# 4 Synaptic Transmission

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## OVERVIEW

The nervous system is composed of specialized cellular circuits that allow an animal to perform tasks essential for survival. Neurons are organized to form these circuits, and they transmit electrical and chemical signals among themselves to process sensory input, initiate behavioral responses, and regulate an animal's internal physiology. The critical link between neurons that permits communication and establishes the foundation for neuronal circuitry is called the *synapse*, and this chapter will discuss fundamental synaptic properties.

Synapses are sites of close cellular contact where fast, highly localized transmission of chemical and electrical signals can occur. The human brain has approximately $10^{11}$neurons that form about $10^{15}$ synapses. By comparison, the simple nematode worm *C. elegans* has exactly 320 neurons with only about 7600 synapses. The capacity of the human brain to form such an astronomical number of synapses has surely contributed to the success of our species and its vast repertoire of behaviors. In order to understand how synapses confer such complexity of neuronal circuitry, it is important to explore the details of information transfer at the synapse.

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The process of communication between neurons, termed *synaptic transmission*, is also key to developing better medical treatments of neurologic conditions for several reasons. The causes of several mental disorders and neuromuscular diseases can be traced to dysfunctional synapses. Synapses are also the locus of action for several neurotoxins and psychoactive drugs (some of which can cause debilitating and life-long addictions). Finally, determining how synapses transmit signals and how neuronal circuits are remodeled and modulated at the synaptic level will eventually allow us to understand the basis of neuronal learning and memory.

Synapses vary widely in shape, size, and functional capability. Presumably, such architectural and functional diversities are tailored for the specialized information transfer and processing needs of individual neurons and circuits. For example, many synapses function as high-fidelity relay stations. The connection between motor neurons and muscle fibers (termed the *neuromuscular junction*), the giant synapses in the mammalian and aviary auditory systems involved in sound localization, and the squid giant synapse, which allows a rapid escape behavior, are all examples of high-fidelity relays. These are synapses where reliability is at a premium, and the synaptic architecture is designed as a fail-safe mechanism for information transfer. Other synapses, such as the bouton-type

synapses of the cortex and hippocampus, often fail to transmit signals and are thus considered comparatively unreliable. These bouton synapses, however, have the capacity to become more fail-safe with repetitive use. This type of change in synaptic strength is an example of *plasticity* and is thought to underlie the long-lasting storage of information acquired through repetitive use of an associated neuronal circuit. In other words, the specific strengthening of a particular set of synaptic connections may form the basis for some types of learning and memory. Equally important may be the weakening of synaptic connections, a process that could either cause the loss of certain synaptic memory or endow the freedom for retasking a particular neuronal circuit. Thus, synapses must be considered as highly dynamic and plastic structures that can adapt their output to match the demands imposed by their current information processing needs. In this sense, the brain is not "hard wired" and differs fundamentally from an electronic computer.

One consequence of evolution that unifies biology and medicine is the cross-species commonality of underlying mechanisms for critical physiologic processes such as synaptic transmission. From genomes to protein structure and function, common molecular motifs are homologously conserved across phylogenetically distant species. Neurobiologists have thus been able to use non-human animal models as a means to study and understand synaptic function. Because of an unparalleled ease of access, much of the pioneering work in the field of synaptic transmission comes from studies of the frog neuromuscular junction and squid giant synapse. In addition, relatively new preparations such as the giant bipolar cell synapse from goldfish retina and calyx of Held synapse in the mammalian brain stem have shed much new light on our understanding of synaptic function. These and many other preparations have yielded a wealth of information about synapses and revealed several general principles that apply directly to synaptic transmission in the human brain. It is these general principles of synaptic transmission that will be reviewed in this chapter.

## 1. PROPERTIES OF CHEMICAL AND ELECTRICAL SYNAPSES

Neurons communicate using morphologically and functionally specialized sites of close contact called synapses. Synaptic transmission can be electrical or chemical, though the vast majority of synapses in the mammalian brain are chemical. At *chemical synapses*, molecules of neurotransmitter are released from a presynaptic terminal into a narrow extracellular gap (about 20 to 50 nm) called the *synaptic cleft*. The transmitter molecules then diffuse and bind to recognition sites on target receptors at the plasma membrane of a postsynaptic neuron. This type of synaptic transmission is fast, site-specific, and highly plastic.

A different type of synaptic transmission occurs at *electrical synapses*. Here, proteins form *gap-junctions*, which create a conductive pore between two neurons. This pore is a ionotropic transmembrane channel composed of connexin proteins on the plasma membrane of each neuron that allows ions and small molecules (e.g., cAMP, ATP, $Ca^{2+}$, $IP_3$) to cross between cells. The cytoplasm of two neurons connected by a gap junction is thus physically continuous, and the resulting low-resistance channel allows *electrical coupling*. Transmission at electrical synapses is *bidirectional*, although some gap junctions may transmit better in one direction (i.e., they show *rectification*).

Although electrical coupling limits the variety of signaling between neurons (electrical activity in one neuron is identically passed to its connected partner), it allows even faster communication than does chemical signaling and can synchronize the activity of a group of cells that must work in concert. For example, every neighboring cell in the heart is connected via gap junctions, and the resultant electrical coupling allows the tissue-wide coordination of cardiac contractions.

Gap junctions are not, however, static structures. Many tissues contain gap junctions during development, which are then lost as the nervous system matures. In addition, gap junction conductances can be modulated by phosphorylation and/or neurotransmitters in order to alter the dynamic state of entire neuronal circuits. In the retina, for example, circadian changes in dopamine levels modulate the opening of gap junctions and allow retinal circuitry to adapt its light sensitivity from day to night.

By contrast, chemical synapses are far more complex than their electrical counterparts. Chemical synapses depend on an elaborate cascade of protein-protein and lipid-protein interactions that have only recently been explored at the molecular level. Some of the differences between electrical and chemical synapses are listed in Figure 1. Chemical synapses occur between axon endings (*presynaptic terminals*) that contain neurotransmitter-filled *synaptic vesicles* and postsynaptic neurons with clusters of neurotransmitter receptors. These two elements are separated by the synaptic cleft. (*See* Fig. 2 for an electron microscope image of a conventional brain synapse and Fig. 3 for a schematic

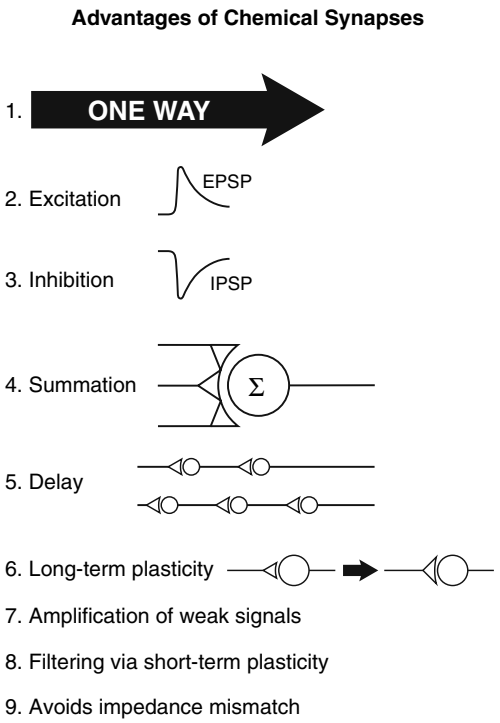


**Fig. 1.** The multiple advantages of chemical synapses. **(1)** Chemical synapses are mostly unidirectional and transmit from presynaptic to postsynaptic neurons. Information is thus relayed sequentially to different cells in a neural circuit. **(2)** Synapses can produce an excitatory postsynaptic potential (EPSP) causing the postsynaptic neuron to fire APs. **(3)** Synapses can also produce an inhibitory postsynaptic potential (IPSP) suppressing postsynaptic firing of APs. **(4)** Several small synaptic potentials can be summed by the postsynaptic cell before it fires an AP. This allows the neuron to integrate information from several different sources. **(5)** Chemical synapses introduce a short synaptic delay in transmission, and this can be used for calculating the timing of sensory inputs. In the example shown, information can be routed via a disynaptic or a trisynaptic pathway. **(6)** Synaptic strength or efficacy is plastic and can undergo changes on a long timescale (hours or days). Synaptic morphology and functional properties can thus change with experience. This is indicated by the larger synaptic connection. **(7)** Synapses can amplify a weak presynaptic signal. **(8)** Synaptic strength or efficacy is also plastic on a short timescale (milliseconds to seconds). This short-term synaptic plasticity can cause synaptic depression or fatigue if the synapse is stimulated at high frequencies. Thus, high-frequency stimulation may be filtered and not transmitted as effectively as low-frequency stimulation. **(9)** Synaptic transmission avoids impedance mismatch problems that may occur at electrical synapses between neurons of different sizes. (Modified from Gardner, D. Synaptic transmission. In: *Neuroscience in Medicine*, edited by Conn, M.P. J.B. Lippincott, Philadelphia, 1995).

diagram of the main elements in a synapse.) Chemical synapses are therefore polarized and primarily mediate synaptic transmission from the presynaptic terminal to the postsynaptic neuron.

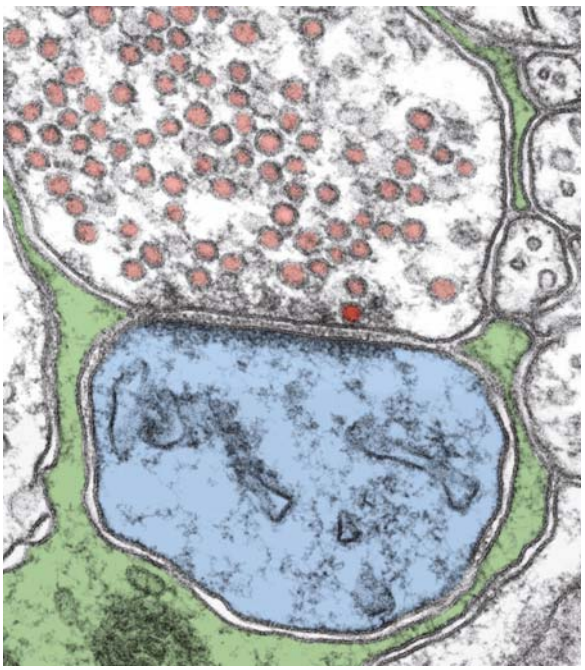

**Fig. 2.** An electron micrograph of a CNS synapse. This example of a synaptic bouton-type synapse is located in the "molecular layer" of rat cerebellum. A single *en passant* bouton of the parallel fibers synapses onto a single Purkinje cell spine. Note the multiple synaptic vesicles in the presynaptic bouton terminal. Several vesicles seem to be linked by thin filaments in the cytoplasm. On average, the vesicles have a diameter of about 40 nm. One synaptic vesicle is clearly docked to the presynaptic membrane. Note also the narrow synaptic cleft, which contains a "fuzzy" set of electron-dense material (this probably includes cell adhesion proteins that span the cleft). The opposing postsynaptic membrane in the postsynaptic spine has an electron-dense postsynaptic density (PSD), where glutamate receptors and modulatory proteins are located. A thin glial process wraps itself around the synaptic cleft and postsynaptic spine and also partially around the presynaptic bouton-type terminal. (Electron micrograph courtesy of Constantino Sotelo, Instituto de Neurociencias de Alicante, Spain) (*see* Color Plate 1, following p. 378).

Unlike electrical synapses, the synaptic cleft separating presynaptic and postsynaptic membranes does not permit any direct electrical coupling between neurons (or any degree of cytoplasmic mixing). The synaptic cleft is spanned by several different kinds of *adhesion molecules* (e.g., cadherins, immunoglobulin cell adhesion molecules, neurexins, neurogligins, integrins, etc.) that provide mechanical stability and align presynaptic vesicle fusion sites (*active zones*) opposite to clusters of postsynaptic neurotransmitter receptors. A hallmark of the active zone that has been revealed by electron microscopy is a set of *docked vesicles* situated close to the plasma membrane (from 2 to 10 vesicles per active zone ideally positioned for

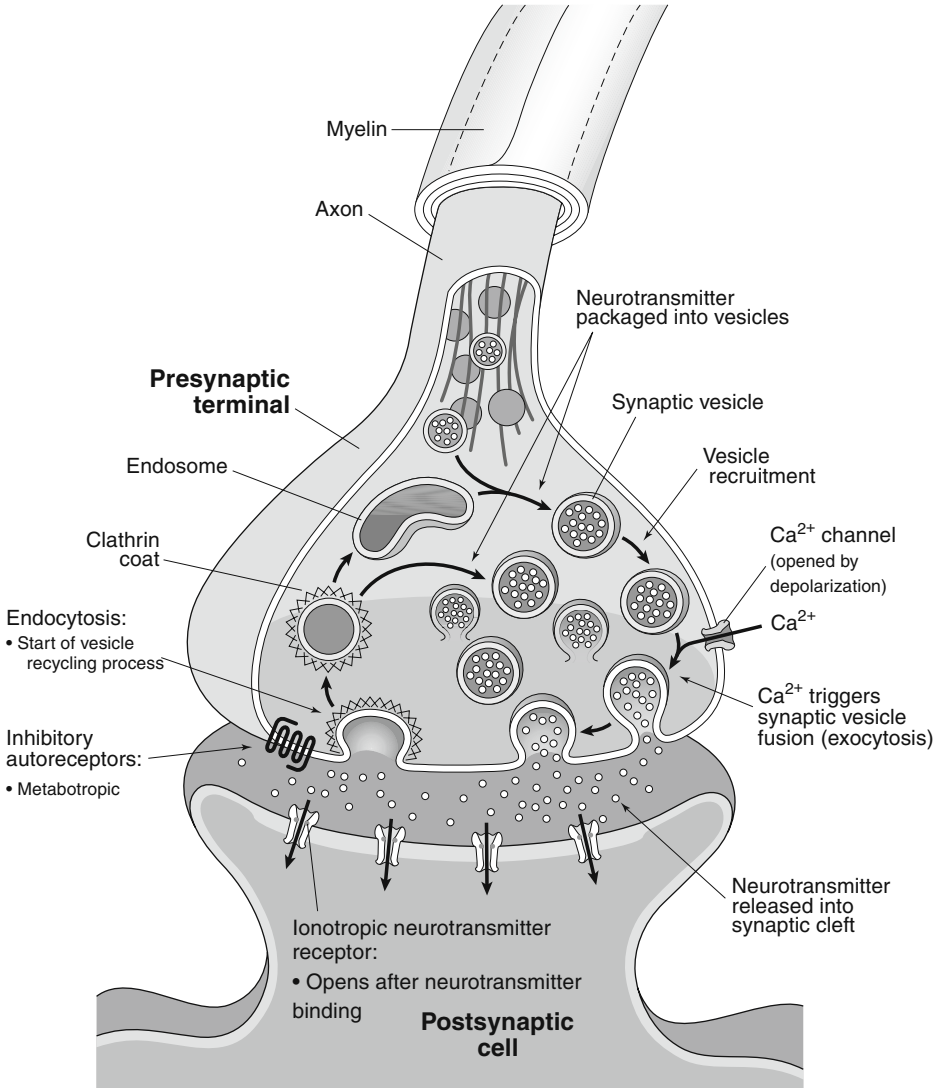


**Fig. 3.** Chemical synapses and synaptic vesicle recycling. Schematic diagram of the main events involved in chemical synaptic transmission at a typical bouton-type synapse. The presynaptic terminal (or bouton) is filled with neurotransmitter containing synaptic vesicles. Some vesicles are in the cytosol, constituting a reserve pool of vesicles, and some are docked at the presynaptic membrane, constituting a readily releasable pool of vesicles. Reserve vesicles can be recruited to the docked pool. A presynaptic AP depolarizes the nerve terminal and opens $Ca^{2+}$ channels located near the docked pool of vesicles. $Ca^{2+}$ ions trigger synaptic vesicle fusion or exocytosis. Neurotransmitter is thus released into the synaptic cleft where it binds to postsynaptic ionotropic receptors. This binding of neurotransmitter causes ion channels to open, depolarizing or hyperpolarizing the postsynaptic cell. Neurotransmitter can also bind to metabotropic receptors on the presynaptic membrane, and these can inhibit further release. Synaptic vesicle membrane that has fused with the presynaptic membrane is retrieved by endocytosis. One common form of endocytosis is clathrin-mediated endocytosis, which forms clathrin coats on endocytosed vesicles. Retrieved vesicles are then recycled via fusion to endosomes or directly back to the reserve vesicle pool where they are refilled with neurotransmitter. (Modified from Augustine, G.A. Synaptic transmission. In: *Neuroscience*, edited by Purves et al, 2001.)

immediate release). A second set of synaptic vesicles is commonly found in reserve further from the active zone, and both vesicle clusters are often thought of as discrete pools with functional differences in terms of chemical signaling. In direct apposition to the active zone, the postsynaptic membrane contains an electron-dense area called the *postsynaptic density* (PSD). The PSD holds receptors for neurotransmitters, cytoskeletal and scaffolding proteins, and many enzymes localized to trigger signaling cascades.

Chemical transmission is initiated when an action potential (AP) invades the presynaptic terminal. The resulting membrane depolarization opens voltage-gated $Ca^{2+}$ selective ion channels, and $Ca^{2+}$ enters

the presynaptic neuron. This $Ca^{2+}$ is the trigger for *exocytosis*, the process by which docked, neurotransmitter-filled synaptic vesicles fuse with the presynaptic membrane to release their contents into the synaptic cleft. The neurotransmitter is then free to diffuse across the synaptic cleft and bind to target receptors on the postsynaptic plasma membrane. These receptors are termed *ligand-gated*, and many of them are ion-selective channels that open in response to neurotransmitter binding. When these ion-selective channels open, extracellular ions flow into the postsynaptic neuron to produce either an *excitatory* or *inhibitory postsynaptic potential* (EPSP or IPSP). The type of postsynaptic potential depends largely on the particular neurotransmitter released from the presynaptic neuron and the specific receptors expressed on the postsynaptic membrane. EPSPs transiently shift the membrane potential toward more positive values, or depolarize the membrane, whereas IPSPs generally hyperpolarize the membrane. Unlike electrical synapses, chemical synapses can either maintain or invert the sign of a presynaptic signal by transforming a presynaptic excitation to a postsynaptic excitation or inhibition.

Presynaptic terminals are often less than a micrometer in diameter and frequently release only a few synaptic vesicles per AP. The effect of a small quantity of neurotransmitter on the postsynaptic membrane (the EPSP or IPSP) may therefore be insufficient for triggering a postsynaptic AP. The postsynaptic neuron, though, can be studded with up to several thousand presynaptic terminals (or boutons), and simultaneous EPSPs and IPSPs are then integrated by the postsynaptic neuron. This process of *summation* allows the postsynaptic neuron to collect input from a variety of synapses before firing its own AP. Summation of multiple inputs, along with strengthening or weakening of particular synapses, allows the brain a vast computational capacity that would be otherwise impossible with more limited and static circuitry.

Because chemical synaptic transmission is such an intricate, multistep process, there is an inherent time lag, or *synaptic delay*, that occurs between a presynaptic depolarization and a postsynaptic response. This delay, which varies between 0.1 and 0.5 ms, depends on the architecture of a particular synapse. Together with other timing cues, such as those introduced by axons of differing length, some neurons are capable of comparing sensory inputs from organ pairs such as the eyes or ears. For example, certain neurons in the auditory brain stem localize sound by comparing inputs from two different synapses carrying signals from each ear. These neurons are *coincidence detectors* for signals arriving from each ear, and the auditory neural circuitry is precisely constructed to accommodate delays introduced by axons of differing length across several synapses.

Synapses are highly dynamic connections that can undergo both short-term and long-term changes in their morphology and transmission strength. A brief burst (or tetanus) of neural stimulation can transiently increase or decrease the amplitude of EPSPs or IPSPs. These ubiquitous phenomena are called *short-term facilitation* (increased postsynaptic potentials) or *short-term depression* (or synaptic fatigue). Synapses usually recover from short-term facilitation or depression within a few seconds. On the other hand, prolonged high-frequency stimulation of synaptic pairs can sometimes cause a *long-term potentiation* of EPSPs that can last for hours or even days. Conversely, prolonged lower-frequency stimulation of the same synapse pair may induce *long-term depression* of EPSPs. Two different synaptic inputs can therefore associate to produce what may be a simple cellular underpin for learning and memory.

Short-term depression may also act as a *frequency-selective filter*. During a tetanus, short-term depression will become increasingly potent as the stimulation frequency increases. Stimulation beyond a certain frequency is therefore filtered out at the synapse level, effectively changing the operational range of an associated neural circuit. Frequency-dependent filters are quite useful in electronics (e.g., to reduce noise and select for particular frequencies), and presumably neural circuits also make use of this synaptic property in analogous ways.

Chemical synapses also have an advantage over electrical synapses in dealing with the problem of *impedance mismatch*. When a small presynaptic cell, which has a proportionally small membrane capacitance, synapses with a larger postsynaptic cell, the smaller cell must be able to evoke a postsynaptic current of sufficient size and speed to bring the larger cell to AP threshold. If the two cells are connected via gap junctions, the smaller cell would not be able to effectively charge the membrane capacitance of the lager cell via the electronic spread of its membrane potential. Chemical synapses, however, avoid this problem by using vesicles filled with neurotransmitter that can be released several at a time. Each vesicle contains many thousand molecules of neurotransmitter, which in turn open many thousand postsynaptic ionotropic receptors. A weak presynaptic signal may therefore be amplified chemically to produce a

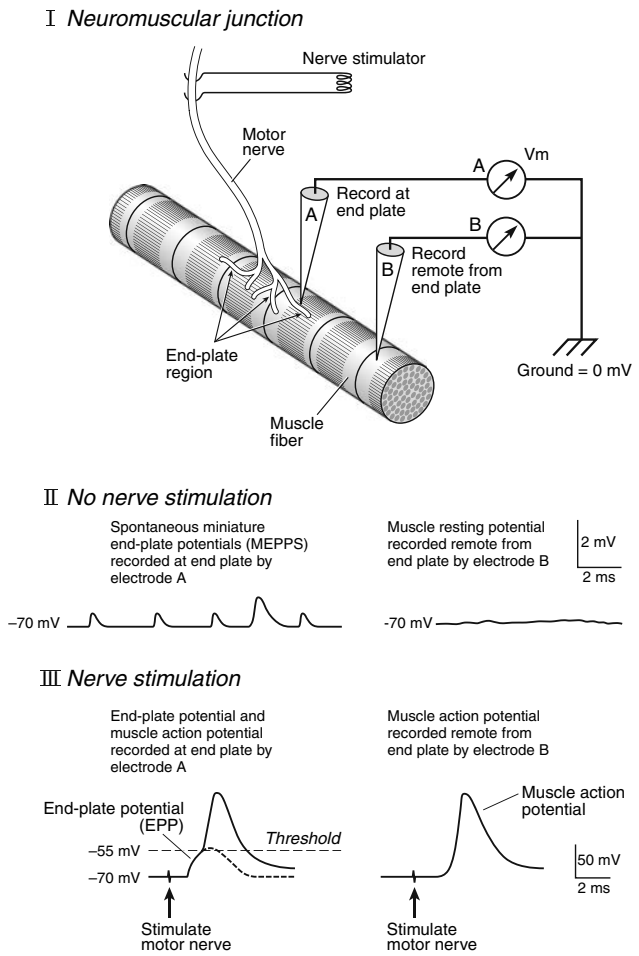


**Fig. 4.** The neuromuscular junction. **(I)** Schematic diagram of electrophysiologic recordings from the frog neuromuscular junction. Electrical stimulation of the motor nerve causes APs to invade the nerve terminal where they elicit transmitter release. An intracellular electrode with tip placed inside the muscle and near to the end-plate region (electrode *A*) can record changes in membrane voltage $V_m$ relative to the ground potential, which is set to 0 mV. **(II)** With no nerve stimulation, small and spontaneous miniature end-plate potentials (MEPPs) are recorded by electrode *A*, but not by the more distantly placed electrode *B*, which records only the resting membrane potential of –70 mV. MEPPs are caused by the spontaneous fusion or exocytosis of single synaptic vesicles. **(III)** Upon nerve stimulation, a large end-plate potential (EPP) is observed in the motor nerve. The EPP depolarizes the nerve above the threshold for triggering a muscle AP. Electrode *B* also records an AP, as APs actively propagate down the muscle fiber.

comparatively larger response in the postsynaptic neuron. Such *amplification* is of particular importance at the neuromuscular junction, where the postsynaptic cell is a large muscle fiber (Fig. 4).

One challenge for chemical synaptic transmission involves rapid clearance of neurotransmitter molecules from the cleft. In order to maintain the ability for rapid and discrete signaling, it is important that neurotransmitter does not linger in the vicinity of postsynaptic receptors causing them to remain active for prolonged periods. Though simple diffusion plays a large role in removing neurotransmitter molecules from the synaptic cleft, complete removal requires specialized enzymes. In most cases, *transporters* accomplish the task of neurotransmitter removal. Transporters are enzymes localized on the plasma membrane of neurons and glial cells, which use existing electrochemical gradients to shuttle molecules of neurotransmitter back into the cell. Pharmacologically, transporters are the locus of action for several drugs, both addictive and therapeutic. Cocaine is a specific blocker of the dopamine transporter, and the antidepressant drug Prozac (Fluoxetine hydrochloride) inhibits the serotonin transporter. At the neuromuscular junction, a different tactic is used for clearing neurotransmitter. Here, an enzyme called *acetylcholinesterase* degrades the transmitter acetylcholine in the synaptic cleft before reuptake. This enzyme is critical, and inhibiting it leads to rapid and profound paralysis. Acetylcholinesterase is the target for some insecticides, the nerve gas sarin, and the crippling autoimmune disorder myasthenia gravis.

Finally, we point out that neurotransmitters released at chemical synapses may also bind *metabotropic receptors* located on both the presynaptic and postsynaptic membranes. Unlike ligand-gated ionotropic receptors, metabotropic receptors have a higher affinity for their ligand and do not directly gate an ion channel. When located on the presynaptic terminal inside or near the synaptic cleft, they are known as *autoreceptors* because neurotransmitter released from the same cell feeds back to affect presynaptic function. Metabotropic receptors interact with bound G proteins, which couple to other effector proteins (like phosphodiesterases or ion channels), and metabotropic ligand binding is responsible for activating these associated G-protein pathways. Each activated metabotropic receptor can activate several hundred G proteins, and each activated G protein can then interact with several hundred effector proteins. This allows for a high degree of signaling amplification.

In summary, the greater flexibility and plasticity available to chemical synapses has made them the favored mode of synaptic transmission in the brains of vertebrates and invertebrates (e.g., the worn *C. elegans* has about 7000 chemical synapses but only 600 electrical synapses). For the rest of this chapter, the term *synapse* will be synonymous with the chemical synapse.

## 2. A MODEL SYNAPSE: THE NEUROMUSCULAR JUNCTION

The frog neuromuscular junction (NMJ) was the first synapse to be thoroughly investigated. It has many advantages for the study of synaptic transmission, including its ability for easy access, stimulation, and electrical recording. Figure 4 shows a schematic diagram of the frog NMJ. A single motor nerve axon terminates in several branches on a single muscle fiber. This area of multiple synapses is called the *end-plate region*. A recording electrode that impales the muscle fiber just underneath the end-plate region (electrode A in Fig. 4) will record a resting membrane potential of about –70 mV. In addition, several spontaneous miniature end-plate potentials (MEPPs or mini-EPSPs) will also be superimposed on the resting membrane potential. These electrical events were first recorded by Fatt and Katz in 1951. A recording electrode placed at some distance from the end-plate (electrode B in Fig. 4) will not detect these MEPPs because *electrotonic attenuation* reduces their already small amplitude (0.5 mV) to levels below the basal noise. Subsequently, in 1954 del Castilho and Katz noticed that the amplitudes of the MEPPs were remarkably consistent and that end-plate potentials (EPPs) frequently appeared as multiples of a standard size. The EPP therefore appeared to be composed of discrete units, or *quanta*, corresponding with unitary MEPPs. They called the standard MEPP amplitude the *quantal size* and denoted it with the symbol $q$.

Returning to Fig. 4, when a single AP was stimulated in the motor nerve, an end-plate potential was recorded by electrode A after a short delay. The shape of the EPP was similar to that of the MEPP, but its size was several-fold larger. The constant scaling factor between the EPP and MEPP was denoted by $m$, called the *quantal content* of the EPP. The EPP amplitude invariably exceeded the threshold for action-potential generation, so a muscle AP was also observed first at the end-plate (electrode A) and then further away (electrode B). Del Castilho and Katz further assumed that the end-plate contained several discrete sites for quantal release. Supposing that a number of these release sites, denoted $N$, were functional at any given time and had an average *probability of release* ($P_r$), they postulated that $m = NP_r$. This elegant statistical analysis of neurotransmitter release still shapes our modern quantitative views of synaptic function.

The morphologic correlates of $q$, $m$, and $N$ are thought to be the synaptic vesicle, the number of vesicle fusions, and the number of functional active zones in the nerve terminal, respectively. Synaptic vesicles are homogeneous in size (about 50 nm in diameter at the NMJ) and are believed to contain the same amount of neurotransmitter. Interestingly, certain mutants of the fruit fly *Drosophila* (called *lap* mutants) have unusually large synaptic vesicles and correspondingly larger MEPPs. At the frog NMJ, there are about 300 active zones. This redundancy, or high $N$ value, allows for a small $P_r$ at individual active zones but a large overall $m$ value. In other words, there is a large safety factor at the NMJ so that it can function as a fail-safe relay to trigger muscle APs. One caveat to this general rule occurs when stimulation frequency is high. In this case, $P_r$ is drastically reduced and failures in AP transmission can occur.

## 3. PRESYNAPTIC EXOCYTOSIS IS $CA^{2+}$ DEPENDENT

Neurotransmitter release occurs when synaptic vesicles fuse with the presynaptic plasma membrane. This process of exocytosis is triggered by the influx of free $Ca^{2+}$ ions into the nerve terminal. Depolarization of the nerve terminal opens voltage-gated $Ca^{2+}$ selective channels, and because calcium concentrations are much higher in the extracellular space than in the cytosol, calcium flows into the cell according to its electrochemical driving force. This flux of ions produces a current that can be measured, for example, using the *two-electrode voltage clamp* technique. This type of *$Ca^{2+}$ current* recording was first demonstrated by Llinás and colleagues. When the postsynaptic neuron is impaled by a third electrode for recording EPSPs, it becomes possible to examine the relationship between a presynaptic $Ca^{2+}$ current and a postsynaptic EPSP (Fig. 5). Small step depolarizations of the nerve terminal from –60 to –30 mV elicit a small, slow $Ca^{2+}$ current and relatively small EPSP in the postsynaptic cell. A stronger presynaptic depolarization from –60 to 0 mV will evoke a larger, more rapid $Ca^{2+}$ current and much larger EPSP. Similarly, short depolarizations will produce smaller EPSPs than will longer-duration depolarizations of the same magnitude. Using this method for comparing presynaptic and postsynaptic events, the relationship between calcium influx and postsynaptic response was found to be nonlinear.

Results from the squid giant axon synapse confirmed previous experiments in the frog NMJ showing that transmitter release depends exponentially on $Ca^{2+}$ concentration in the extracellular medium (by a 4th power relationship). Physiologic $Ca^{2+}$ ion concentrations are

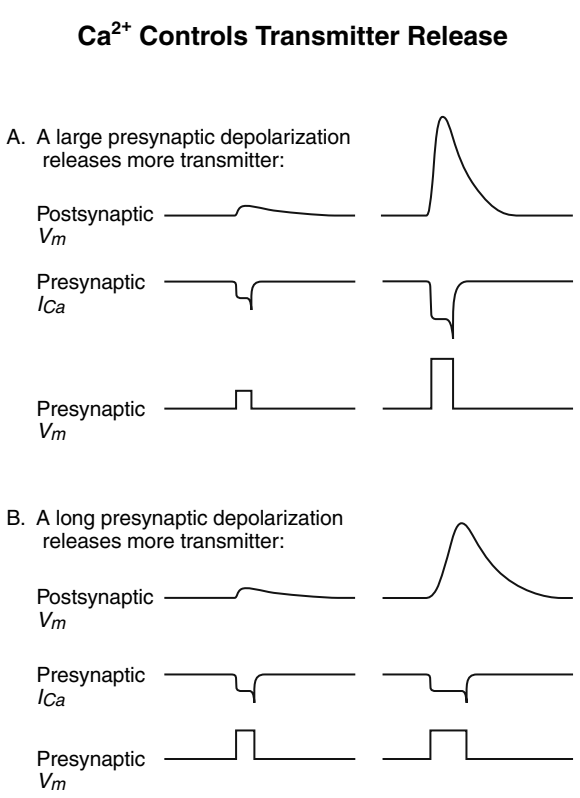


**Fig. 5.** $Ca^{2+}$ ions and synaptic transmission. Schematic diagram of electrophysiologic recordings from the squid giant synapse. Simultaneous presynaptic and postsynaptic voltage-clamp recordings. **(A)** A step-like depolarization of the presynaptic terminal (*bottom trace*) causes the opening of voltage-gated $Ca^{2+}$ channels and the activation of a presynaptic $Ca^{2+}$ current. The resulting $Ca^{2+}$ influx triggers transmitter release and a postsynaptic potential change in the postsynaptic cell. A small amplitude presynaptic depolarization elicits a small postsynaptic response, whereas a larger depolarization causes a larger $Ca^{2+}$ current and a larger postsynaptic potential. **(B)** A short depolarization causes a short $Ca^{2+}$ current and a brief and small postsynaptic potential, whereas a longer depolarization causes a longer $Ca^{2+}$ current and a larger postsynaptic potential.

about 2 mM extracellularly, and intracellular free $Ca^{2+}$ is around 100 nM. This imbalance results in a large electrochemical driving force toward calcium entry when $Ca^{2+}$ channels are open, and local $Ca^{2+}$ concentrations near the cytosolic mouth of these channels can reach levels as high as 100 to 300 μM for tens to hundreds of microseconds. Upon entry, calcium ions are thought to bind one or more proteins on docked synaptic vesicles, which act as a sensor for initiating the fusion process. The fusion sensor protein is thus activated by calcium for an extremely brief period, a fact that may help explain the extremely phasic or transient nature of neurotransmitter release.

One candidate protein for the $Ca^{2+}$ fusion sensor is called *synaptotagmin*. It has two so-called C2 domains (similar to the protein kinase C [PKC] $Ca^{2+}$-binding domain) that bind $Ca^{2+}$. After binding calcium, synaptotagmin partially inserts itself into phospholipids of the plasma membrane to bind *SNARE-type* proteins crucial for vesicle fusion. SNARE proteins come in two varieties: vesicular (v-SNAREs) and target (t-SNAREs). The v-SNAREs are found on synaptic vesicles, whereas the t-SNAREs reside on the plasma membrane. In order for vesicle fusion to occur, v-SNAREs and t-SNAREs must associate to form a tight *core-complex* that is extremely resistant to unbinding. The SNARE core complex is highly energetically favorable and requires ATP hydrolysis for unbinding. It is believed that this complex serves as a mechanical hairpin that, when triggered, facilitates mixing of the synaptic vesicle and plasma membrane lipids for vesicle fusion. Evidence that SNARE proteins are essential for vesicle fusion comes from bacterial neurotoxins that selectively degrade SNARE proteins. These toxins are highly potent and require only a few molecules to completely block synaptic transmission. Botulinum toxin, now routinely used for cosmetic applications, is an example of such a compound.

Free $Ca^{2+}$ may regulate other processes aside from vesicle fusion. For example, the recruitment of synaptic vesicles from reserve pools to the docked or *readily releasable pool* is accelerated by elevated intracellular $Ca^{2+}$. Endocytosis, the process of synaptic vesicle reuptake, may also be regulated by $Ca^{2+}$ at some synapses, and short-term facilitation of EPSPs can result from residual $Ca^{2+}$ accumulation during a tetanus. In addition, $Ca^{2+}$ activates different kinases and phosphatases, which regulate several forms of long-term morphologic and functional synaptic plasticity.

After synaptic vesicles fuse with the plasma membrane, they are recycled back into the nerve terminal (Fig. 3). The process of vesicular membrane reinternalization (or retrieval) from the plasma membrane is called *endocytosis*, and the synapse uses several forms of this process. Some endocytosis is very fast and occurs with a time constant of about 1 s. Other forms are slower (time constant of 10 to 20 s), and are probably mediated by *clathrin*-coated pits that form on the plasma membrane. Endocytosing vesicles require a GTPase called *dynamin* to "pinch off" from the plasma membrane into the intracellular space. Interestingly, the *Drosophila* mutant *shibire* has a temperature-sensitive defect in dynamin and becomes paralyzed at elevated temperatures (e.g., 29°C). Electron microscopy reveals that the nerve terminals of these paralyzed flies are

devoid of cytoplasmic synaptic vesicles. Furthermore, the plasma membrane is found to have a string of coated invaginations that cannot pinch off. This observation indicates that the terminals are incapable of completing endocytosis and cannot recycle their vesicular membrane after fusion. Accordingly, the surface area of the terminals is enlarged, and there are no vesicles available for continued exocytosis. This dramatic phenotype clearly demonstrates the importance of vesicle recycling for the continuous operation of a synapse. It also illustrates that severe *vesicle pool depletion* will block synaptic transmission.

## 4. NEUROTRANSMITTERS AND THEIR RECEPTORS IN THE MAMMALIAN BRAIN

A large proportion of synapses in the mammalian brain are excitatory and use the amino acid *glutamate* as their neurotransmitter. Glutamate is sequestered into vesicles by a *glutamate transporter* protein in the vesicular membrane. Synaptic vesicles are acidic (pH = 5.7), and the energy from their proton concentration gradient is used to transport neurotransmitter into the vesicle. Synaptic vesicles therefore require a proton ATPase to acidify their interior (or lumen). There are two broad categories of synaptic vesicle proteins: transport proteins (e.g., proton pumps, $Na^+/Ca^{2+}$ exchangers, and $Cl^-$ ion transporters) and trafficking/fusion proteins (e.g., v-SNAREs, synaptotagmin, synapsin). Once glutamate is released into the synaptic cleft, it diffuses away quickly (within milliseconds) and binds to *plasma membrane glutamate transporters* located in presynaptic and postsynaptic neurons and glia (or astrocytes). These transporters use existing sodium and potassium gradients to drive glutamate back into the cytoplasm. Neurotransmitter is recycled in this manner, and because excessive glutamate is toxic for neurons and can lead to cell death, the external glutamate concentration is tightly controlled by this reuptake process.

On the postsynaptic cell, glutamate receptors can be classified into two general types: ionotropic and metabotropic receptors. As noted previously, ionotropic receptors directly gate ion channels, whereas metabotropic receptors are coupled to G proteins. There are three kinds of ionotropic glutamate receptors, each named after the glutamate analogue they bind preferentially: α-amino-3-hydroxy-5-methyl-4-isoxalane propionate (AMPA), N-methyl-D-aspartate (NMDA), and kainate. Glutamate and the synthetic compound AMPA are potent *agonists* for the AMPA-type receptor. The AMPA receptor also has specific *antagonists* such as the compounds 6-cyano-7-nitroguinoxaline-2,3-dione (CNQX) and 6-nitro-7-sulphamobenzoquinoxaline-2,3-dione (NBQX). These do not affect the NMDA receptor. Glutamate binding to the AMPA receptor opens a nonselective cation channel permeable to both $Na^+$ and $K^+$ ions; an event that tends to bring a negative resting membrane potential toward 0 mV. AMPA receptors have intrinsically fast kinetics and desensitize within milliseconds given a continuous pulse of glutamate. The fast EPSPs observed at excitatory synapses are mediated by AMPA receptor activation. NMDA receptors have slower kinetics, use glycine as a co-agonist, and do not desensitize quickly. They are often colocalized at the PSD with AMPA receptors. NMDA and kainate receptors have also been found recently in some CNS presynaptic nerve terminals, but their function is not well understood.

The major inhibitory neurotransmitters in the brain are *GABA* and *glycine*. These transmitters are similarly packaged into vesicles by vesicular GABA/glycine transporters expressed on the membrane of synaptic vesicles. Other neurotransmitters in the mammalian brain include acetylcholine, ATP, adenosine, and several amine transmitters (e.g., dopamine, noradrenaline [or norepinephrine], adrenaline [or epinephrine], serotonin, and histamine). The *catecholamine* transmitters (dopamine, noradrenaline, and adrenaline) are all synthesized from the essential amino acid tyrosine in a common biosynthetic pathway. Catecholamines are important in the brain, not only as neurotransmitters, but also as *neuromodulators* that have widespread effects on neuronal circuits. Interestingly, vesicular amine transporters are targets for several pharmacologic agents. For example, the antipsychotic drugs reserpine and tetrabenazine inhibit amine transporters, and the psychostimulants amphetamine and "ecstasy (3-Y-methylenedioxy-N-methylamphetamine)" are thought to dissipate the pH gradient of synaptic vesicles containing amine transmitters.

There are three types of GABA receptors, termed $GABA_A$, $GABA_B$, and $GABA_C$. The $GABA_A$ and $GABA_C$ receptors are ionotropic, whereas the $GABA_B$ receptor is metabotropic. The $GABA_A$ receptor is blocked by bicuculline and desensitizes quickly, whereas $GABA_C$ receptors desensitize much more slowly and are insensitive to bicuculline. GABA binding to the $GABA_A$ or $GABA_C$ receptor opens an anion-selective $Cl^-$ channel that tends to bring the membrane potential toward the equilibrium potential of $Cl^-$ (about –60 to –80 mV, depending on intracellular $Cl^-$ concentration). This hyperpolarization usually inhibits the postsynaptic neuron from firing APs. $GABA_B$ receptors are also known to have

inhibitory function. For example, the $GABA_B$ receptors of some presynaptic terminals inhibit $Ca^{2+}$ channels and cause a reduction of transmitter release. Glycine receptors are ionotropic (anion-selective $Cl^-$ channels) and can have very rapid kinetics of activation and deactivation.

## 5. THE INTERPLAY OF EXCITATION AND INHIBITION

A simple neural circuit that demonstrates how excitatory and inhibitory synapses are combined to produce a functionally significant behavior is the myotatic (or "knee-jerk") spinal reflex (Fig. 6). When a hammer is tapped on the extensor muscle, sensory axons carry the information from the extensor muscle toward the spinal cord. These or any other axons that carry information to the brain or spinal cord are called *afferents*. Motor axons, or *efferents*, carry information away from the brain or spinal cord and initiate a behavioral response to the hammer tap (an upward jerk of the leg). Along their path, the sensory afferents branch to make synaptic contact with both motor neurons of the ventral horn and spinal *interneurons* (i.e., neurons that lie entirely in the spinal cord). The sensory axon synaptic terminals release glutamate and are excitatory, whereas the interneurons release inhibitory neurotransmitters (GABA and glycine). The sensory neurons thus excite motor neurons that make synaptic contact with the extensor muscle and cause it to contract. At the same time, the sensory axon terminals also excite local inhibitory interneurons that synapse onto the motor neurons innervating the flexor muscle. This causes a relaxation of the flexor and permits the opposing extensor muscle to dominate the behavioral response.

Electrophysiologic recordings from the sensory, interneuron, and motor neurons of the myotatic spinal circuit provide insight into how the circuit operates (Fig. 6). There are several types of electrophysiologic recordings. *Extracellular recording* with an electrode (usually metal) placed near the neuron measures the all-or-nothing APs produced by the neuron. *Intracellular recordings* where the electrode (usually a glass micropipette filled with a conducting solution) impales the cell (like in Fig. 4) can detect smaller, subthreshold synaptic potentials. *Patch-clamp recordings*, where a glass electrode is placed on the membrane of the cell, are very low noise recordings that can even detect single channel currents. Examples of extracellular recordings from spinal neurons involved in the myotatic reflex are shown in Fig. 6. Neurons usually have a low level of spontaneous AP firing, even in the absence of any synaptic or sensory input. The hammer tap to

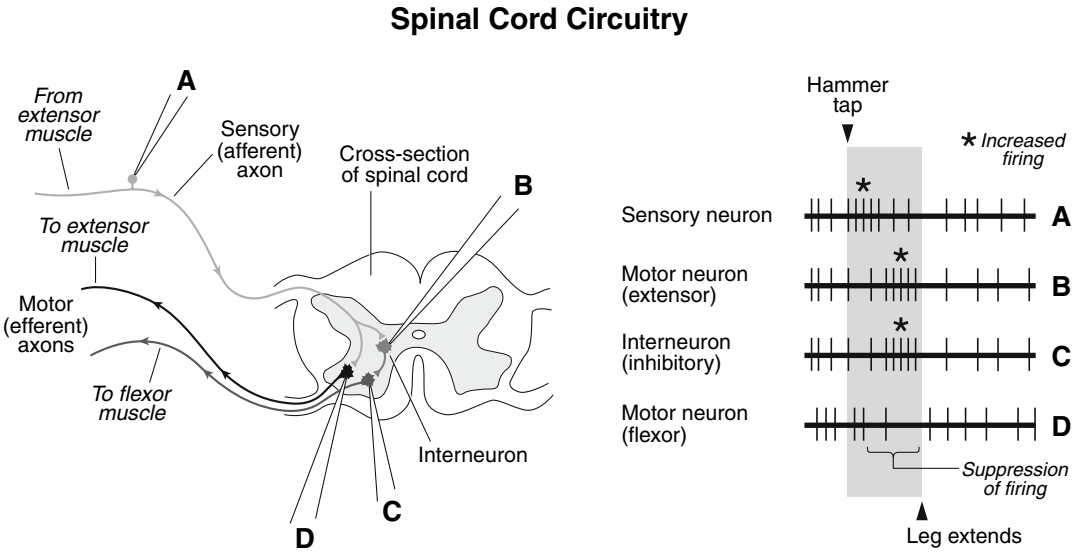


**Fig. 6.** A reflex circuit in the spinal cord. Schematic diagram of spinal cord circuitry. Extracellular electrophysiologic recordings from the four specified neurons are shown on the right-hand panel. A gentle hammer tap to the knee causes a burst of APs to travel along the sensory axons (recorded by electrode *A*) and toward the neurons of the spinal cord. The sensory axon branches into two pathways exciting the motor neurons connected to the extensor muscle (recorded by electrode *D*) and certain interneurons in the spinal cord (recorded by electrode *B*). The interneurons then inhibit the firing of the motor neurons connected to the flexor muscle (recorded by electrode *C*). The hammer tap thus causes the reflex of leg extension. (Modified from Augustine, G.A., Chapter 1. In: *Neuroscience*, edited by Purves et al, 2001.)

the knee elicits a burst of APs in the sensory neuron, which is followed after a brief delay by a burst of APs in the motor (extensor) neurons and interneurons. The interneurons then inhibit the firing of the flexor motor neurons. The end result is a leg extension. Recordings of AP onset, duration, and frequency thus provide a real-time picture of neuronal activity. By using the complementary intracellular and patch-clamp recording techniques, the mechanisms underlying circuit function can be determined.

## 6. SYNAPSES ARE HETEROGENEOUS AND CAN BE SPECIALIZED

Synapses can exhibit different functional properties and architectures depending on their specific information transfer and processing needs. We will next discuss ribbon-type and calyx-type synapses found in the retina and brain stem as examples of highly specialized synapses. We then summarize some of the hallmark properties of the more typical bouton-type synapses found in the cortex and other parts of the brain.

*Ribbon-type synapses* are found in the vertebrate retina and the cochlea. Retinal photoreceptors and bipolar cells and cochlear hair cells transmit sensory information via this type of synapse. Light and sound stimuli produce tonic and graded membrane depolarizations in these cells, which elicits the graded release of neurotransmitter from the specialized active zones called *synaptic ribbons*. These synapses are specialized to transmit the large amounts of sensory information involved in vision and hearing.

One of the techniques used to study the synaptic release of neurotransmitter from these cells is time-resolved *membrane capacitance measurements*, which are based on the patch-clamp recording technique. Electrical membrane capacitance is proportional to the surface area of a cell. When there is an increase in cell surface area (e.g., during exocytosis), membrane capacitance increases. Similarly, when surface area decreases (e.g., during endocytosis), membrane capacitance deceases. Net changes in cell surface area of $<1\%$ can be detected by this exquisitely sensitive technique. An example of a membrane capacitance ($C_m$) measurement is shown in Fig. 7. This $C_m$ measurement was obtained from the whole-cell patch-clamp recording of an isolated synaptic terminal of a goldfish retinal bipolar cell. The terminal's baseline $C_m$ value is constant until a step depolarization (from a holding potential of –60 mV to –10 mV) is given during the gray bar (Fig. 7A). This depolarization opens

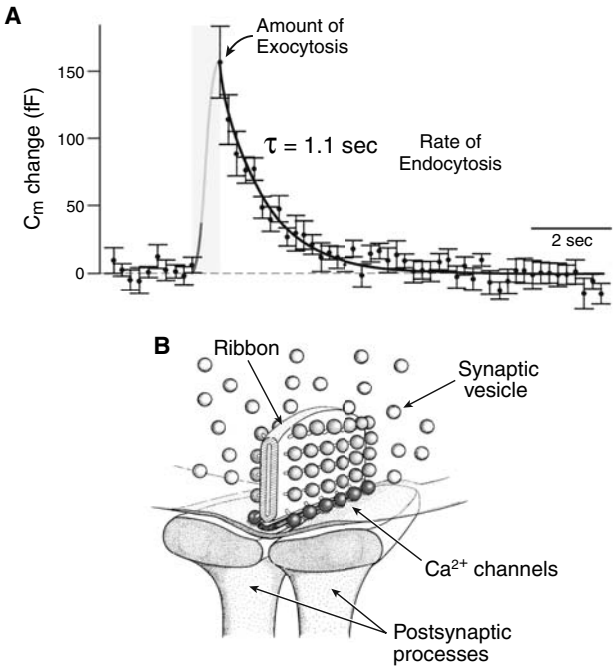


**Fig. 7.** Synaptic transmission at a ribbon synapse. **(A)** Membrane capacitance ($C_m$) measurements from the ribbon-type synaptic terminal of bipolar cells in the goldfish retina. A step depolarization (from the a holding potential of –60 mV to –10 mV), given during the period marked by a gray bar, elicits a jump in $C_m$ of about 150 femtofarad (fF). This corresponds with the fusion (or exocytosis) of about 6000 synaptic vesicles with the presynaptic plasma membrane. After the jump in $C_m$, the capacitance decays back to the original baseline following a single exponential time course. The time constant $\tau = 1.1$ s is a measure of the rate of membrane retrieval (endocytosis). **(B)** A three-dimensional schematic drawing of the ribbon-type active zone of bipolar cell synaptic terminals. The electron-dense "ribbon" sheet has a halo of tethered synaptic vesicles. Vesicles located in the bottom row (*black vesicles*) are docked to the plasma membrane and are close to $Ca^{2+}$ channels. They constitute a readily releasable pool of vesicles. The other vesicles (*gray vesicles*) tethered to the ribbon structure are thought to be next in line for fusion. (Modified from von Gersdorff, H. Synaptic ribbons: versatile signal transducers. *Neuron* 2001;29:7–10).

$Ca^{2+}$ channels, and the resulting influx of $Ca^{2+}$ into the terminal triggers the fusion of synaptic vesicles with the plasma membrane along with an increase in the terminal's surface area. This is detected as a jump in $C_m$ immediately after the depolarization. The size of the jump is 150 femtofarad. Because each synaptic vesicle has a diameter of about 30 nm and a capacitance of 26.4 attofarad, the $C_m$ jump corresponds with the fusion of about 6000 synaptic vesicles. A strong depolarization can thus elicit the fusion of several thousand vesicles at ribbon synapses. Large vesicle

pools that can be released quickly are a characteristic of ribbon-type synapses, and this property allows them to release small or large amounts of transmitter depending on the degree and speed of the presynaptic depolarization. After the jump in $C_m$, membrane capacitance decays back to the original baseline following a single exponential time course. The exponential time constant of $\tau = 1.1\,s$ is a measure of the rate of membrane retrieval (endocytosis). Fused synaptic vesicle membrane can thus be quickly reinternalized and recycled into the terminal.

Figure 7B diagrams the unique architecture of a ribbon-type active zone as seen by electron microscopy. An electron-dense "ribbon" sheet has a halo of tethered synaptic vesicles. Vesicles located in the bottom row (black vesicles) are docked to the plasma membrane. They are close to $Ca^{2+}$ channels and presumably poised for rapid exocytosis, constituting an immediately releasable pool of vesicles. The other vesicles (gray vesicles) tethered to the ribbon structure are thought to be next in line for fusion. After these vesicles fuse, the synapse is refractory to subsequent release for a few seconds. The vesicles tethered to the synaptic ribbon may thus be the morphologic correlate of a *readily releasable pool* of synaptic vesicles.

A second type of specialized synapse is located in the mammalian auditory brain stem, where *calyx-type synapses* involved in calculating the location of sound sources are found. The morphology of the synapse is shown in Fig. 8. The large calyx-type synaptic terminal has hundreds of small *conventional active zones* in adult animals. Each conventional active zone has about 2 to 10 docked vesicles and a cluster of reserve vesicles, as depicted in Fig. 2 and Fig. 3. At the calyx of Held, a single presynaptic AP evokes the rapid release of about 200 to 300 synaptic vesicles. This produces a large EPSC and EPSP that safely cross the threshold for the postsynaptic AP (Fig. 9). Thus synaptic transmission is very safe (free of spike failures) and fast at this specialized synapse. In addition, each conventional active zone in the calyx of Held terminal has a different release probability. During a stimulus consisting of a train of presynaptic APs, this heterogeneity of release probabilities means that some active zones (with high release probability) will release transmitter early during the stimulus train, whereas others (with low release probability) will release late in the stimulus train. This synapse is thus able to faithfully follow a presynaptic train of APs, even when this train occurs at very high frequency (e.g., 800 Hz). The large number of active zones also ensures a short synaptic delay

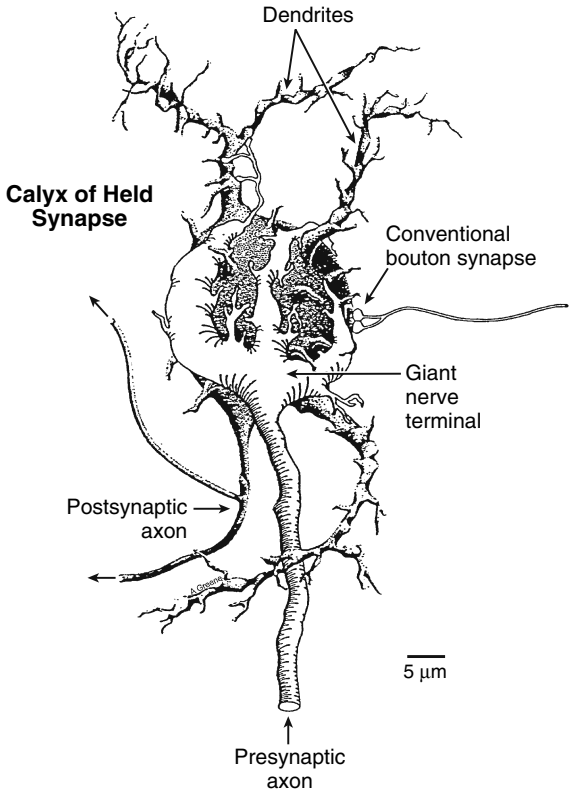


**Fig. 8.** The calyx of Held synapse. A diagram of the adult calyx of Held, a glutamatergic nerve terminal in the mammalian auditory brain stem. Notice the large-caliber axon (4 to 12 μm) that gives rise to the calyx terminal. The postsynaptic cell has relatively short dendrites and an axon with a collateral branch. A typical bouton-type terminal is indicated for comparison. Most synapses in the brain are conventional bouton-type synapses formed on postsynaptic dendrites. (Modified from Morest, D.K. et al. Stimulus coding at the caudal levels of the cat's auditory nervous system. In: *Basic Mechanisms of Hearing*, edited by Möller, A.R. Academic Press, New York, 1973.)

because the EPSP is very fast and large (Fig. 9 and Fig. 10). This leads to a precise preservation of AP timing. The ability of the postsynaptic neuron to follow presynaptic APs with high fidelity and short synaptic delays are features that help in the processing of sound localization in this auditory pathway synapse.

Some synapses, like the neuromuscular junction, the calyx-type brain-stem synapse, and the squid giant synapse, are relatively large and guarantee fail-safe transmission. In adult animals, these synapses are relatively fixed in their transmission characteristics. Most synapses in the mammalian brain are, however, more plastic and physically small (diameter of $<1$ μm; Fig. 8). They produce small EPSPs and have a low release probability. This makes them rather unreliable

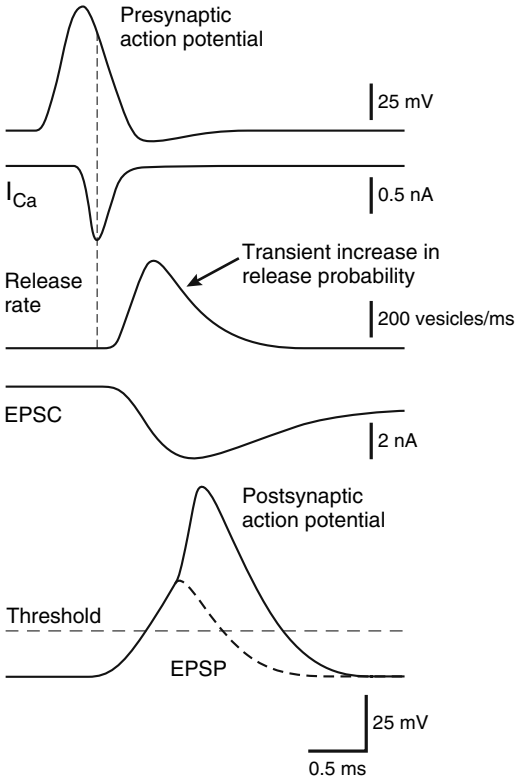


**Fig. 9.** Synaptic transmission at a conventional active zone synapse: the calyx of Held. A presynaptic AP in the calyx nerve terminal triggers the opening of voltage-dependent $Ca^{2+}$ channels, which cause a $Ca^{2+}$ current that occurs during the downstroke phase of the AP. $Ca^{2+}$ influx triggers the fusion of synaptic vesicles that release glutamate into the synaptic cleft. The rate of glutamate release (or vesicle fusion) rises rapidly after the $Ca^{2+}$ current and then decays rapidly. The time between the peak of the $Ca^{2+}$ current and the peak of the release rate is 0.5 ms. Glutamate binding to postsynaptic receptors opens ion channels in the postsynaptic membrane that are permeable of $Na^+$ and $K^+$ ions (the postsynaptic receptors are called AMPA-type glutamate receptors). This ion influx generates an excitatory postsynaptic current (EPSC) that depolarizes the postsynaptic neuron creating a fast and large excitatory postsynaptic potential (EPSP). The time between the peak of the release rate and the peak of the EPSC is 0.4 ms. The large EPSP quickly crosses the AP threshold. Thus a postsynaptic AP is generated in the postsynaptic neuron without failure and with minimal synaptic delay (Modified from von Gersdorff, H. and Borst, J.G.G. Short-term plasticity at the calyx of Held. *Nat Rev Neuro sci* 2002; 3: 53–64.)

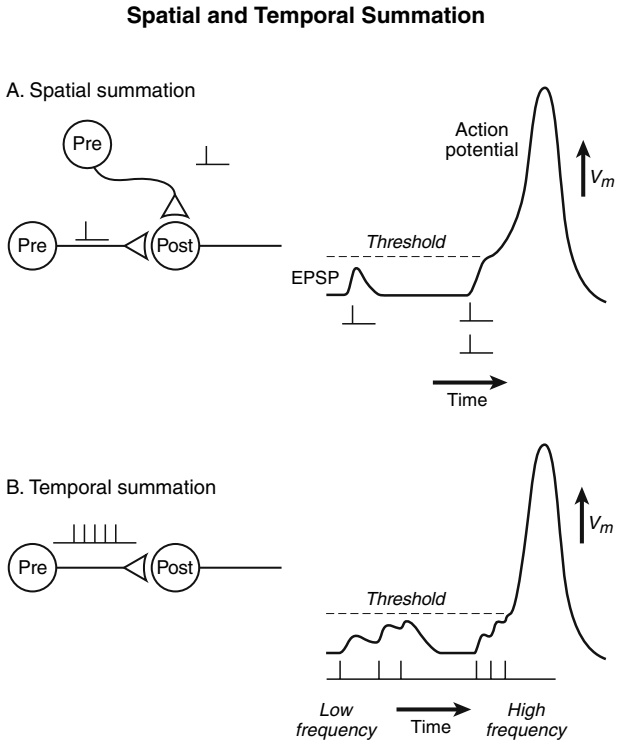


**Fig. 10.** Spatial and temporal summation at bouton-type synapses. **(A)** Spatial summation. Schematic diagram showing how the input from two small, bouton-type presynaptic terminals can summate to produce a suprathreshold excitatory postsynaptic potential (EPSP). The input from just one bouton is not enough to trigger an AP in the postsynaptic cell. However, if the two inputs elicit simultaneous EPSPs in the postsynaptic cell, the summed depolarization is enough to trigger an AP. **(B)** Temporal summation. Low-frequency stimulation may not be enough to trigger an AP in the postsynaptic cell. However, high-frequency stimulation may cause the individual EPSPs is summate fast enough to trigger an AP. The importance of the relative timing of EPSPs is thus evident from these two examples. (Modified from Gardner, D. Synaptic transmission. In: *Neuroscience in Medicine*, edited by Conn, M.P. J.B. Lippincott, Philadelphia, 1995.)

in transmitting signals. These synapses are called conventional *bouton-type synapses*. Their small EPSPs may, nevertheless, summate on a postsynaptic neuron to help it fire APs (Fig. 10). The relative timing of presynaptic APs and resulting EPSPs is critical for *spatial* or *temporal summation* (Fig. 10). The strength with which a postsynaptic neuron will be stimulated will thus depend on the individual strength of the separate bouton-type synapses that make contact with its dendrites and soma and the relative timing of transmitter release. Whether an EPSP generates a spike (AP) or not depends on the amplitude of the EPSP and the *spike threshold* of the postsynaptic neuron. In addition, the nature of the transmission (excitatory or inhibitory) depends on the neurotransmitter type (e.g., glutamate [Glu] is excitatory and GABA is inhibitory), the postsynaptic ionotropic receptor type (e.g., glutamate or GABA receptor ion channels), and on the reversal potentials for the ionic currents present on the postsynaptic neuron (Fig. 11). The reversal potentials for the EPSC (mediated by Glu receptors, which are permeable mainly to $Na^+$ and $K^+$ ions)

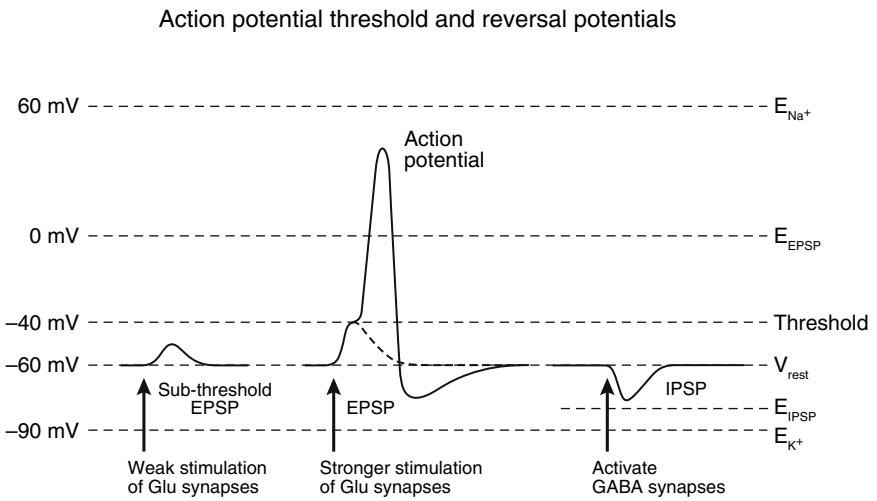


**Fig. 11.** Synaptic transmission and reversal potentials: excitation and inhibition. A subthreshold excitatory postsynaptic potential (EPSP) is elicited in a postsynaptic neuron. This can be generated by a single excitatory volley or by the recruitment of only a few axons and/or synapses onto the postsynaptic neuron. The recruitment of more afferent axons with stronger stimulation causes more excitatory glutamatergic synapses to release glutamate (Glu). Likewise, the more coincident activation of several Glu synapses can generate a larger and faster EPSP, which reaches the threshold for AP firing. The reversal potential for the EPSP ($E_{EPSP}$) is located near 0 mV because the AMPA-type and NMDA-type receptors that mediate the EPSP are transmitter-gated ion channels that are equally permeable to $Na^+$ and $K^+$ ions. Activation of GABAergic synapses generates an inhibitory postsynaptic potential (IPSP) that has a reversal potential ($E_{IPSP}$) at around –80 mV because GABA receptors are transmitter-gated ion channels selectively permeable to $Cl^-$ ions. In this example, the neuron's resting membrane potential ($V_{rest}$) is –60 mV, and the threshold for AP firing is –40 mV, which is where $Na^+$ channels begin to open significantly with higher probability. The Nernst reversal potential (or equilibrium potential) for $Na^+$ ions ($E_{Na}$) is +60 mV and for $K^+$ ions ($E_K$) is –90 mV. Because $E_{EPSP} >$ threshold, glutamate is an excitatory neurotransmitter, whereas $E_{IPSP} <$ threshold makes GABA an inhibitory neurotransmitter. Note how the IPSP tends to inhibit the triggering of APs. GABAergic synapses thus tend to reduce the excitability of adult mammalian neurons.

and the IPSC (mediated by GABA receptors, which are selectively permeable to $Cl^-$ ions) will in their turn depend on the concentration of $Na^+$, $K^+$, and $Cl^-$ ions in the inside and outside of the synapse (Fig. 11; *see also* Chapter 3).

Bouton-type synapses of the CNS can also change their properties dramatically after certain patterns of neuronal activity. This aspect of synaptic plasticity is a way of storing new information acquired by experience in the synaptic strength of a particular synapse. The small size of bouton-type synapses also allows for a large number of synapses to be packed in a small volume, thus increasing the computational capacity of the brain. Often, one presynaptic bouton-type terminal synapses onto one spine-like dendritic structure of a postsynaptic neuron (as depicted in Fig. 3), and a single dendrite can have hundreds to thousands of *postsynaptic spines* (*see* Fig. 2 for an electron microscope image of a spine). Each bouton-type terminal typically has one conventional active zone with about 2 to 10 docked vesicles and a cluster of reserve vesicles in its cytosol. In total, the whole bouton has about 200 vesicles. Accordingly, these synapses have a small readily releasable pool estimated to be about 10 vesicles. Neuromodulators, such as noradrenaline and dopamine, can also change the output of bouton-type synapses, making them especially flexible transducers of information.

## 7. SHORT-TERM AND LONG-TERM SYNAPTIC PLASTICITY

After a train of presynaptic APs (or a tetanic stimulus), the corresponding postsynaptic potentials can grow in amplitude (a process called *short-term facilitation*) or decrease in amplitude (a process called *short-term depression*). Often, synapses display first short-term facilitation followed by short-term depression or, alternatively, just short-term depression. There are multiple synaptic mechanisms that may underlie these forms of short-term synaptic plasticity. For example, after the first presynaptic AP in a stimulus train, the $Ca^{2+}$ concentration in the terminal decays back to resting levels. However, this decay may take several milliseconds to be completed depending on the $Ca^{2+}$ buffering capacity of the terminal. The second stimuli in the train may thus elevate $Ca^{2+}$

concentrations to levels higher than that of the first stimulus. Given the highly nonlinear dependence of transmitter release on $Ca^{2+}$, short-term facilitation may therefore be due to the high resting $Ca^{2+}$ concentrations reached during a stimulus train.

Short-term depression may be caused by presynaptic or postsynaptic mechanisms. During a stimulus train, the pool of readily releasable vesicles may get depleted at a rate faster than the replenishment rate by newly recruited vesicles. The resulting depletion of the readily releasable pool of vesicles will thus cause synaptic depression. The presynaptic $Ca^{2+}$ current may also become progressively inactivated during a stimulus train leading to decreased release. Alternatively, postsynaptic factors may also lead to reduced EPSPs or IPSPs, as postsynaptic ionotropic receptors may desensitize and/or saturate (i.e., the receptors may become insensitive to further neurotransmitter release). Stimulation at very high frequencies often leads to short-term depression. Thus, high-frequency inputs may be strongly filtered from a neuronal circuit by short-term plasticity.

Some synapses can change their release characteristics for a period of hours to days after receiving a particular stimulus pattern. This form of long-term plasticity is commonly found in the mammalian hippocampus and cortex. Synaptic strength may thus be increased (a process called *long-term potentiation*) or reduced (a process called *long-term depression*). One mechanism for long-term potentiation involves the properties of the AMPA- and NMDA-type receptors located on postsynaptic dendritic spines. These receptors bind glutamate and then open channels permeable to cations. The release of glutamate from bouton-type presynaptic terminals thus produces a rapid AMPA receptor–mediated EPSPs that transiently depolarizes the spine. Glutamate binds also to the slower activating and inactivating NMDA receptors colocalized with the AMPA receptors on the spine. However, when the spine is initially at its resting membrane potential, external $Mg^{2+}$ ions block the NMDA channel and no current flows through the channel, even as its transmitter-activated gate is slowly opened by glutamate. On the other hand, if the dendritic spine has been previously depolarized by other nearby synaptic inputs, the $Mg^{2+}$ block is removed and the NMDA channel pore can now pass current upon glutamate binding. The NMDA receptor is thus both a voltage-dependent and ligand-gated channel, with the voltage dependence arising from the voltage-dependent $Mg^{2+}$ block of the channel pore. NMDA receptors, unlike most AMPA receptors, are permeable to $Ca^{2+}$ ions. Thus the NMDA receptor–mediated postsynaptic current will increase $Ca^{2+}$ concentrations in the spine, leading to the activation of *$Ca^{2+}$-dependent kinases* that may phosphorylate the AMPA receptor and thus augment its current. In addition, $Ca^{2+}$ ions in the spine may trigger the release of *retrograde messengers* that feed back onto the bouton terminal to increase its release probability. These molecular events may thus produce long-term changes in synaptic strength. The NMDA receptor can thus operate as a *coincidence detector* that detects spine depolarization by other synaptic inputs and glutamate release from its own opposing bouton terminal. This association of different synaptic inputs, which are activated at specific times, and the resulting selective strengthening of a particular synapse may constitute a cellular mechanism for learning and memory.

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