NMDA and AMPA receptors to the total excitatory postsynaptic current (EPSC) can be quantified using pharmacological antagonists in a voltage-clamp experiment (Figure 13–9). Since NMDA receptors are largely inhibited by Mg^{2+} at the normal resting potential of most neurons, the EPSC is predominantly determined by charge flow through the AMPA receptors. This current has very rapid rising and decay phases. However, as a neuron becomes depolarized and Mg^{2+} is driven out of the mouth of the NMDA receptors, more charge flows through them. Thus, the NMDA receptor-channel conducts current maximally when two conditions are met: Glutamate is present, and the cell is depolarized. That is, the NMDA receptor acts as a molecular "coincidence detector," opening during the concurrent activation of the presynaptic and postsynaptic cells. In addition, because of its intrinsic kinetics of ligand gating, the current through the NMDA receptor-channel rises and decays with a much slower time course than the current through AMPA receptor-channels. As a result, the NMDA receptors contribute to a late, slow phase of the EPSC and EPSP.

As most glutamatergic synapses contain AMPA receptors that are capable of triggering an action potential by themselves, what is the function of the NMDA receptor? At first glance, the function of these receptors is even more puzzling because their intrinsic channel is normally blocked by Mg^{2+} at the resting potential. However, the high permeability of the NMDA receptor-channels to Ca^{2+} endows them with the special ability to produce a marked rise in intracellular [Ca^{2+}] that can activate various calcium-dependent signaling cascades, including several different protein kinases (Chapters 15 and 53). Thus, NMDA receptor activation can translate electrical signals into biochemical ones. Some of these biochemical reactions lead to long-lasting changes in synaptic strength through a set of processes called long-term synaptic plasticity, which are important for refining synaptic connections during early development and regulating neural circuits in the adult brain, including circuits critical for long-term memory.

The Properties of the NMDA Receptor Underlie Long-Term Synaptic Plasticity

In 1973, Tim Bliss and Terje Lomo found that a brief period of high-intensity and high-frequency synaptic stimulation (known as a tetanus) leads to *long-term potentiation* (LTP) of excitatory synaptic transmission in the hippocampus, a region of the mammalian brain required for many forms of long-term memory (Figure 13–10; see Chapters 53 and 54). Subsequent studies demonstrated that LTP requires Ca^{2+} influx through the NMDA receptor-channels, which open in response to the combined effect of glutamate release and strong postsynaptic depolarization during the tetanic stimulation. LTP is blocked if the tetanus is delivered in the presence of APV, which blocks the NMDA receptors, or if the postsynaptic neuron is injected with a compound that chelates intracellular Ca^{2+}.

The rise of Ca^{2+} in the postsynaptic cell is thought to potentiate synaptic transmission by activating postsynaptic biochemical cascades that trigger the insertion of additional AMPA receptors into the postsynaptic membrane. Under some circumstances, postsynaptic Ca^{2+} can trigger production of a retrograde messenger, a chemical signal that enhances transmitter release from the presynaptic terminal (Chapter 14). As we will discuss later, the Ca^{2+} accumulation and biochemical activation are largely restricted to the individual spines that are activated by the tetanic stimulation. As a result, LTP is input-specific; only those synapses that are activated during the tetanic stimulation are potentiated.

The prolonged high-frequency presynaptic firing required to induce LTP is unlikely to be achieved under physiological conditions. However, a more physiologically relevant form of plasticity, termed spike-timing-dependent plasticity (STDP), can be induced if a single presynaptic stimulus is paired at low frequency with the triggered firing of one or more postsynaptic action potentials, providing sufficient depolarization to relieve Mg^{2+} block of the NMDA receptor pore. The presynaptic activity must precede postsynaptic firing, following a rule proposed in 1949 by the psychologist Donald Hebb for how individual neurons could become grouped together into functional assemblies during associative memory storage. A number of lines of evidence now suggest that LTP, STDP, or related processes provide an important cellular mechanism for memory storage (Chapters 53 and 54) and fine-tuning synaptic connections during development (Chapter 49).

NMDA Receptors Contribute to Neuropsychiatric Disease

Unfortunately, there is also a downside to recruiting Ca^{2+} through the NMDA receptors. Excessively high concentrations of glutamate are thought to result in an overload of Ca^{2+} in the postsynaptic neurons, a condition that can be toxic to neurons. In tissue culture, even a brief exposure to high concentrations of glutamate can kill many neurons, an action called *glutamate excitotoxicity.* High concentrations of intracellular Ca^{2+} are thought to activate calcium-dependent proteases and phospholipases and lead to the production of free radicals that are toxic to the cell.

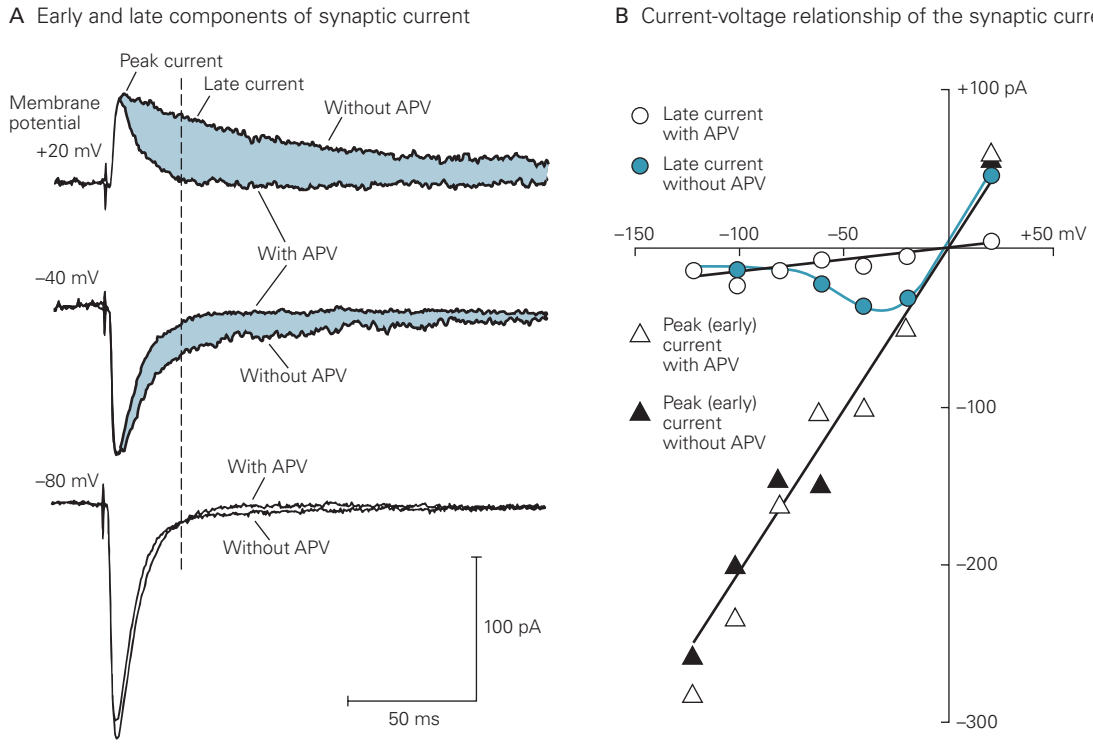


Figure 13–9 The contributions of the AMPA and NMDA receptor-channels to the excitatory postsynaptic current. These voltage-clamp current records are from a cell in the rat hippocampus. Similar receptor-channels are present in motor neurons and throughout the brain. (Adapted, with permission, from Hestrin et al. 1990.)

A. The drug APV selectively binds to and blocks the NMDA receptor. Shown here is the excitatory postsynaptic current (EPSC) before and during application of 50 μM APV at three different membrane potentials. The difference between the traces (**blue region**) represents the contribution of the NMDA receptor-channel to the EPSC. The current that remains in the presence of APV is the contribution of the AMPA receptor-channels. At –80 mV, there is no current through the NMDA receptor-channels because of pronounced Mg^{2+} block (see Figure 13–8). At –40 mV, a small late inward current through NMDA receptor-channels is evident. At +20 mV, the late component is more prominent and has reversed to become an outward current. The time 25 ms after the peak of the synaptic current (**dashed line**) is used for the calculations of late current in part B.

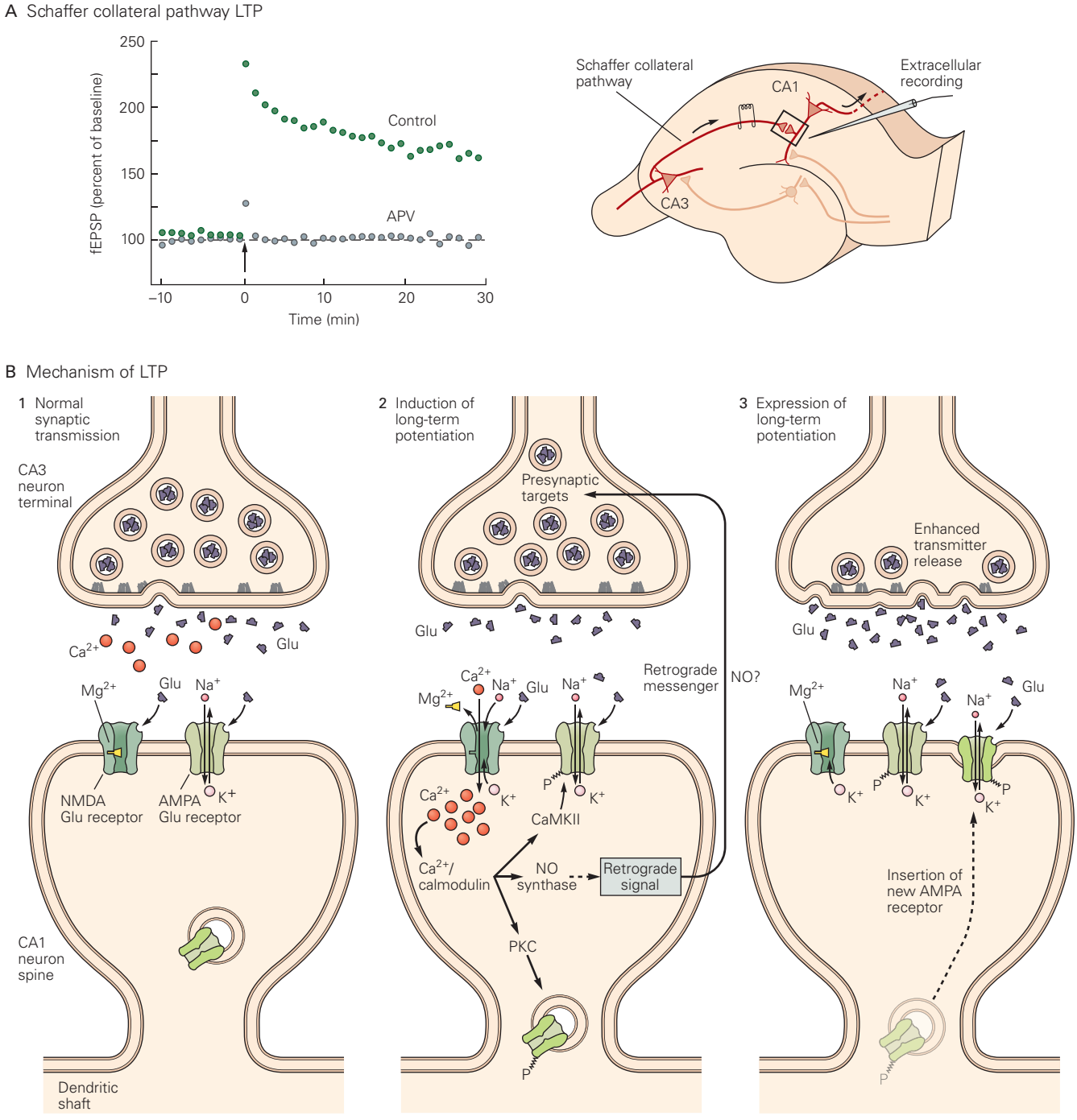
B. The postsynaptic currents through the NMDA and AMPA receptor-channels differ in their dependence on the membrane potential. The current through the AMPA receptor-channels contributes to the early phase of the synaptic current (**filled triangles**). The early phase is measured at the peak of the synaptic current and plotted here as a function of membrane potential. The current through the NMDA receptor-channels contributes to the late phase of the synaptic current (**filled circles**). The late phase is measured 25 ms after the peak of the synaptic current, a time at which the AMPA receptor component has decayed almost to zero (see part A). Note that the AMPA receptor-channels behave as simple resistors; current and voltage have a linear relationship. In contrast, current through the NMDA receptor-channels is nonlinear and increases as the membrane is depolarized from –80 to –40 mV, owing to progressive relief of the Mg^{2+} block. The reversal potential of both receptor-channel types is at 0 mV. The components of the synaptic current in the presence of 50 μm APV are indicated by the **unfilled circles** and **triangles**. Note how APV blocks the late (NMDA receptor) component of the EPSC but not the early (AMPA receptor) component.

Glutamate toxicity may contribute to cell damage after stroke, to the cell death that occurs with episodes of rapidly repeated seizures experienced by patients who have status epilepticus, and to degenerative diseases such as Huntington disease. Agents that selectively block the NMDA receptor may protect against the toxic effects of glutamate and have been tested clinically. The hallucinations that accompany NMDA receptor blockade have so far limited the usefulness of such compounds. A further complication of attempts to control excitotoxicity by blocking NMDA receptor function is that physiological levels of NMDA receptor activation may actually protect neurons from damage and cell death.

Not all of the physiological and pathophysiological effects mediated by the NMDA receptor may result from Ca^{2+} influx. There is increasing evidence that binding of glutamate to the NMDA receptor may cause a conformational change in the receptor that activates downstream intracellular signaling pathways independently of ion

flux. Such metabotropic functions of the NMDA receptor may contribute to long-term depression, a form of synaptic plasticity in which low-frequency synaptic activity produces a long-lasting decrease in glutamatergic synaptic transmission, the opposite of LTP. Metabotropic actions of the NMDA receptor may also contribute to the effect of β-amyloid, the peptide fragment implicated in Alzheimer disease, in depressing synaptic function.

A number of lines of evidence implicate NMDA receptor malfunction in schizophrenia. Pharmacological blockade of NMDA receptors with drugs such as phencyclidine or the general anesthetic ketamine, a derivative of PCP, produces symptoms that resemble the hallucinations associated with schizophrenia; in contrast, certain antipsychotic drugs enhance current through the NMDA receptor-channels. A particularly



striking link with schizophrenia is seen in anti-NMDA receptor encephalitis, an autoimmune disorder in which the production of antibodies to the NMDA receptor reduces levels of the receptor in the membrane. Individuals with this disorder often experience severe seizures, most likely a result of the loss of inhibitory tone because of a reduction in NMDA receptor excitation in GABAergic interneurons, as well as psychoses, including hallucinations and other symptoms resembling schizophrenia. Treatments that reduce antibody levels often lead to complete remission of these symptoms. The idea that a decrease in NMDA receptor function may contribute to the symptoms of schizophrenia is further supported by recent genome-wide linkage analysis suggesting an association between the *NR2A* gene and schizophrenia. One additional link between the NMDA receptor and neuropsychiatric disorders is provided by the finding that low doses of ketamine exert a rapid and powerful antidepressant action.

Fast Inhibitory Synaptic Actions Are Mediated by Ionotropic GABA and Glycine Receptor-Channels Permeable to Chloride

Although glutamatergic excitatory synapses account for the vast majority of synapses in the brain, inhibitory synapses play an essential role in the nervous system both by preventing too much excitation and by regulating the firing patterns of networks of neurons. IPSPs in spinal motor neurons and most central neurons are generated by the amino acid neurotransmitters GABA and glycine.

GABA acts on both ionotropic and metabotropic receptors. The $GABA_A$ receptor is an ionotropic receptor that directly opens a Cl^- channel. The $GABA_B$ receptor is a metabotropic receptor that activates a second-messenger cascade, which often indirectly activates a K^+ channel (Chapter 15). Glycine, a less common inhibitory transmitter in the brain, also activates ionotropic receptors that directly open Cl^- channels. Glycine is the major transmitter released in the spinal cord by the interneurons that inhibit antagonist motorneurons.

Ionotropic Glutamate, GABA, and Glycine Receptors Are Transmembrane Proteins Encoded by Two Distinct Gene Families

The individual subunits that form the $GABA_A$ and glycine receptors are encoded by two distinct but closely related sets of genes. More surprisingly, these receptor subunits are structurally related to the nicotinic ACh receptor subunits, even though the latter select for cations and are therefore excitatory. Thus, as we saw above (Figure 13–4), the three types of receptor subunits are members of one large gene family.

Figure 13–10 (Opposite) NMDA receptor-dependent long-term potentiation of synaptic transmission at Schaffer collateral synapses.

A. Tetanic stimulation of the Schaffer collateral pathway for 1 second (**arrow**) induces LTP at the synapses between the presynaptic terminals of CA3 pyramidal neurons and the postsynaptic dendritic spines of CA1 pyramidal neurons. The graph shows the size of the synaptic response (extracellular field EPSP or **fEPSP**) as a percentage of the initial response prior to induction of LTP. At these synapses, LTP requires activation of the NMDA receptor-channels in the CA1 neurons; LTP is completely blocked when the tetanus is delivered in the presence of the NMDA receptor antagonist APV. (Adapted from Morgan and Teyler 2001.)

B. A model for the mechanism of long-term potentiation at Schaffer collateral synapses.

1. During normal, low-frequency synaptic transmission, glutamate (**Glu**) released from the terminals of CA3 Schaffer collateral axons binds to both NMDA and AMPA receptors in the postsynaptic CA1 neurons (specifically at the postsynaptic membrane of dendritic spines, the site of excitatory input). Sodium and potassium ions flow through the AMPA receptors but not through the NMDA receptor-channels, because their pores are blocked by Mg^{2+} at negative membrane potentials.

2. During a high-frequency tetanus, the large depolarization of the postsynaptic membrane (caused by the large amount of glutamate release resulting in strong activation of the AMPA receptors) relieves the Mg^{2+} blockade of the NMDA receptor-channels, allowing Ca^{2+}, Na^+, and K^+ to flow through these channels. The resulting increase of Ca^{2+} in the dendritic spine activates calcium-dependent protein kinases—calcium/calmodulin–dependent kinase (**CaMKII**) and protein kinase C (**PKC**)—leading to induction of LTP.

3. Second-messenger cascades activated during induction of LTP have two main effects on synaptic transmission. Phosphorylation through activation of protein kinases, including PKC, enhances current through the AMPA receptor-channels, in part by causing insertion of new receptors into the postsynaptic CA1 neuron. In addition, the postsynaptic cell releases (in ways that are still not understood) retrograde messengers that diffuse to the presynaptic terminal to enhance subsequent transmitter release. One such retrograde messenger may be nitric oxide (**NO**), produced by the enzyme NO synthase (shown in panel B-2).

Like the nicotinic ACh receptor-channels, the $GABA_A$ and glycine receptor-channels are pentamers. The $GABA_A$ receptors are usually composed of two α-, two β-, and one γ- or δ-subunit and are activated by the binding of two molecules of GABA in clefts formed between the two α- and β-subunits. The glycine receptors are composed of three α- and two β-subunits and require the binding of up to three molecules of ligand to open. The transmembrane topology of each $GABA_A$ and glycine receptor subunit is similar to that of a nicotinic ACh receptor subunit, consisting of a large extracellular ligand-binding domain followed by four hydrophobic transmembrane α-helices (labeled M1, M2, M3, and M4), with the M2 helix forming the lining of the channel pore (Figure 13–4A). However, the amino acids flanking the M2 domain are strikingly different from those of the nicotinic ACh receptor. As discussed in Chapter 12, the pore of the ACh receptor contains rings of negatively charged acidic residues that help the channel select for cations over anions. In contrast, the GABA and glycine receptor-channels contain either neutral or positively charged basic residues at the homologous positions, which contribute to the selectivity of these channels for anions.

Most of the major classes of receptor subunits are encoded by multiple related genes. Thus, there are six types of $GABA_A$ α-subunits (α1–α6), three β-subunits (β1–β3), three γ-subunits (γ1–γ3), and one δ-subunit. The genes for these different subtypes are often differentially expressed in different types of neurons, endowing their inhibitory synapses with distinct properties. The possible combinatorial arrangements of these subunits in a fully assembled pentameric receptor provides an enormous potential diversity of receptors.

The $GABA_A$ and glycine receptors play important roles in disease and in the actions of drugs. $GABA_A$ receptors are the target for several types of drugs that are clinically important and socially abused, including general anesthetics, benzodiazepines, barbiturates, and alcohol. General anesthetics, either gases or injectable compounds, induce loss of consciousness and are therefore widely used during surgery. Benzodiazepines are antianxiety agents and muscle relaxants that include diazepam (Valium), lorazepam (Ativan), and clonazepam (Klonopin). Zolpidem (Ambien) is a benzodiazepine compound that promotes sleep. The barbiturates comprise a distinct group of hypnotics that includes phenobarbital and secobarbital.

The different classes of compounds—GABA, general anesthetics, benzodiazepines, barbiturates, and alcohol—bind to different sites on the receptor but act similarly to increase the opening of the GABA receptor-channel. For example, whereas GABA binds to a cleft between the α- and β-subunits, benzodiazepines bind to a cleft between the α- and γ-subunits. In addition, the binding of any one of these classes of drug influences the binding of the others. For example, a benzodiazepine (or a barbiturate) binds more strongly to the receptor-channel when GABA also is bound, and this tight binding helps stabilize the channel in the open state. In this manner, the various compounds all enhance inhibitory synaptic transmission.

How do these different compounds, all acting on $GABA_A$ receptors to promote channel opening, produce such diverse behavioral and psychological effects, for example, reducing anxiety versus promoting sleep? It turns out that many of these compounds bind selectively to specific subunit types, which can be expressed in different types of neurons in different regions of the brain. For example, zolpidem binds selectively to $GABA_A$ receptors containing the α_1- subunit. In contrast, the anxiolytic effect of benzodiazepines requires binding to the α_2- and γ-subunits.

In addition to being important pharmacological targets, the $GABA_A$ and glycine receptors are targets of disease and poisons. Missense mutations in the α-subunit of the glycine receptor underlie an inherited neurological disorder called *familial startle disease* (or *hyperekplexia*), characterized by abnormally high muscle tone and exaggerated responses to noise. These mutations decrease the opening of the glycine receptor and so reduce the normal levels of inhibitory transmission in the spinal cord. The poison strychnine, a plant alkaloid compound, causes convulsions by blocking the glycine receptor and decreasing inhibition. Nonsense mutations that result in truncations of $GABA_A$ receptor α- and γ-subunits have been implicated in congenital forms of epilepsy.

Chloride Currents Through $GABA_A$ and Glycine Receptor-Channels Normally Inhibit the Postsynaptic Cell

The function of GABA receptors is intimately linked to their biophysical properties. Eccles and his colleagues determined the ionic mechanism of the IPSP in spinal motor neurons by systematically changing the level of the resting membrane potential in a motor neuron while stimulating a presynaptic inhibitory interneuron (Figure 13–11).

When the motor neuron membrane is held at the normal resting potential (−65 mV), a small hyperpolarizing potential is generated when the presynaptic interneuron is stimulated. When the motor neuron membrane is held at −70 mV, no change in potential

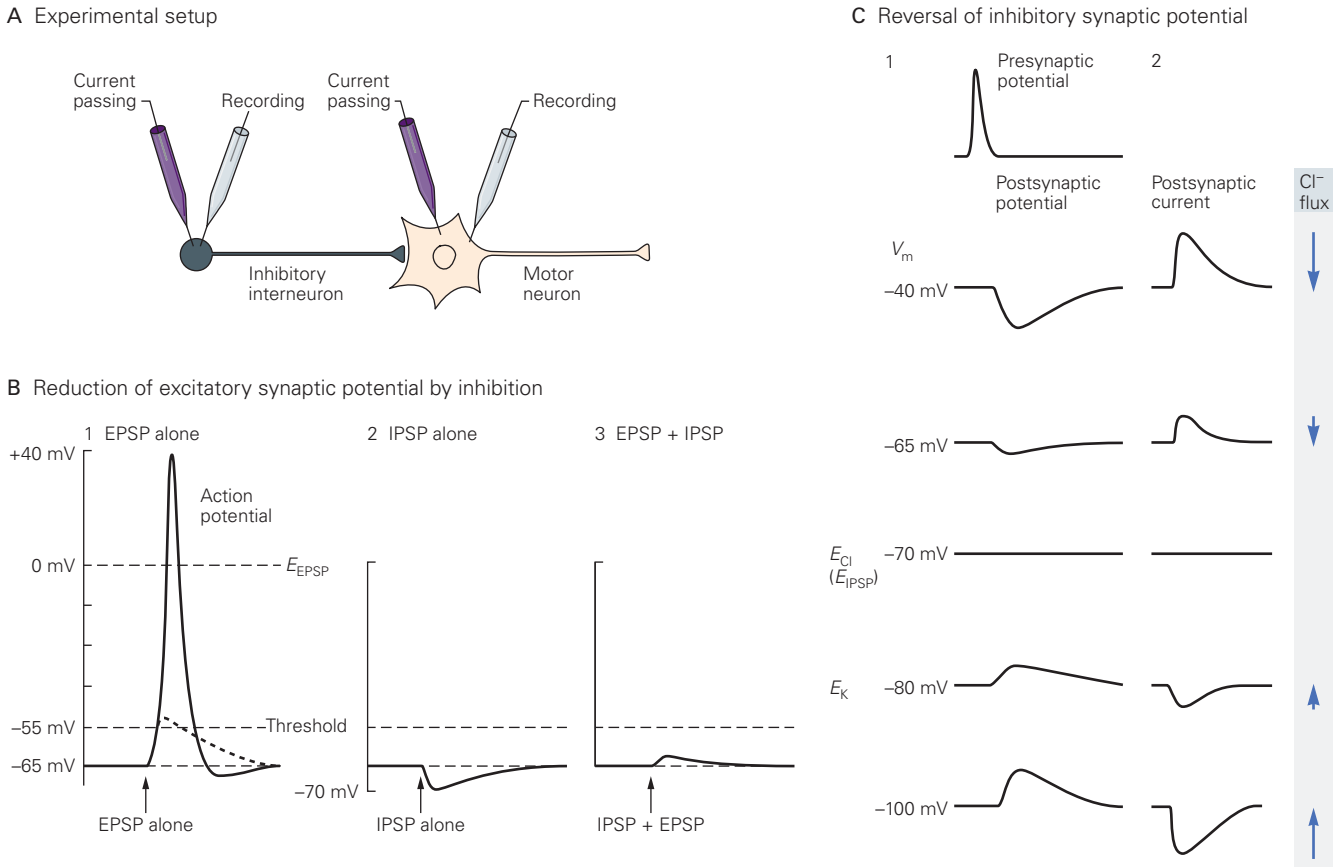


Figure 13–11 Inhibitory actions at chemical synapses result from the opening of ion channels selective for chloride.

A. In this hypothetical experiment, two electrodes are placed in the presynaptic interneuron and two in the postsynaptic motor neuron. The current-passing electrode in the presynaptic cell is used to produce an action potential; in the postsynaptic cell, it is used to alter the membrane potential systematically prior to the presynaptic input.

B. Inhibitory actions counteract excitatory actions. **1.** A large EPSP occurring alone depolarizes the membrane toward E_{EPSP} and exceeds the threshold for generating an action potential. **2.** An IPSP alone moves the membrane potential away from the threshold toward E_{Cl}, the equilibrium potential for Cl^- (–70 mV). **3.** When inhibitory and excitatory synaptic potentials occur together, the effectiveness of the EPSP is reduced and prevented from reaching the threshold for an action potential.

C. The IPSP and inhibitory synaptic current reverse at E_{Cl}. **1.** A presynaptic spike produces a hyperpolarizing IPSP at the resting membrane potential (–65 mV). The IPSP is larger when the membrane potential is set at –40 mV due to the increased inward driving force on Cl^-. When the membrane potential is set at –70 mV the IPSP is nullified. This reversal potential for the IPSP occurs at E_{Cl}. With further hyperpolarization of the membrane, the IPSP is inverted to a depolarizing postsynaptic potential (at –80 and –100 mV) because the membrane potential is negative to E_{Cl}. **2.** The reversal potential of the inhibitory postsynaptic current measured under voltage clamp. An inward (negative) current flows at membrane potentials negative to the reversal potential (corresponding to an efflux of Cl^-), and an outward (positive) current flows at membrane potentials positive to the reversal potential (corresponding to an influx of Cl^-). (**Up arrows** = efflux; **down arrows** = influx.)

is recorded when the interneuron is stimulated. But at potentials more negative than –70 mV, the motor neuron generates a *depolarizing* response following stimulation of the inhibitory interneuron. This reversal potential of –70 mV corresponds to the Cl^- equilibrium potential in spinal motor neurons (the extracellular concentration of Cl^- is much greater than the intracellular concentration). Thus, at –70 mV, the tendency of Cl^- to diffuse into the cell down its chemical concentration gradient is balanced by the electrical force (the negative membrane potential) that opposes Cl^- influx. Replacement of extracellular Cl^- with an impermeant anion reduces the size of the IPSP and shifts the reversal potential to more positive values in accord with the predictions of the Nernst equation. Thus, the IPSP results from an increase in Cl^- conductance.

The currents through single GABA and glycine receptor-channels, the unitary currents, have been measured using the patch-clamp technique. Both transmitters activate Cl^- channels that open in an all-or-none manner, similar to the opening of ACh and glutamate-gated channels. The inhibitory effect of GABA and glycine on neuronal firing depends on two related mechanisms. First, in a typical neuron, the resting potential of −65 mV is slightly more positive than E_{Cl} (−70 mV). At this resting potential, the chemical force driving Cl^- into the cell is slightly greater than the electrical force opposing Cl^- influx—that is, the electrochemical driving force on Cl^- ($V_m - E_{Cl}$) is positive. As a result, the opening of Cl^- channels leads to a positive current, based on the relation $I_{Cl} = g_{Cl}\ (V_m - E_{Cl})$. Because the charge carrier is the negatively charged Cl^- ion, the positive current corresponds to an influx of Cl^- into the neuron, down its electrochemical gradient. This causes a net increase in the negative charge on the inside of the membrane—the membrane becomes hyperpolarized.

However, some central neurons have a resting potential that is approximately equal to E_{Cl}. In such cells, an increase in Cl^- conductance does not change the membrane potential—the cell does not become hyperpolarized—because the electrochemical driving force on Cl^- is nearly zero. However, the opening of Cl^- channels in such a cell still inhibits the cell from firing an action potential in response to a near-simultaneous EPSP. This is because the depolarization produced by an excitatory input depends on a weighted average of the batteries for all types of open channels—that is, the batteries for the excitatory and inhibitory synaptic conductances and the resting conductances—with the weighting factor equal to the total conductance for a particular type of channel (see Chapter 12, Postscript). Because the battery for Cl^- channels lies near the resting potential, opening these channels helps hold the membrane near its resting potential during the EPSP by increasing the weighting factor for the Cl^- battery.

The effect that the opening of Cl^- channels has on the magnitude of an EPSP can also be described in terms of Ohm's law. Accordingly, the amplitude of the depolarization during an EPSP, ΔV_{EPSP} is given by:

$$\Delta V_{EPSP} = I_{EPSP}/g_l$$

where I_{EPSP} is the excitatory synaptic current and g_l is the conductance from all other channels open in the membrane, including resting channels and transmitter-gated Cl^- channels. Because the opening of the Cl^- channels increases the resting conductance, ie, makes the neuron more leaky, the depolarization during the EPSP decreases. This consequence of synaptic inhibition is called the *short-circuiting* or *shunting* effect.

By counteracting synaptic excitation, synaptic inhibition can exert powerful control over action potential firing in neurons that are spontaneously active because of the presence of intrinsic pacemaker channels. This function, called the *sculpting* role of inhibition, shapes the pattern of firing in such cells (Figure 13–12). In fact, this sculpting role of inhibition likely happens in all neurons, leading to the temporal patterning of neuronal spiking and to the control of the synchronization of neural circuits.

The different biophysical properties of synaptic conductances can be understood as distinct mathematical operations carried out by the postsynaptic neuron. Thus, inhibitory inputs that hyperpolarize the cell perform a *subtraction* on the excitatory inputs, whereas the shunting effect of the conductance increase performs a *division.* Adding excitatory inputs (or removing nonshunting inhibitory inputs) results in *summation.* Finally, the combination of an excitatory input with the removal of an inhibitory shunt produces a *multiplication.* These arithmetic effects, however, are often mixed and can vary with time as the membrane potential of neurons constantly varies, leading to changes in the driving force on Cl^- through $GABA_A$ receptor-channels.

In some cells, such as those with metabotropic $GABA_B$ receptors, inhibition is caused by the opening of K^+ channels. Because the K^+ equilibrium potential of neurons (E_K = −80 mV) is always negative to the resting potential, opening K^+ channels inhibits the cell even

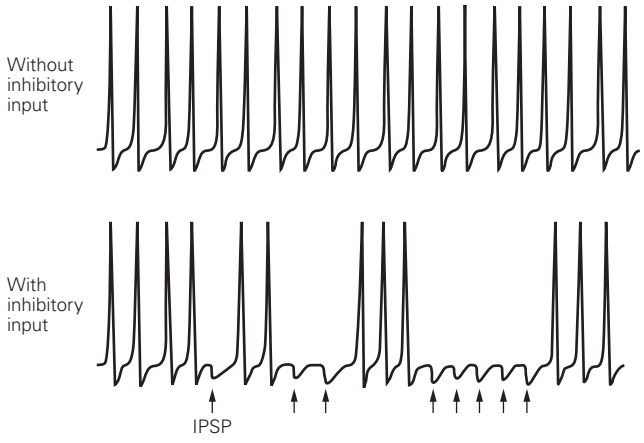


Figure 13–12 Inhibition can shape the firing pattern of a spontaneously active neuron. Without inhibitory input, the neuron fires continuously at a fixed interval. With inhibitory input (**arrows**), some action potentials are inhibited, resulting in a distinctive pattern of impulses.

more profoundly than opening Cl^- channels (assuming a similar-size synaptic conductance), generating a more "subtractive" inhibition. $GABA_B$ responses turn on more slowly and persist for a longer time compared with $GABA_A$ responses.

Paradoxically, under some conditions, the activation of $GABA_A$ receptors in brain cells can cause excitation. This is because the influx of Cl^- after intense periods of stimulation can be so great that the intracellular Cl^- concentration increases substantially. It may even double. As a result, the Cl^- equilibrium potential may become more positive than the resting potential. Under these conditions, the opening of Cl^- channels leads to Cl^- efflux and depolarization of the neuron. Such depolarizing Cl^- responses occur normally in many neurons in newborn animals, where the intracellular Cl^- concentration tends to be high even at rest. This is because the K^+-Cl^- cotransporter responsible for maintaining low intracellular Cl^- is expressed at low levels during early development (Chapter 9). Depolarizing Cl^- responses may also occur in the distal dendrites of more mature neurons and perhaps also at their axon initial segment. Such excitatory $GABA_A$ receptor actions in adults may contribute to epileptic discharges in which large, synchronized, and depolarizing GABA responses are observed.

Some Synaptic Actions in the Central Nervous System Depend on Other Types of Ionotropic Receptors

A minority of fast excitatory synaptic actions in the brain are mediated by the neurotransmitter serotonin (5-HT) acting at the $5\text{-}HT_3$ class of ionotropic receptor-channels. These pentameric receptors, which are made up of subunits with four transmembrane segments, are structurally similar to nicotinic ACh receptors. Like the ACh receptor-channels, $5\text{-}HT_3$ receptor-channels are permeable to monovalent cations and have a reversal potential near 0 mV.

Ionotropic receptors for adenosine triphosphate (ATP) serve an excitatory function at other selected synapses and constitute a third family of transmitter-gated ion channels. These so-called purinergic receptors (named for the purine ring in adenosine) occur on smooth muscle cells innervated by sympathetic neurons of the autonomic ganglia as well as on certain central and peripheral neurons. At these synapses, ATP activates an ion channel that is permeable to both monovalent cations and Ca^{2+}, with a reversal potential near 0 mV. Several genes coding for this family of ionotropic ATP receptors (termed the *P2X receptors*) have been identified. The amino acid sequence and subunit structure of these ATP receptors are different from the other two ligand-gated channel families. An X-ray crystal structure of the P2X receptor reveals that it has an exceedingly simple organization in which three subunits, each containing only two transmembrane segments, surround a central pore (Figure 13–4C).

Excitatory and Inhibitory Synaptic Actions Are Integrated by Neurons Into a Single Output

Each neuron in the central nervous system is constantly bombarded by an array of synaptic inputs from many other neurons. A single motor neuron, for example, may be the target of as many as 10,000 different presynaptic terminals. Some are excitatory, others inhibitory; some are strong, others weak. Some inputs contact the motor cell on the tips of its apical dendrites, others on proximal dendrites, some on the dendritic shaft, others on the soma. The different inputs can reinforce or cancel one another. How does a given neuron integrate these signals into a coherent output?

As we saw earlier, the synaptic potentials produced by a single presynaptic neuron typically are not large enough to depolarize a postsynaptic cell to the threshold for an action potential. The EPSPs produced in a motor neuron by most stretch-sensitive afferent neurons are only 0.2 to 0.4 mV in amplitude. If the EPSPs generated in a single motor neuron were to sum linearly, at least 25 afferent neurons would have to fire together and release transmitter to depolarize the trigger zone by the 10 mV required to reach threshold. But at the same time the postsynaptic cell is receiving excitatory inputs, it may also be receiving inhibitory inputs that prevent the firing of action potentials by either a subtractive or shunting effect.

The net effect of the inputs at any individual excitatory or inhibitory synapse will therefore depend on several factors: the location, size, and shape of the synapse; the proximity and relative strength of other synergistic or antagonistic synapses; and the resting potential of the cell. And, in addition, all of this is exquisitely dependent on the timing of the excitatory and inhibitory input. Inputs are coordinated in the postsynaptic neuron by a process called *neuronal integration.* This cellular process reflects the task that confronts the nervous system as a whole. A cell at any given moment has two options: to fire or not to fire an action potential. Charles Sherrington described the brain's ability to choose between competing alternatives as the *integrative action of the nervous system.*

He regarded this decision making as the brain's most fundamental operation (see Chapter 56).

Synaptic Inputs Are Integrated at the Axon Initial Segment

In most neurons, the decision to initiate an action potential output is made at one site: the axon initial segment. Here, the cell membrane has a lower threshold for action potential generation than at the cell body or dendrites because it has a higher density of voltage-dependent Na^+ channels (Figure 13–13). With each increment of membrane depolarization, more Na^+ channels open, providing a higher density of inward current (per unit area of membrane) at the axon initial segment than elsewhere in the cell.

At the initial segment, the depolarization increment required to reach the threshold for an action potential (–55 mV) is only 10 mV from the resting level of –65 mV. In contrast, the membrane of the cell body must be depolarized by 30 mV before reaching its threshold (–35 mV). Therefore, synaptic excitation first discharges the region of membrane at the initial segment, also called the *trigger zone.* The action potential generated at this site then depolarizes the membrane of the cell body to threshold and at the same time is propagated along the axon .

Because neuronal integration involves the summation of synaptic potentials that spread to the trigger zone, it is critically affected by two passive membrane properties of the neuron (Chapter 9). First, the membrane time constant helps determine the time course of the synaptic potential in response to the EPSC, thereby controlling *temporal summation*, the process by which consecutive synaptic potentials are added together in the postsynaptic cell. Neurons with a large membrane time constant have a greater capacity for temporal summation than do neurons with a shorter time constant (Figure 13–14A). As a result, the longer the time constant, the greater is the likelihood that two consecutive inputs will summate to bring the cell membrane to its threshold for an action potential.

Second, the *length* constant of the cell determines the degree to which the EPSP decreases as it spreads

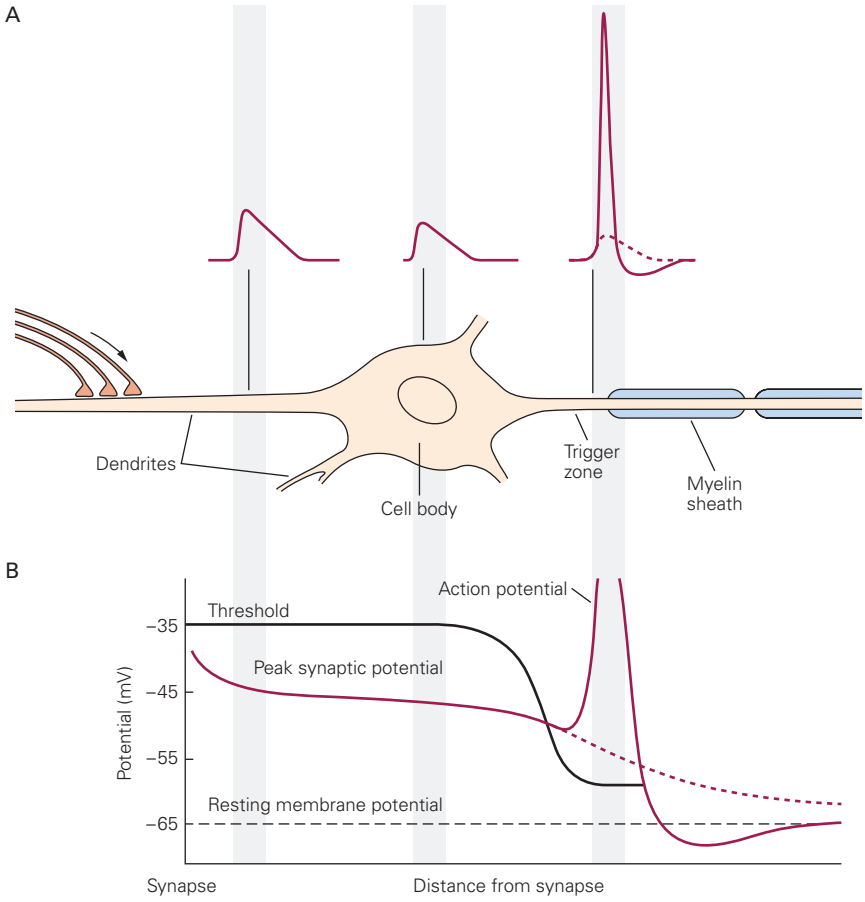


Figure 13–13 A synaptic potential arising in a dendrite can generate an action potential at the axon initial segment. (Adapted, with permission, from Eckert et al. 1988.)

A. An excitatory synaptic potential originating in the dendrites decreases with distance as it propagates passively to the soma. Nevertheless, an action potential can be initiated at the trigger zone (the axon initial segment) because the density of the Na^+ channels in this region is high and thus the threshold for an action potential is low.

B. Comparison of the threshold for initiation of the action potential at different sites in the neuron (corresponding to drawing A). An action potential is generated when the amplitude of the synaptic potential exceeds the threshold. The **dashed line** shows the decay of the synaptic potential if no action potential is generated at the axon initial segment.