The Neuron
BY CHARLES F. STEVENS

It is the individual nerve cell, the building block of the brain. It transmits nerve impulses over a single long fiber (the axon) and receives them over numerous short fibers (the dendrites).

Neurons, or nerve cells, are the building blocks of the brain. Although they have the same genes, the same general organization and the same biochemical apparatus as other cells, they also have unique features that make the brain function in a very different way from, say, the liver. The important specializations of the neuron include a distinctive cell shape, an outer membrane capable of generating nerve impulses, and a unique structure, the synapse, for transferring information from one neuron to the next.

The human brain is thought to consist of 10^11 neurons, about the same number as the stars in our galaxy. No two neurons are identical in form. Nevertheless, their forms generally fall into only a few broad categories, and most neurons share certain structural features that make it possible to distinguish three regions of the cell: the cell body, the dendrites, and the axon. The cell body contains the nucleus of the neuron and the biochemical machinery for synthesizing enzymes and other molecules essential to the life of the cell. Usually the cell body is roughly spherical or pyramid shaped. The dendrites are delicate tube-like extensions that tend to branch repeatedly and form a bushy tree around the cell body. They provide the main physical surface on which the neuron receives incoming signals. The axon extends away from the cell body and provides the pathway over which signals can travel from the cell body for long distances to other parts of the brain and the nervous system. The axon differs from the dendrites both in structure and in the properties of its outer membrane. Most axons are longer and thinner than dendrites and exhibit a different branching pattern: whereas the branches of dendrites tend to cluster near the cell body, the branches of axons tend to arise at the end of the fiber where the axon communicates with other neurons.

The functioning of the brain depends on the flow of information through elaborate circuits consisting of networks of neurons. Information is transferred from one cell to another at specialized points of contact: the synapses. A typical neuron may have anywhere from 1,000 to 10,000 synapses and may receive information from something like 1,000 other neurons. Although synapses are most often made between the axon of one cell and the dendrite of another, there are other kinds of synaptic junctions: between axon and axon, between dendrite and dendrite and between axon and cell body.

At a synapse the axon usually enlarges to form a terminal button, which is the information-delivering part of the junction. The terminal button contains many spherical structures called synaptic vesicles, each of which can hold several thousand molecules of chemical transmitter. On the arrival of a nerve impulse at the terminal button, some of the vesicles discharge their contents into the narrow cleft that separates the button from the membrane of another cell's dendrite, which is designed to receive the chemical message. Hence information is relayed from one neuron to another by means of a transmitter. The "firing" of a neuron—the generation of nerve impulses—reflects the activation of hundreds of synapses by impinging neurons. Some synapses are excitatory in that they tend to promote firing, whereas others are inhibitory and so are capable of canceling signals that otherwise would excite a neuron to fire.

Although neurons are the building blocks of the brain, they are not the only kind of cell in it. For example, oxygen and nutrients are supplied by a dense network of blood vessels. There is also a need for connective tissue, particularly at the surface of the brain. A major class of cells in the central nervous system is the glial cells, or glia. The glia occupy essentially all the space in the nervous system not taken up by the neurons themselves. Although the function of the glia is not fully understood, they provide structural and metabolic support for the delicate meshwork of the neurons.

One other kind of cell, the Schwann cell, is ubiquitous in the nervous system. All axons appear to be jacketed by Schwann cells. In some cases the Schwann cells simply enclose the axon. In other cases, the Schwann cell wraps itself around the axon in the course of embryonic development, giving rise to the multiple dense layers of insulation known as myelin. The myelin sheath is interrupted every millimeter or so along the axon by narrow gaps called the nodes of Ranvier. In axons that are sheathed in this way the nerve impulse travels by jumping from node to node, where the extracellular fluid can make direct contact with the cell membrane. The myelin sheath seems to have evolved as a means of conserving the neuron's metabolic energy. In general myelinated nerve fibers conduct nerve impulses faster than unmyelinated fibers.

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other side, the interior of the axon is about 70 millivolts negative with respect to the exterior. In their classic studies of nerve-impulse transmission in the giant axon of the squid a quarter of a century ago, A. L. Hodgkin, A. F. Huxley and Bernard Katz of Britain demonstrated that the propagation of the nerve impulse coincides with sudden changes in the permeability of the axon membrane to sodium and potassium ions. When a nerve impulse starts at the origin of the axon, having been triggered in most cases by the cell body in response to dendritc synapses, the voltage difference across the axon membrane is locally lowered. Immediately ahead of the electrically altered region (in the direction in which the nerve impulse is propagated) channels in the membrane open and let sodium ions pour into the axon. The process is self-reinforcing: the flow of sodium ions through the membrane opens more channels and makes it easier for other ions to follow. The sodium ions that enter change the internal potential of the membrane from negative to positive. Soon after the sodium channels open they close, and another group of channels open that let potassium ions flow out. This outflow restores the voltage inside the axon to its resting value of 70 millivolts. The sharp positive and then negative charge, which shows up as a "spike" on an oscilloscope, is known as the action potential and is the electrical manifestation of the nerve impulse. The wave of voltage sweeps along until it reaches the end of the axon much as a flame travels along the fuse of a firecracker.

This brief description of the nerve impulse illustrates the importance of channels for the electrical activity of neurons and underscores two fundamental properties of channels: specificity and gating. I shall discuss these two properties in turn. Channels are selectively permeable and selective in a very wide range. For example, one type of channel lets sodium ions pass through and largely excludes potassium ions, whereas another type of channel does the reverse. The selectivity, however, is seldom absolute. One type of channel that is fairly nonselective allows the passage of about 85 sodium ions for every 100 potassium ions; another more selective type passes only about seven sodium ions for every 100 potassium ions. The first type, known as the acetylcholine-activated channel, has a pore about 8 nanometers in diameter that is filled with water. The second type, known as the potassium channel, has a much smaller opening and contains less water. The sodium ion is about 30 percent smaller than the potassium ion. The exact molecular structure that enables the larger ion to pass through the cell membrane was not readily than the smaller, one is not known. The general principles that underlie the discrimination, however, are understood. They involve interactions between ions and parts of the channel structure in conjunction with a particular ordering of water molecules within the pore.

The gating mechanism that regulates the opening and closing of membrane channels takes two main forms. One type of channel, mentioned above in the description of the nerve impulse, opens and closes in response to voltage differences across the cell membrane. It is therefore said to be voltage-gated. A second type of channel is chemically gated. Such channels respond only slightly at all to voltage changes but open when a particular molecule—a transmitter—binds to a receptor region on the channel protein. Chemically gated channels are found in the receptive membranes of synapses and are responsible for translating the chemical signals produced by axon terminals into ion permeability changes during synaptic transmission. It is customary to name chemically gated channels according to their neurotransmitter. In one speaks of acetylcholine-activated channels or GABA-activated channels. (GABA is gamma-aminobutyric acid.) Voltage-gated channels are generally named for the ion that passes through the channel most readily.

Proteins commonly change their shape as they function. Such alterations in shape, known as conformational changes, are dramatic for the contractile proteins responsible for cell motion, but they are no less important in many enzymes and other proteins. Conformational changes in channel proteins form the basis for gating as they serve to open and close the channel by slight movements of critically placed portions of the molecule that unblock and block the pore.

When either voltage-gated or chemically gated channels open and allow ions to pass, one can measure the resulting electric current. Quite recently it has become possible in a few instances to record the current flowing through a single channel, so that the opening and closing can be directly detected. One finds that the length of time a channel stays open varies with the voltage at which the channel is held open. The random nature of the gating process arises from the haphazard collision of water molecules and other molecules with the structural elements of the channel.

In addition to ion pumps and channels neurons depend on other classes of membrane proteins for carrying out essential nervous system functions. One of the important proteins is the enzyme adenylate cyclase, which helps to regulate the intracellular substance cyclic adenosine monophosphate (cyclic AMP). Cyclic nucleotides such as cyclic AMP take part in cell functions whose mechanisms are not yet understood in detail. The membrane enzyme adenylate cyclase appears to have two chief subunits, one catalytic and the other regulatory. The catalytic subunit promotes the formation of cyclic AMP. Various regulatory subunits, which are thought to be physically distinct from the catalytic one, can bind specific molecules (including transmitters that open and close channels) in order to control intracellular levels of cyclic AMP. The various types of regulatory subunit are named according to the molecule that normally binds to them; one, for example, is called serotonin-activated ade-

SYNAPTIC TERMINAL occupies most of this electron micrograph made by John E. Henn as of the University of California School of Medicine in San Francisco and Thomas S. Reese of the National Institutes of Health. The cell separating the presynaptic membrane from the postsynaptic one undulates across the lower part of the picture. The large dark structures are mitochondria. The many rounded bodies are vesicles that hold transmitter. The fuzzy dark thickenings along the cleft are thought to be principal sites of transmitter release.

ACETYLCHOLINE-ACTIVATED CHANNELS are densely packed in the postsynaptic membrane of a cell in the electric organ of a tetrapod, a fish that can administer an electric shock. This electron micrograph shows the platinum-plated replica of a membrane that had been frozen and etched. The size of the platinum particles limits the resolution to features larger than about two nanometers. According to recent evidence the channel protein molecules, which measure 8.5 nanometers across, consists of three main subunits forming a unit whose narrowest dimension is 8 nanometers. The micrograph was made by Henn as and S. R. Sulzer,
**AXON MEMBRANE** separates fluids that differ greatly in their content of sodium ions (colored dot) and potassium ions (black dot). The extracellular fluid is about 10 times richer in sodium ions than in potassium ions; in the interior fluid the ratio is the reverse. The membrane is penetrated by proteins that act as selective channels for preferentially passing either sodium or potassium ions. In the resting state, when no nerve impulses are being transmitted, the two types of channel are closed and an ion pump maintains the ionic disequilibrium by pumping out sodium ions in exchange for potassium ions. The interior of the axon is normally about 70 millivolts negative with respect to the exterior. If this voltage difference is reduced by the arrival of a nerve impulse, the sodium channel opens, allowing sodium ions to flow into the axon. An instant later the sodium channel closes and the potassium channel opens, allowing an outflow of potassium ions. The sequential opening and closing of the two kinds of channel effects the propagation of the nerve impulse, which is illustrated below.

**PROPSATION OF NERVE IMPULSE** along the axon coincides with a local increase in flow of sodium ions (+) followed by an outflow of potassium ions (-) through channels that are "gated," or controlled, by voltage changes across the axon membrane. The electrical event that sends a nerve impulse traveling down the axon normally originates in the cell body. The impulse begins with a slight depolarization, or reduction in the negative potential, across the membrane of the axon where it leaves the cell body. The slight voltage shift opens some of the sodium channels, shifting the voltage still further. The increased flow of sodium ions accelerates until the interior surface of the membrane is locally positive. The voltage reversal closes the sodium channels and opens the potassium channels. The outflow of potassium ions quickly restores the negative potential. The voltage reversal, caused by the action potential, propagates itself down the axon (1, 2). After a brief recovery period a second impulse can follow (3). The impulse propagation speed is that measured in the giant axon of the squid. 

**RESPONSE OF A SINGLE MEMBRANE CHANNEL** to the transmitter compound acetylcholine is revealed by a recently developed technique that has been applied by Ervin Nahor and Joseph H. Steinbach. The squid axon membrane contains two kinds of channels, which are present in postsynaptic membranes, allowing the passage of roughly equal numbers of sodium and potassium ions. The record shows the flow of current through a single channel in the postsynaptic membrane of a frog muscle activated by the compound acetylcholine, which mimics action of acetylcholine but keeps channels open longer. Experiments show that channels open on an all-or-none basis and stay open for random lengths of time.

**SODIUM CHANNELS IN AN AXON** also operate in simple open-or-shut manner as well as independently of one another, according to investigations conducted by Frederick J. Sigworth of the Yale University School of Medicine. During the propagation of a nerve impulse about 10,000 channels normally open in a myelinated region of the axon membrane, namely a node of Ranvier. The upper curve depicts the sodium conductance as a function of time. The lower trace, recorded at a 12-fold amplification of the upper one, shows fluctuations in permeability around the average due to the random opening and closing of channel.
FROG NEUROMUSCULAR JUNCTION appears in this electron micrograph made by Henry. The synaptic cleft separates the axon at the upper left from the muscle cell at the lower right. Synaptic vesicles cluster along the presynaptic membrane, with two synaptic contacts visible near the center. Postsynaptic membrane of the muscle cell exhibits a feature that is not seen in other synapses: the membrane forms postsynaptic folds opposite each contact. Freeze-fracture replicas of synaptic membrane are shown on opposite page.

The process is terminated by a phenomenon called sodium inactivation. Voltage differences across the membrane that cause sodium channels to open also drive them into an especially closed conformation different from the conformation characteristic of the channel's resting state. This second closed conformation, called the inactivated state, develops more slowly than the activation process, so that channels remain open briefly before they are closed by inactivation. The channels remain in the inactivated state for some milliseconds and then return to the normal resting state. The complete cycle of activation and inactivation normally involves the opening and closing of thousands of sodium channels. How can one tell whether the increase in overall membrane permeability reflects the opening and closing of a number of channels in an all-or-none manner or whether it reflects the operation of channels that have individually graded permeabilities? The question has been partly answered by a new technique that relates fluctuations in membrane permeability to the inherent probabilistic nature of conformational changes in the channel proteins. One can trigger repeated episodes of channel opening and calculate the average permeability at a particular time and also the exact permeability on a given trial. The exact permeability fluctuates 10 percent or so around a mean value. Analysis of the fluctuations shows that the sodium channels open in an all-or-none manner and that each channel opening increases the conductance of the membrane by 8 X 10^-12 reciprocal ohms. One of the principal challenges in understanding the neuron is the development of a complete theory that will describe the behavior of the sodium channels and relate it to the molecular structure of the channel protein.

As I noted briefly above, axons also have voltage-gated potassium channels that help to terminate the nerve impulse by letting potassium ions flow out of the axon, thereby counteracting the inward flow of sodium ions. In the cell body of the neuron, the situation is still more complex, because there the membrane is traversed by five types of channel. The different channels open at different rates, stay open for various intervals and are preferentially permeable to different species of ions (sodium, potassium or calcium). The presence of the five types of channel in the cell body of the neuron, compared with only two in the axon, gives rise to a more complex mode of nerve-
impulse generation. If an axon is presented with a maintained stimulus, it generates only a single impulse at the onset of the stimulus. Cell bodies, however, generate a train of impulses with no refractory periods that reflects the intensity of the stimulus.

Some axons are able to generate nerve impulses over a wide range of frequencies, from one or fewer per second to several hundred per second. All nerve impulses have the same amplitude, so that the number of impulses generated per unit of time, a system known as frequency coding. The larger the magnitude of the stimulus to be conveyed, the faster the rate of firing.

When a nerve impulse has traveled the length of the axon and has arrived at a terminal button, one of a variety of transmitters is released from the presynaptic membrane. The transmitter diffuses to the postsynaptic membrane, where it induces the opening of chemically gated channels. Ions flowing through the open channels bring about the voltage changes known as postsynaptic potentials.

Many details of the events leading to exocytosis have recently been elucidated. The fusion of vesicles to the presynaptic membrane is evidently triggered by a rapid but transient increase in the calcium ion concentration at the terminal button of the axon. The arrival of a nerve impulse at the terminal opens calcium channels that are voltage-gated and allows calcium to flow into the termi- nal button. This postsynaptic calcium ion concentration is brief, however, because the terminal contains a special apparatus that removes free calcium ions and returns its concentration to the normal level. Calcium spikes in the free-calcium level lead to the fusion of transmitter-filled vesicles with the presynaptic membrane, but the precise mechanism of this important process is not yet understood.

Interesting details of the structure of the terminal membrane have been revealed by the freeze-fracture technique, a method that splits the layers of the bilayer membrane and exposes the intrins membrane proteins for examination by electron microscopy. In the frog neuromuscular junction a double row of large membrane proteins runs the width of each synapse. Synaptic vesicles become attached to or near the proteins. Only these vesicles then fuse to the membrane and release their transmitter; other vesicles are not held in reserve.
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