antibodies that block one type of receptor for ACh cause *myasthenia gravis*, a disease characterized by fatigue and muscle weakness.

Much less is known about ACh in the brain. Recent discoveries suggest, however, that it may be critical for normal attention, memory, and sleep. Because ACh-releasing neurons die in Alzheimer's patients, finding ways to restore this neurotransmitter is one goal of current research. Drugs that inhibit acetylcholinesterase are presently the main drugs used to treat Alzheimer's disease.

Amino acids Amino acids, widely distributed throughout the body and the brain, serve as the building blocks of proteins. Certain amino acids can also serve as neurotransmitters in the brain.

The neurotransmitters *glycine* and *gamma-aminobutyric acid* (GABA) inhibit the firing of neurons. The activity of GABA is

increased by *benzodiazepines* (e.g., Valium) and by anticonvulsant drugs. In Huntington's disease, a hereditary disorder that begins during midlife, the GABA-producing neurons in brain centers that coordinate movement degenerate, thereby causing uncontrollable movements.

Glutamate and *aspartate* act as excitatory signals, activating, among others, *N-methyl-d-aspartate* (NMDA) receptors, which have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in a developing animal. The stimulation of NMDA receptors may promote beneficial changes in the brain, whereas overstimulation can cause nerve cell damage or cell death in trauma and stroke.

Key questions remain about the NMDA receptor's precise structure, regulation, location, and function. Developing drugs to block or stimulate activity at NMDA receptors holds promise for improving brain function and treating neurological and psychiatric disorders.

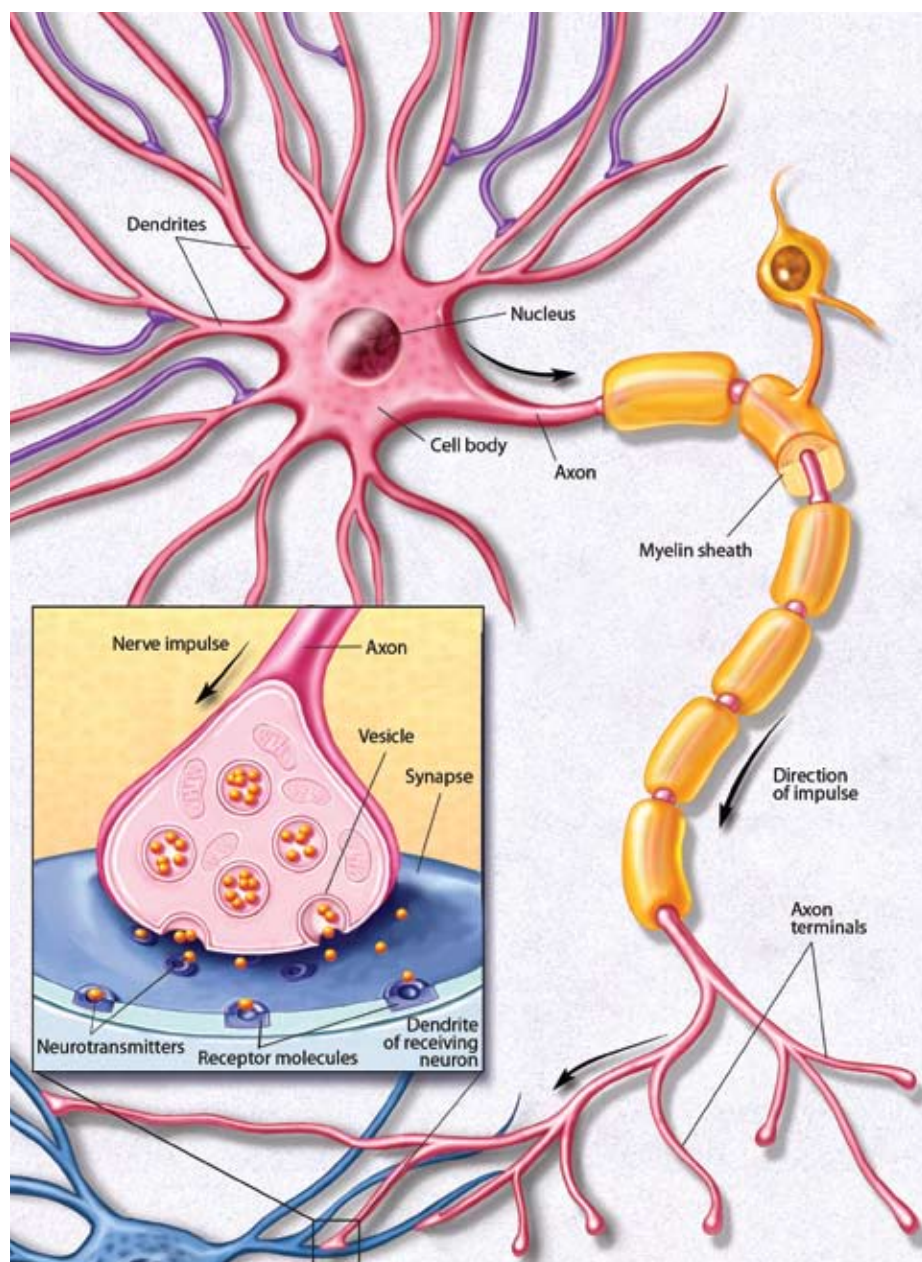
Catecholamines *Dopamine* and *norepinephrine* are widely present in the brain and peripheral nervous system. Dopamine is present in three principal circuits in the brain; these circuits control movement, cause psychiatric symptoms such as psychosis, and regulate hormonal responses.

The dopamine circuit that regulates movement has been directly linked to disease. Due to dopamine deficits in the brain,

people with Parkinson's disease show symptoms including muscle tremors, rigidity, and difficulty in moving. Thus, medical scientists have found that the administration of *levodopa*, a substance from which dopamine is synthesized, is an effective treatment for Parkinson's, allowing patients to walk and perform skilled movements more successfully.

Another dopamine circuit is thought to be important for cognition and emotion; abnormalities in this system have been implicated in schizophrenia. Because drugs that block certain dopamine receptors in the brain are helpful in diminishing psychotic symptoms, learning more about dopamine is important to understanding mental illness.

In a third circuit, dopamine regulates the endocrine system. Dopamine directs the hypothalamus to manufacture hormones and hold them in the pituitary gland for release into the bloodstream or to trigger the release of hormones held within cells in the pituitary.



NEURON. A neuron fires by transmitting electrical signals along its axon. When signals reach the end of the axon, they trigger the release of neurotransmitters that are stored in pouches called vesicles. Neurotransmitters bind to receptor molecules on the surfaces of adjacent neurons. The point of virtual contact is known as the synapse.

Nerve fibers containing norepinephrine are present throughout the brain. Deficiencies in this transmitter occur in patients with Alzheimer's disease, Parkinson's disease, and *Korsakoff's syndrome*, a cognitive disorder associated with chronic alcoholism. Thus, researchers believe norepinephrine may play a role in both learning and memory. Norepinephrine is also secreted by the sympathetic nervous system in the periphery to regulate heart rate and blood pressure. Acute stress increases the release of norepinephrine from sympathetic nerves and the adrenal medulla.

Serotonin This neurotransmitter is present in the brain and other tissues, particularly blood platelets and the lining of the digestive tract. In the brain, serotonin has been implicated in sleep, mood, depression, and anxiety. Because serotonin controls the different switches affecting various emotional states, scientists believe these switches can be manipulated by analogs, chemicals with molecular structures similar to that of serotonin. Drugs that alter serotonin's action, such as *fluoxetine*, relieve symptoms of depression and obsessive-compulsive disorder.

Peptides These are chains of amino acids linked together. Peptides differ from proteins, which are much larger and have more complex combinations of amino acids.

In 1973, scientists discovered receptors for opiates on neurons in several regions of the brain, suggesting that the brain must make substances very similar to opium. Shortly thereafter, scientists made their first discovery of an opiate produced by the brain that resembles morphine, an opium derivative used medically to kill pain. They named it *enkephalin*, literally meaning "in the head." Soon after, other types of opioid peptides, *endorphins*, were discovered. Endorphins, whose name comes from endogenous morphine, act like opium or morphine to kill pain or cause sleepiness.

The precise role of the naturally occurring opioid peptides is unclear. A simplistic hypothesis is that they are released by brain neurons in times of stress to minimize pain and enhance adaptive behavior. The presence of opioid peptides may explain, for example, why injuries received during the stress of combat are often not noticed until hours later. Neurons containing these opioid peptides, however, are not limited to pain-sensing circuits.

Opioids and their receptors are closely associated with pathways in the brain that are activated by painful or tissue-damaging stimuli. These signals are transmitted to the *central nervous system* — the brain and spinal cord — by special sensory nerves, small myelinated fibers, and tiny unmyelinated *C fibers*. Scientists have discovered that some *C fibers* contain a peptide called *substance P* that causes the sensation of burning pain. The active component of chili peppers, *capsaicin*, causes the release of substance P.

Trophic factors Researchers have discovered several small proteins in the brain that are necessary for the development, function, and survival of specific groups of neurons. These small proteins are made in brain cells, are released locally in the brain, and bind to receptors expressed by specific neurons. Researchers also have identified genes that code for receptors and are involved in the signaling mechanisms of trophic factors. These findings are expected to result in a greater understanding of how trophic factors work in the brain. This information should also prove useful for the design of new therapies for brain disorders of development and for degenerative diseases, including Alzheimer's disease and Parkinson's disease.

Hormones In addition to the nervous system, the *endocrine system* is a major communication system of the body. While the nervous system uses neurotransmitters as its chemical signals, the endocrine system uses hormones for its chemical signals. The pancreas, kidneys, heart, adrenal glands, gonads, thyroid, parathyroid, thymus, and pituitary gland are sources of hormones. The endocrine system works in large part through the pituitary gland, which secretes hormones into the blood. Because fragments of endorphins are released from the pituitary gland into the bloodstream, they might also function as endocrine hormones. This system is very important for the activation and control of basic behavioral activities such as sex, emotion, responses to stress, and the regulation of body functions, including growth, reproduction, energy use, and metabolism. Actions of hormones show the brain to be very malleable and capable of responding to environmental signals.

The brain contains receptors for thyroid hormones and the six classes of steroid hormones — *androgens*, *estrogens*, *progestins*, *glucocorticoids*, *mineralocorticoids*, and *vitamin D*. The receptors are found in selected populations of neurons in the brain and relevant organs in the body. Thyroid and steroid hormones bind to receptor proteins that in turn bind to DNA and regulate the action of genes. This can result in long-lasting changes in cellular structure and function.

The brain has receptors for many hormones; for example, the metabolic hormones *insulin*, insulinlike growth factor, *ghrelin*, and *leptin*. These hormones are taken up from the blood and act to affect neuronal activity and certain aspects of neuronal structure.

In response to stress and changes in our *biological clocks*, such as day and night cycles and jet lag, hormones enter the blood and travel to the brain and other organs. In the brain, hormones alter the production of gene products that participate in synaptic neurotransmission as well as the structure of brain cells. As a result, the circuitry of the brain and its capacity for neurotransmission are changed over a course of hours to days. In this way, the brain adjusts its performance and control of behavior in response to a changing environment. Hormones are important agents of protection and adaptation, but stress

and stress hormones, such as the glucocorticoid cortisol, can also alter brain function, including learning. Severe and prolonged stress can cause permanent brain damage.

Reproduction in females is a good example of a regular, cyclic process driven by circulating hormones: The neurons in the hypothalamus produce *gonadotropin-releasing hormone* (GnRH), a peptide that acts on cells in the pituitary. In both males and females, this causes two hormones — the *follicle-stimulating hormone* (FSH) and the *luteinizing hormone* (LH) — to be released into the bloodstream. In males, these hormones are carried to receptors on cells in the testes, where they release the male hormone testosterone, an androgen, into the bloodstream. In females, FSH and LH act on the ovaries and cause the release of the female hormones estrogen and progesterone. Testosterone, estrogen, and progesterone are often referred to as sex hormones.

In turn, the increased levels of testosterone in males and estrogen in females act back on the hypothalamus and pituitary to decrease the release of FSH and LH. The increased levels of sex hormones also induce changes in cell structure and chemistry that lead to an increased capacity to engage in sexual behavior. Sex hormones also exert widespread effects on many other functions of the brain such as attention, motor control, pain, mood, and memory.

Sexual differentiation of the brain is caused by sex hormones acting in fetal and early postnatal life, although recent evidence points to genes on the Y chromosome contributing to this process. Scientists have found statistically and biologically significant differences between the brains of men and women that are similar to sex differences found in experimental animals. These include differences in the size and shape of brain structures in the hypothalamus and the arrangement of neurons in the cortex and hippocampus. Sex differences go well beyond sexual behavior and reproduction and affect many brain regions and functions, ranging from mechanisms for perceiving pain and dealing with stress to strategies for solving cognitive problems. Although differences exist, the brains of men and women are more similar than they are different.

Anatomical differences have also been reported between the brains of heterosexual and homosexual men. Research suggests that hormones and genes act early in life to shape the brain in terms of sex-related differences in structure and function, but scientists are still putting together all the pieces of this puzzle.

Gases Scientists identified a new class of neurotransmitters that are gases. These molecules — *nitric oxide* and *carbon monoxide* — do not act like other neurotransmitters. Being gases, they are not stored in any structure, certainly not in synaptic storage structures. Instead, they are made by enzymes as they are needed and released from neurons by diffusion. Rather than acting at receptor sites,

these gases simply diffuse into adjacent neurons and act upon chemical targets, which may be enzymes.

While exact functions for carbon monoxide have not been determined, nitric oxide has already been shown to play several important roles. For example, nitric oxide neurotransmission governs erection in the penis. In nerves of the intestine, it governs the relaxation that contributes to the normal movements of digestion. In the brain, nitric oxide is the major regulator of the intracellular messenger molecule — *cyclic GMP*. In conditions of excess glutamate release, as occurs in stroke, neuronal damage following the stroke may be attributable in part to nitric oxide.

Second messengers

Substances that trigger biochemical communication within cells, after the action of neurotransmitters at their receptors, are called second messengers; these intracellular effects may be responsible for long-term changes in the nervous system. They convey the chemical message of a neurotransmitter (the first messenger) from the cell membrane to the cell's internal biochemical machinery. Second-messenger effects may endure for a few milliseconds to as long as many minutes.

An example of the initial step in the activation of a second-messenger system involves *adenosine triphosphate* (ATP), the chemical source of energy in cells. ATP is present throughout the cytoplasm of all cells. For example, when norepinephrine binds to its receptors on the surface of the neuron, the activated receptor binds a G protein on the inside of the membrane. The activated G protein causes the enzyme *adenylyl cyclase* to convert ATP to *cyclic adenosine monophosphate* (cAMP). The second messenger, cAMP, exerts a variety of influences within the cell, ranging from changes in the function of ion channels in the membrane to changes in the expression of genes in the nucleus, rather than acting as a messenger between one neuron and another.

Second messengers also are thought to play a role in the manufacture and release of neurotransmitters and in intracellular movements and carbohydrate metabolism in the *cerebrum* — the largest part of the brain, consisting of two hemispheres — as well as the processes of growth and development. In addition, direct effects of second messengers on the genetic material of cells may lead to long-term alterations in cellular functioning and ultimately in behavior.