15

Transmitter Release

Some of the brain's most remarkable abilities, such as learning and memory, are thought to emerge from the elementary properties of chemical synapses, where the presynaptic cell releases chemical transmitters that activate receptors in the membrane of the postsynaptic cell. At most central synapses, transmitter is released from the presynaptic cell at presynaptic boutons, varicosities along the axon (like beads on a string) filled with synaptic vesicles and other organelles that contact postsynaptic targets. At other synapses, including the neuromuscular junction, transmitter is released from presynaptic terminals at the end of the axon. For convenience, we will refer to both types of release sites as presynaptic terminals. In the last three chapters, we saw how postsynaptic receptors control ion channels that generate the postsynaptic potential. Here we consider how electrical and biochemical events in the presynaptic terminal lead to the rapid release of small-molecule neurotransmitters, such as acetylcholine (ACh), glutamate, and γ-aminobutyric acid (GABA), that underlie fast synaptic transmission. In the next chapter, we examine the chemistry of the neurotransmitters themselves as well as the biogenic amines (serotonin, norepinephrine, and dopamine) and neuropeptides, which underlie slower forms of intercellular signaling.

Transmitter Release Is Regulated by Depolarization of the Presynaptic Terminal

What event at the presynaptic terminal leads to the release of transmitter? Bernard Katz and Ricardo Miledi first demonstrated the importance of depolarization of the presynaptic membrane. For this purpose, they used

the giant synapse of the squid, a synapse large enough to permit insertion of electrodes into both pre- and postsynaptic structures. Two electrodes are inserted into the presynaptic terminal—one for stimulating and one for recording—and one electrode is inserted into the postsynaptic cell for recording the excitatory postsynaptic potential (EPSP), which provides an index of transmitter release (Figure 15–1A).

After the presynaptic neuron is stimulated and fires an action potential, an EPSP large enough to trigger an action potential is recorded in the postsynaptic cell. Katz and Miledi then asked how the presynaptic action potential triggers transmitter release. They found that as voltage-gated Na^+ channels are blocked by application of tetrodotoxin, successive action potentials become progressively smaller. As the action potential is reduced in size, the EPSP decreases accordingly (Figure 15–1B). When the Na^+ channel blockade becomes so profound as to reduce the amplitude of the presynaptic spike below 40 mV (positive to the resting potential), the EPSP disappears altogether. Thus, the amount of transmitter release (as measured by the size of the postsynaptic depolarization) is a steep function of the amount of presynaptic depolarization (Figure 15–1C).

Katz and Miledi next investigated how presynaptic depolarization triggers transmitter release. The action potential is produced by an influx of Na^+ and an efflux of K^+ through voltage-gated channels. To determine

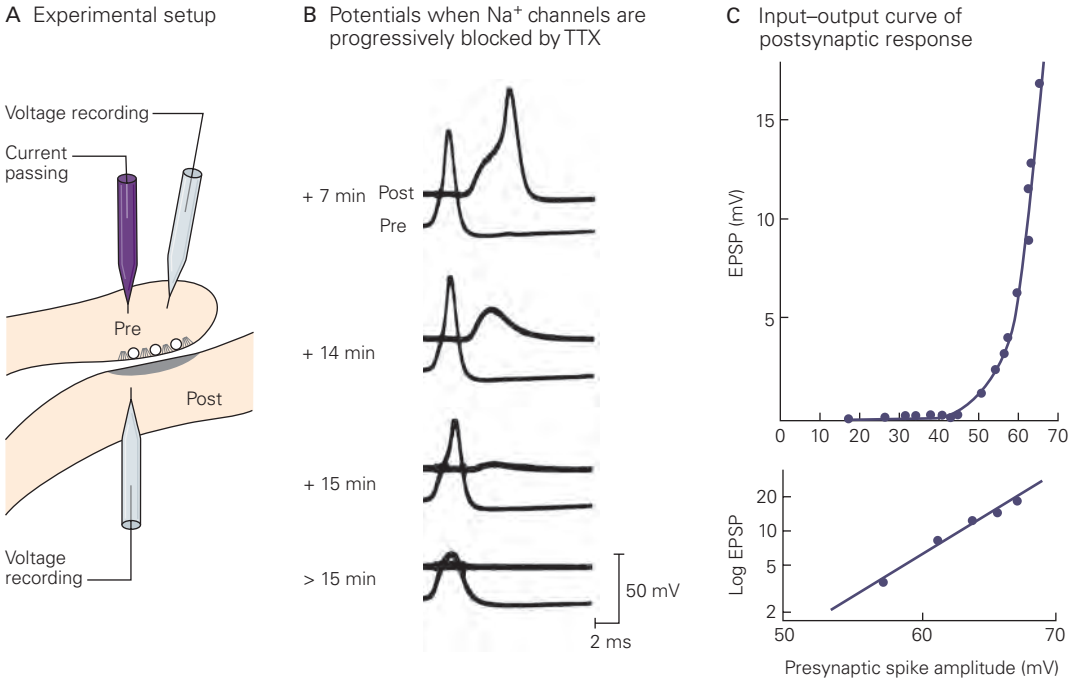

Figure 15–1 Transmitter release is triggered by changes in presynaptic membrane potential. (Adapted, with permission, from Katz and Miledi 1967a.)

A. Voltage recording electrodes are inserted in both the pre- and postsynaptic fibers of the giant synapse in the stellate ganglion of a squid. A current-passing electrode is also inserted presynaptically to elicit a presynaptic action potential.

B. Tetrodotoxin (TTX) is added to the solution bathing the cell to block the voltage-gated Na^+ channels that underlie the action potential. The amplitudes of both the presynaptic action potential and the excitatory postsynaptic potential (EPSP) gradually decrease as more and more Na^+ channels are blocked. After 7 minutes, the presynaptic action potential can still produce a suprathreshold EPSP that triggers an action potential in the postsynaptic cell. After about 14 to 15 minutes, the presynaptic spike gradually becomes smaller and produces smaller postsynaptic depolarizations. When the presynaptic spike is reduced to 40 mV or less, it fails to produce an EPSP. Thus, the size of the presynaptic depolarization (here provided by the action potential) controls the magnitude of transmitter release.

C. The dependence of the amplitude of the EPSP on the amplitude of the presynaptic action potential is the basis for the input–output curve for transmitter release. This relation is obtained by stimulating the presynaptic nerve during the onset of the blockade by TTX of the presynaptic Na^+ channels, when there is a progressive reduction in the amplitude of the presynaptic action potential and postsynaptic depolarization. The upper plot demonstrates that a 40-mV presynaptic action potential is required to produce a postsynaptic potential. Beyond this threshold, there is a steep increase in amplitude of the EPSP in response to small increases in the amplitude of the presynaptic potential. The relationship between the presynaptic spike and the EPSP is logarithmic, as shown in the lower plot. A 13.5-mV increase in the presynaptic spike produces a 10-fold increase in the EPSP.

whether Na^+ influx or K^+ efflux is required to trigger transmitter release, Katz and Miledi first blocked the Na^+ channels with tetrodotoxin. They then asked whether direct depolarization of the presynaptic membrane, by current injection, would still trigger transmitter release. Indeed, depolarization of the presynaptic membrane beyond a threshold of about 40 mV positive to the resting potential elicits an EPSP in the postsynaptic cell even with the Na^+ channels blocked. Beyond that threshold, progressively greater depolarization leads to progressively greater amounts of transmitter release. This result shows that presynaptic Na^+ influx is not necessary for release; it is important only insofar as it depolarizes the membrane enough for transmitter release to occur (Figure 15–2B).

To examine the contribution of K^+ efflux to transmitter release, Katz and Miledi blocked the voltage-gated K^+ channels with tetraethylammonium at the same time that they blocked the voltage-sensitive Na^+ channels with tetrodotoxin. They then injected a depolarizing current into the presynaptic terminals and found that the EPSPs were of normal size, indicating that normal transmitter release occurred (Figure 15–2C). Thus, neither Na^+ nor K^+ flux is required for transmitter release.

In the presence of tetraethylammonium, the current pulse elicits presynaptic depolarization throughout the duration of the pulse because the K^+ current that normally repolarizes the presynaptic membrane is blocked. As a result, transmitter release is sustained throughout the current pulse as reflected in the prolonged depolarization of the postsynaptic cell (Figure 15–2C). Quantification of the sustained depolarization was used by Katz and Miledi to determine a complete input–output curve relating presynaptic depolarization to transmitter release (Figure 15–2D). They confirmed the steep dependence of transmitter release on presynaptic depolarization. In the range of depolarization over which transmitter release increases (40–70 mV

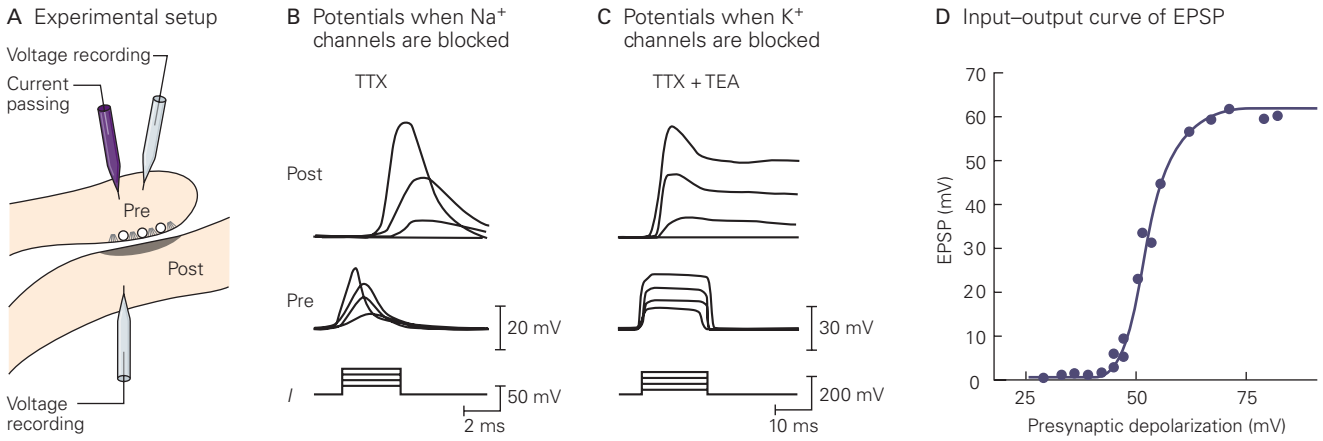

Figure 15–2 **Transmitter release is not directly triggered by the opening of presynaptic voltage-gated Na^+ or K^+ channels.** (Adapted, with permission, from Katz and Miledi 1967a.)

A. Voltage recording electrodes are inserted in both the pre- and postsynaptic fibers of the giant synapse in the stellate ganglion of a squid. A current-passing electrode has also been inserted into the presynaptic cell.

B. Depolarizing the presynaptic terminal with direct current injection through a microelectrode can trigger transmitter release even after the voltage-gated Na^+ channels are completely blocked by adding tetrodotoxin (**TTX**) to the cell-bathing solution. Three sets of traces represent (from bottom to top) the depolarizing current pulse (*I*) injected into the presynaptic terminal, the resulting potential in the presynaptic terminal (**Pre**), and the EPSP generated by the release of transmitter onto the postsynaptic cell (**Post**). Progressively stronger current pulses in the presynaptic cell produce correspondingly greater depolarizations of the presynaptic terminal. The greater the presynaptic depolarization, the larger is the EPSP. The presynaptic depolarizations are not maintained throughout the duration of the depolarizing current pulse because delayed activation of the voltage-gated K^+ channels causes repolarization.

C. Transmitter release occurs even after the voltage-gated Na^+ channels have been blocked with TTX *and* the voltage-gated K^+ channels have been blocked with tetraethylammonium (**TEA**). In this experiment, TEA was injected into the presynaptic terminal. The three sets of traces represent the same measurements as in part B. Because the presynaptic K^+ channels are blocked, the presynaptic depolarization is maintained throughout the current pulse. The large sustained presynaptic depolarization produces large sustained EPSPs.

D. Blocking both the Na^+ and K^+ channels permits accurate control of presynaptic voltage and the determination of a complete input–output curve. Beyond a certain threshold (40 mV positive to the resting potential), there is a steep relationship between presynaptic depolarization and transmitter release, as measured from the size of the EPSP. Depolarizations greater than a certain level do not cause any additional release of transmitter. The initial presynaptic resting membrane potential was approximately −70 mV.

positive to the resting level), a 10-mV increase in presynaptic depolarization produces as much as a 10-fold increase in transmitter release. Depolarization of the presynaptic membrane above an upper limit produces no further increase in the postsynaptic potential.

Release Is Triggered by Calcium Influx

Katz and Miledi next turned their attention to Ca^{2+} ions. Earlier, Katz and José del Castillo had found that increasing the extracellular Ca^{2+} concentration enhanced transmitter release, whereas lowering the concentration reduced and ultimately blocked synaptic transmission. Because transmitter release is an intracellular process, these findings implied that Ca^{2+} must enter the cell to influence transmitter release.

Previous work on the squid giant axon membrane had identified a class of voltage-gated Ca^{2+} channels, the opening of which results in a large Ca^{2+} influx because of the large inward electrochemical driving force on Ca^{2+}. The extracellular Ca^{2+} concentration, approximately 2 mM in vertebrates, is normally four orders of magnitude greater than the intracellular concentration, approximately 10^{-7} M at rest. However, because these Ca^{2+} channels are sparsely distributed along the axon, they cannot, by themselves, provide enough current to produce a regenerative action potential.

Katz and Miledi found that the Ca^{2+} channels were much more abundant at the presynaptic terminal. There, in the presence of tetraethylammonium and tetrodotoxin, a depolarizing current pulse was sometimes able to trigger a regenerative depolarization that required extracellular Ca^{2+}, a *calcium spike*. Katz and Miledi therefore proposed that Ca^{2+} serves dual functions. It is a carrier of depolarizing charge during the action potential (like Na^+), and it is a special chemical signal—a second messenger—conveying information about changes in membrane potential to the intracellular machinery responsible for transmitter release. Calcium ions are able to serve as an efficient chemical signal because of their low intracellular resting concentration, approximately 10^5-fold lower than the resting concentration of Na^+. As a result, the small amount of Ca^{2+} ions that enter or leave a cell during an action potential can lead to large percentage changes in intracellular Ca^{2+} that can trigger various biochemical reactions. Proof of the importance of Ca^{2+} channels in release has come from more recent experiments showing that specific toxins that block Ca^{2+} channels also block release.

The properties of the voltage-gated Ca^{2+} channels at the squid presynaptic terminal were measured by Rodolfo Llinás and his colleagues. Using a voltage clamp, Llinás depolarized the terminal while blocking the voltage-gated Na^+ channels with tetrodotoxin and the K^+ channels with tetraethylammonium. He found that graded depolarizations activated a graded inward Ca^{2+} current, which in turn resulted in graded release of transmitter (Figure 15–3). The Ca^{2+} current is graded because the Ca^{2+} channels are voltage-dependent like the voltage-gated Na^+ and K^+ channels. Calcium ion channels in squid terminals differ from Na^+ channels, however, in that they do not inactivate quickly but stay open as long as the presynaptic depolarization lasts.

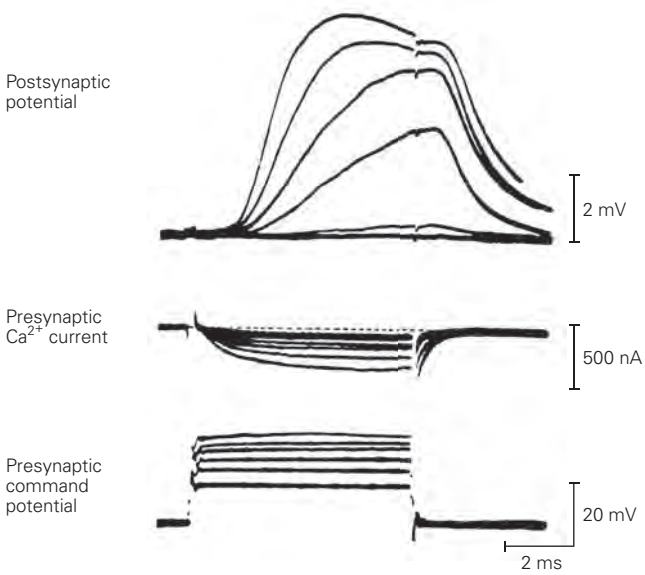

Figure 15–3 Transmitter release is regulated by Ca^{2+} influx into the presynaptic terminals through voltage-gated Ca^{2+} channels. The voltage-sensitive Na^+ and K^+ channels in a squid giant synapse were blocked by tetrodotoxin and tetraethylammonium. The membrane of the presynaptic terminal was voltage-clamped and membrane potential stepped to six different command levels of depolarization (**bottom**). The amplitude of the postsynaptic depolarization (**top**) varies with the size of the presynaptic inward Ca^{2+} current (**middle**) because the amount of transmitter release is a function of the concentration of Ca^{2+} in the presynaptic terminal. The notch in the postsynaptic potential trace is an artifact that results from turning off the presynaptic command potential. (Adapted, with permission, from Llinás and Heuser 1977.)

Calcium channels are largely localized in presynaptic terminals at *active zones*, the sites where neurotransmitter is released, exactly opposite the postsynaptic receptors (Figure 15–4). This localization is important as Ca^{2+} ions do not diffuse long distances from their site of entry because free Ca^{2+} ions are rapidly buffered by Ca^{2+}-binding proteins. As a result, Ca^{2+} influx creates a sharp local rise in Ca^{2+} concentration at the active zones. This rise in Ca^{2+} in the presynaptic terminals can be visualized using Ca^{2+}-sensitive

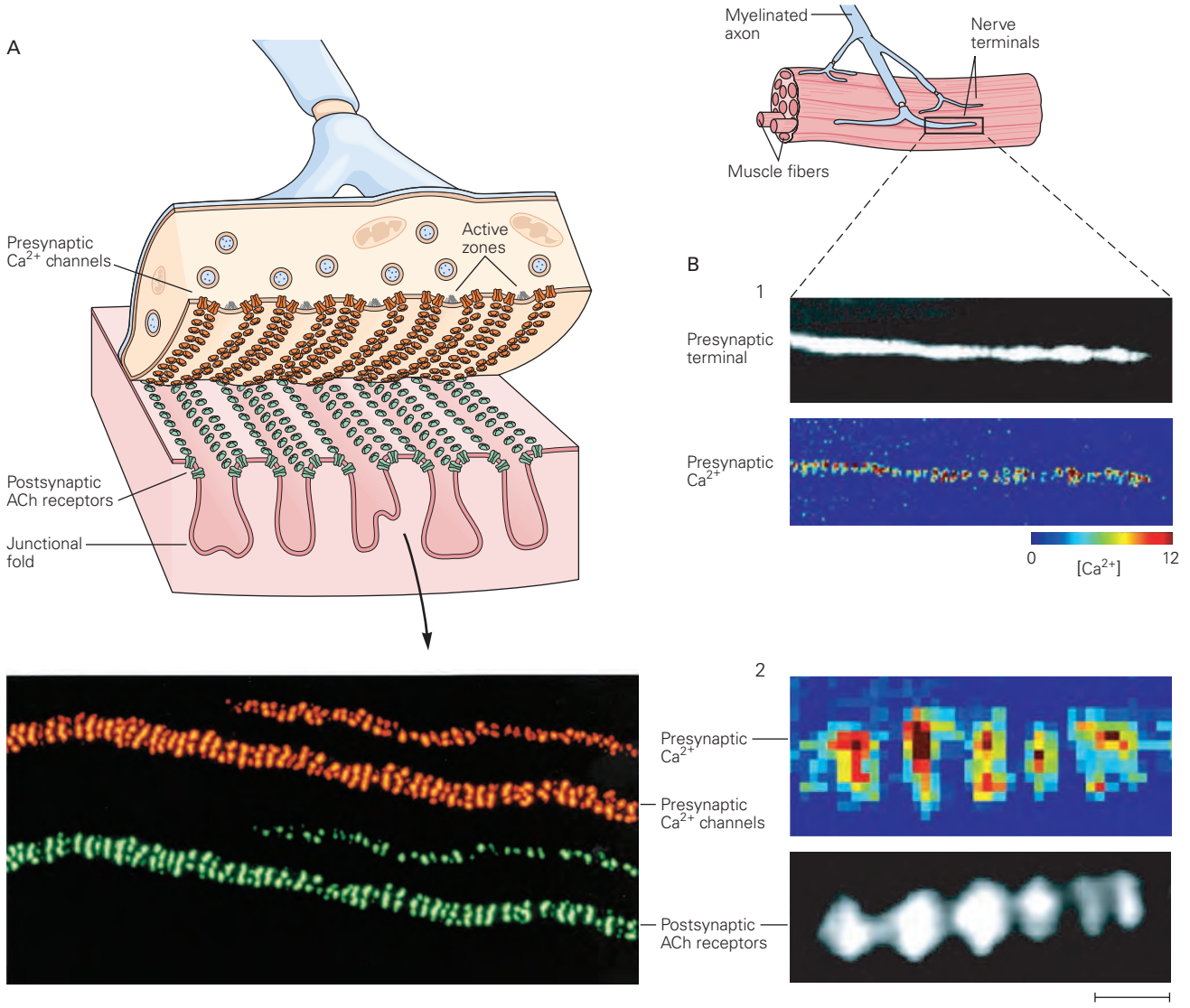

Figure 15–4 **Calcium flowing into the presynaptic nerve terminal during synaptic transmission at the neuromuscular junction is concentrated at the active zone.** Calcium channels in presynaptic terminals at the end-plate are concentrated opposite clusters of nicotinic acetylcholine (**ACh**) receptors on the postsynaptic muscle membrane. Two drawings show the frog neuromuscular junction.

A. The enlarged view shows the microanatomy of the neuromuscular junction with the presynaptic terminal peeled back. A fluorescent image shows the presynaptic Ca^{2+} channels (labeled with a Texas red-coupled marine snail toxin that binds to Ca^{2+} channels) and postsynaptic ACh receptors (labeled with fluorescently tagged α-bungarotoxin, which binds selectively to ACh receptors). The two images are normally superimposed but have been separated for clarity. The patterns of labeling with both probes are in almost precise register, indicating that the active zone of the presynaptic neuron is in almost perfect alignment with the postsynaptic membrane containing the high concentration of ACh receptors. (Reproduced, with permission, from Robitaille, Adler, and Charlton 1990.)

B. Calcium influx in presynaptic terminals is localized at active zones. Calcium can be visualized using Ca^{2+}-sensitive fluorescent dyes. **1.** A presynaptic terminal at a neuromuscular junction filled with the dye fura-2 under resting conditions is shown in the black and white image. The fluorescence intensity of the dye changes as it binds Ca^{2+}. In the color image, color-coded fluorescence intensity changes show local hotspots of intracellular Ca^{2+} in response to a single presynaptic action potential. **Red** indicates regions with a large increase in Ca^{2+}; **blue** indicates regions with little increase in Ca^{2+}. Regular peaks in Ca^{2+} concentration are seen along the terminal, corresponding to the localization of Ca^{2+} channels at the active zones. **2.** The color image shows a high-magnification view of the peak increase in terminal Ca^{2+} levels. The corresponding black and white image shows fluorescence labeling of nicotinic ACh receptors in the postsynaptic membrane, illustrating the close spatial correspondence between areas of presynaptic Ca^{2+} influx and areas of postsynaptic receptors. Scale bar = 2 μm. (Reproduced, with permission, from Wachman et al. 2004. Copyright © 2004 Society for Neuroscience.)

fluorescent dyes (Figure 15–4B). One striking feature of transmitter release at all synapses is its steep and nonlinear dependence on Ca^{2+} influx; a 2-fold increase in Ca^{2+} influx can increase the amount of transmitter released by more than 16-fold. This relationship indicates that at some regulatory site, the *calcium sensor*, the cooperative binding of several Ca^{2+} ions is required to trigger release.

The Relation Between Presynaptic Calcium Concentration and Release

How much Ca^{2+} is necessary to induce release of neurotransmitters? To address this question, Bert Sakmann and Erwin Neher and their colleagues measured synaptic transmission in the calyx of Held, a large synapse in the mammalian auditory brain stem, composed of axons from the cochlear nucleus to the medial nucleus of the trapezoid body. This synapse is specialized for very rapid and reliable transmission to allow for precise localization of sound in the environment.

The calyx forms a cup-like presynaptic terminal that engulfs a postsynaptic cell body (Figure 15–5A). The calyx synapse includes almost a thousand active zones that function as independent release sites. This enables a presynaptic action potential to release a large amount of transmitter that results in a reliably large postsynaptic depolarization. In contrast, individual synaptic boutons of a typical neuron in the brain contain only a single active zone. Because the calyx terminal is large, it is possible to insert electrodes into both the pre- and postsynaptic structures, much as with the squid giant synapse, and directly measure the synaptic coupling between the two compartments. This paired recording allows a precise determination of the time course of activity in the presynaptic and postsynaptic cells (Figure 15–5B).

These recordings revealed a brief lag of 1 to 2 ms between the onset of the presynaptic action potential and the EPSP, which accounts for what Sherrington termed the *synaptic delay.* Because Ca^{2+} channels open more slowly than Na^{+} channels, and the inward Ca^{2+} driving force increases as the neuron repolarizes, Ca^{2+} does not begin to enter the presynaptic terminal in full force until the membrane has begun to repolarize. Surprisingly, once Ca^{2+} enters the terminal, transmitter is rapidly released with a delay of only a few hundred microseconds. Thus, the synaptic delay is largely attributable to the time required to open Ca^{2+} channels. The astonishing speed of Ca^{2+} action indicates that, prior to Ca^{2+} influx, the biochemical machinery underlying the release process must already exist in a primed and ready state. Such rapid kinetics are vital for neuronal information processing and require elegant molecular mechanisms that we shall consider later.

A presynaptic action potential normally produces only a brief rise in presynaptic Ca^{2+} concentration because the Ca^{2+} channels open only for a short time. In addition, Ca^{2+} influx is localized at the active zone. These two properties contribute to a concentrated local pulse of Ca^{2+} that induces a burst of transmitter release (Figure 15–5B). As we shall see later in this chapter, the duration of the action potential regulates the amount of Ca^{2+} that flows into the terminal and thus the amount of transmitter release.

To determine how much Ca^{2+} is needed to trigger release, the Neher and Sakmann groups introduced into the presynaptic terminal an inactive form of Ca^{2+} complexed within a light-sensitive *chemical cage.* They also loaded the terminals with a Ca^{2+}-sensitive fluorescent dye to assay the intracellular free Ca^{2+} concentration. By uncaging the Ca^{2+} ions with a flash of light, they could trigger transmitter release by a uniform and quantifiable increase in Ca^{2+} concentration. These experiments revealed that a rise in Ca^{2+} concentration of less than 1 μM is sufficient to induce release of some transmitter, but approximately 10 to 30 μM Ca^{2+} is required to release the amount normally observed during an action potential. Here again, the relationship between Ca^{2+} concentration and transmitter release is highly nonlinear, consistent with a model in which at least four or five Ca^{2+} ions must bind to the Ca^{2+} sensor to trigger release (Figure 15–5C,D).

Several Classes of Calcium Channels Mediate Transmitter Release

Calcium channels are found in all nerve cells and in many nonneuronal cells. In skeletal and cardiac muscle cells, they are important for excitation-contraction coupling; in endocrine cells, they mediate release of hormones. Neurons contain five broad classes of voltage-gated Ca^{2+} channels: the L-type, P/Q-type, N-type, R-type, and T-type, which are encoded by distinct but closely related genes that can be divided into three gene families based on amino acid sequence similarity. L-type channels are encoded by the Ca_V1 family. Members of the Ca_V2 family comprise P/Q- ($Ca_V2.1$), N- ($Ca_V2.2$), and R-type ($Ca_V2.3$) channels. Finally, T-type channels are encoded by the Ca_V3 gene family. Each channel type has specific biophysical and pharmacological properties and physiological functions (Table 15–1).

Calcium channels are multimeric proteins whose distinct properties are determined by their pore-forming subunit, the α_1-subunit. The α_1-subunit is homologous to the α-subunit of the voltage-gated Na^{+}

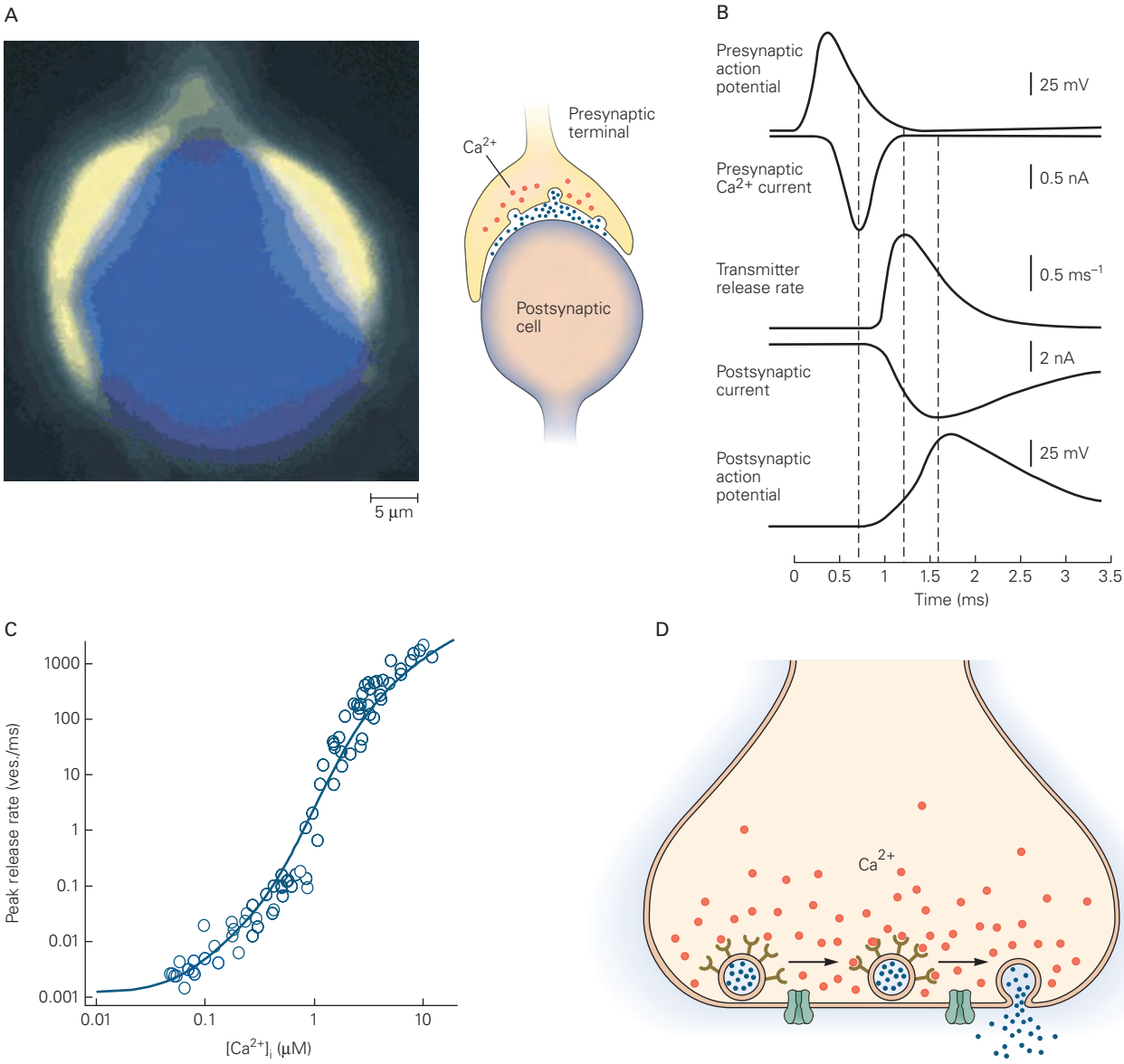

Figure 15–5 The precise relation between presynaptic Ca^{2+} and transmitter release at a central synapse has been measured. (Reproduced, with permission, from Meinrenken, Borst, and Sakmann 2003, and Sun et al. 2007. Parts A and B: Copyright © 2003 John Wiley and Sons.)

A. The large presynaptic terminal of the calyx of Held in the mammalian brain stem engulfs a postsynaptic cell body. The fluorescence image at left shows a calyx filled with a Ca^{2+}-sensitive dye.

B. Time courses for several synaptic events. The **dashed lines** indicate the timing of the peak responses for the Ca^{2+} current, transmitter release, and postsynaptic current.

C. Transmitter release is steeply dependent on the Ca^{2+} concentration in the presynaptic terminal. The calyx was loaded with a caged Ca^{2+} compound that releases its bound Ca^{2+} in response to a flash of ultraviolet light and with a Ca^{2+}-sensitive dye that allows the intracellular Ca^{2+} concentration to be measured. By controlling the intensity of light, one can regulate the increase in Ca^{2+} in the presynaptic terminal. The plot, on a logarithmic scale, shows the relation between the rate of vesicle release and intracellular Ca^{2+} concentration. The **blue line** depicts a fit of the data by a model that assumes that release is triggered by a major Ca^{2+} sensor that binds five Ca^{2+} ions, resulting in a Ca^{2+} cooperativity of five. Due to the nonlinear relationship between $Ca^{2+}$and release, small increments in Ca^{2+} at concentrations of more than 1 µm cause massive increases in release.

D. The release of transmitter from a vesicle requires the binding of five Ca^{2+} ions to a Ca^{2+}-sensing synaptic vesicle protein. In the figure, Ca^{2+} ions bind to five sensors present on a single vesicle; in reality, each sensor molecule binds multiple Ca^{2+} ions.

Table 15–1 Voltage-Gated Ca^{2+} Channels of Neurons

Channel	Former name	Ca^{2+} channel type	Tissue	Blocker	Voltage dependence[1]	Function
$Ca_V1.1–1.4$	$\alpha_{1C,D,F,S}$	L	Muscle, neurons	Dihydropyridines	HVA	Contraction, slow and some limited fast release
$Ca_V2.1$	α_{1A}	P/Q	Neurons	ω-Agatoxin (spider venom)	HVA	Fast release +++
$Ca_V2.2$	α_{1B}	N	Neurons	ω-Conotoxin (cone snail venom)	HVA	Fast release ++
$Ca_V2.3$	α_{1E}	R	Neurons	SNX-482 (tarantula venom)	HVA	Fast release +
$Ca_V3.1–3.3$	$\alpha_{1G,H,I}$	T	Muscle, neurons	Mibefradil (limited selectivity)	LVA	Pacemaker firing

[1]HVA, high voltage activated; LVA, low voltage activated.

channel, comprised of four repeats of a domain with six membrane-spanning segments that includes the S4 voltage-sensor and pore-lining P-region (see Figure 8–10). Calcium channels also have auxiliary subunits (termed α_2, β, γ, and δ) that modify the properties of the channel formed by the α_1-subunit. The subcellular localization in neurons of different types of calcium channels also varies. The N- and P/Q-type Ca^{2+} channels are found predominantly in the presynaptic terminal, whereas L-, R-, and T-type channels are found largely in the soma and dendrites.

Four of the types of voltage-gated Ca^{2+} channels—the L-type, P/Q-type, N-type, and R-type—generally require fairly strong depolarization to be activated (voltages positive to −40 to −20 mV are required) and thus are sometimes loosely referred to as *high-voltage-activated* Ca^{2+} channels (Table 15–1). In contrast, T-type channels open in response to small depolarizations around the threshold for generating an action potential (−60 to −40 mV) and are therefore called *low-voltage-activated* Ca^{2+} channels. Because they are activated by small changes in membrane potential, the T-type channels help control excitability at the resting potential and are an important source of the excitatory current that drives the rhythmic pacemaker activity of certain cells in both the brain and heart.

In neurons, the rapid release of conventional transmitters during fast synaptic transmission is mediated mainly by P/Q-type and N-type Ca^{2+} channels, the channel types most concentrated at the active zone. The localization of N-type Ca^{2+} channels at the frog neuromuscular junction has been visualized using a fluorescence-labeled snail toxin that binds selectively to these channels (see Figure 15–4A). The L-type channels are not found in the active zone and thus do not normally contribute to the fast release of conventional transmitters such as ACh and glutamate. However, Ca^{2+} influx through L-type channels is important for slower forms of release that do not occur at specialized active zones, such as the release of neuropeptides from neurons and of hormones from endocrine cells. As we shall see later, regulation of Ca^{2+} influx into presynaptic terminals controls the amount of transmitter release and hence the strength of synaptic transmission.

Mutations in voltage-gated Ca^{2+} channels are responsible for certain acquired and genetic diseases. Timothy syndrome, a developmental disorder characterized by a severe form of autism with impaired cognitive function and a range of other pathophysiological changes, results from a mutation in the α_1-subunit of L-type channels that alters their voltage-dependent gating, thereby affecting dendritic integration. Different point mutations in the P/Q-type channel α_1-subunit give rise to hemiplegic migraine or epilepsy. Patients with Lambert-Eaton syndrome, an autoimmune disease associated with muscle weakness, make antibodies to the P/Q-type channel α_1-subunit that decrease total Ca^{2+} current (Chapter 57).

Transmitter Is Released in Quantal Units

How does the influx of Ca^{2+} trigger transmitter release? Katz and his colleagues provided a key insight into this question by showing that transmitter is released in discrete amounts they called *quanta.* Each quantum of transmitter produces a postsynaptic potential of fixed size, called the *quantal synaptic potential.* The total postsynaptic potential is made up of a large number of quantal potentials. EPSPs seem smoothly graded in amplitude only because each quantal (or unit) potential is small relative to the total potential.

Katz and Fatt obtained the first clue as to the quantal nature of synaptic transmission in 1951 when they observed spontaneous postsynaptic potentials of approximately 0.5 mV at the nerve-muscle synapse of the frog. Like end-plate potentials evoked by nerve stimulation, these small depolarizing responses are largest at the site of nerve-muscle contact and decay electrotonically with distance (see Figure 12–5). Small spontaneous potentials have since been observed in mammalian muscle and in central neurons. Because postsynaptic potentials at vertebrate nerve-muscle synapses are called end-plate potentials, Fatt and Katz called these spontaneous potentials *miniature end-plate potentials*.

Several results convinced Fatt and Katz that the miniature end-plate potentials represented responses to the release of small amounts of ACh, the neurotransmitter used at the nerve-muscle synapse. The time course of the miniature end-plate potentials and the effects of various drugs on them are indistinguishable from the properties of the end-plate potential. Like the end-plate potentials, the miniature end-plate potentials are enhanced and prolonged by prostigmine, a drug that blocks hydrolysis of ACh by acetylcholinesterase. Conversely, they are abolished by agents that block the ACh receptor, such as curare. The miniature end-plate potentials represent responses to small packets of transmitter that are spontaneously released from the presynaptic nerve terminal in the absence of an action potential. Their frequency can be increased by a small depolarization of the presynaptic terminal. They disappear if the presynaptic motor nerve degenerates and reappear when a new motor synapse is formed.