Two morphological types of synapses are common in the brain: Gray types I and II (named after E. G. Gray, who described them using electron microscopy). Most type I synapses are glutamatergic and excitatory, whereas most type II synapses are GABAergic and inhibitory. Type I synapses have round synaptic vesicles, an electron-dense region (the *active zone*) on the presynaptic membrane, and an even larger electron-dense region in the postsynaptic membrane opposed to the active zone (known as the *postsynaptic density*), which gives type I synapses an asymmetric appearance. Type II synapses have oval or flattened synaptic vesicles and less obvious presynaptic membrane specializations and postsynaptic densities, resulting in a more symmetric appearance (Figure 13–2). (Although type I synapses are mostly excitatory and type II inhibitory, the two morphological types have proved to be only a first approximation to transmitter biochemistry. Immunocytochemistry affords much more reliable distinctions between transmitter types, as discussed in Chapter 16).

Although dendrites are normally postsynaptic and axon terminals presynaptic, all four regions of the nerve cell—axon, presynaptic terminals, cell body, and dendrites—can be presynaptic or postsynaptic sites of chemical synapses. The most common types of contact, illustrated in Figure 13–2, are axodendritic, axosomatic, and axo-axonic (by convention, the presynaptic element is identified first). Excitatory synapses are typically axodendritic and occur mostly on dendritic spines. Inhibitory synapses are normally formed on dendritic shafts, the cell body, and the axon initial segment. Dendrodendritic and somasomatic synapses are also found, but they are rare.

As a general rule, the proximity of a synapse to the axon initial segment is thought to determine its effectiveness. A given postsynaptic current generated at a site near the cell body will produce a greater change in membrane potential at the trigger zone of the axon initial segment, and therefore have a greater influence on action potential output than an equal current generated at more remote sites in the dendrites. This is because some of the charge entering the postsynaptic membrane at a remote site will leak out of the dendritic membrane as the synaptic potential propagates to the cell body (Chapter 9). Some neurons compensate for this effect by placing

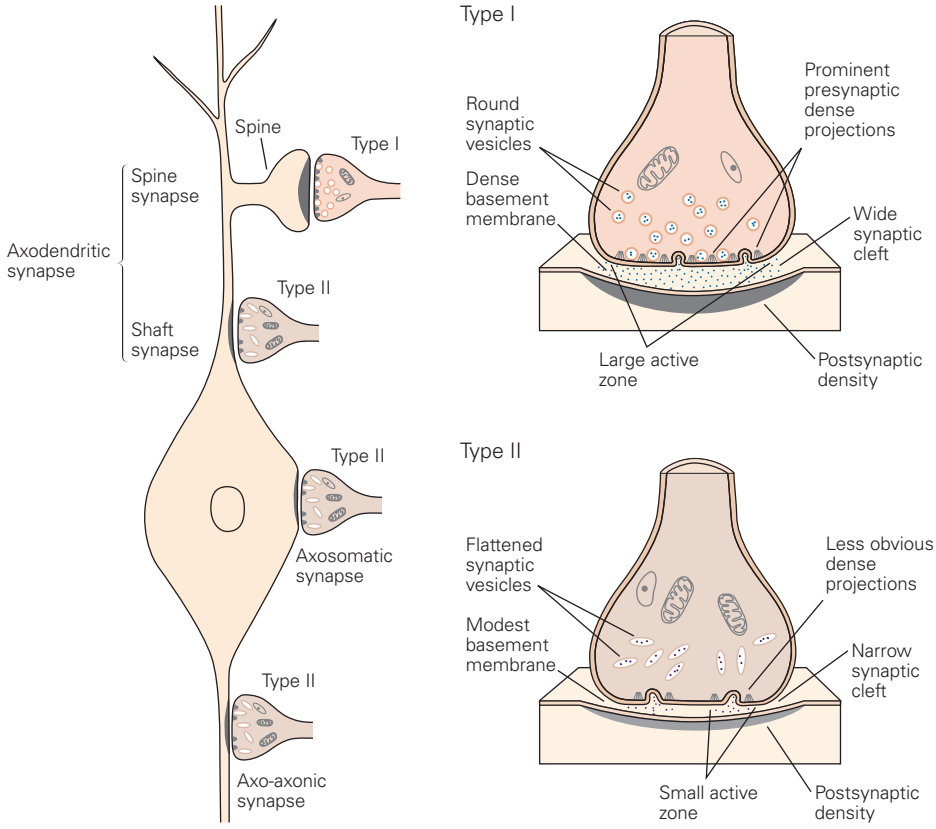

Figure 13–2 The two most common morphological types of synapses in the central nervous system are Gray type I and type II. Type I is usually excitatory, whereas type II is usually inhibitory. Differences include the shape of vesicles, the prominence of presynaptic densities, total area of the active zone, width of the synaptic cleft, and presence of a dense basement membrane. Type I synapses typically contact specialized dendritic projections, called spines, and less commonly contact the shafts of dendrites. Type II synapses contact the cell body (axosomatic), dendritic shaft (axodendritic), axon initial segment (axo-axonic), and presynaptic terminals of another neuron (not shown).

more glutamate receptors at distal synapses than at proximal synapses, ensuring that inputs at different locations along the dendritic tree will have a more equivalent influence at the initial segment. In contrast to axodendritic and axosomatic input, most axoaxonic synapses have no direct effect on the trigger zone of the postsynaptic cell. Instead, they affect neural activity by controlling the amount of transmitter released from the presynaptic terminals (Chapter 15).

Excitatory Synaptic Transmission Is Mediated by Ionotropic Glutamate Receptor-Channels Permeable to Cations

The excitatory transmitter released from the presynaptic terminals of the stretch-receptor sensory neurons is the amino acid L-glutamate, the major excitatory transmitter in the brain and spinal cord. Eccles and his colleagues discovered that the EPSP in spinal motor cells results from the opening of ionotropic glutamate receptor-channels, which are permeable to both Na^+ and K^+. This ionic mechanism is similar to that produced by ACh at the neuromuscular junction described in Chapter 12. Like the ACh receptor-channels, glutamate receptor-channels conduct both Na^+ and K^+ with nearly equal permeability. As a result, the reversal potential for current flow through these channels is 0 mV (see Figure 12–7).

Glutamate receptors can be divided into two broad categories: ionotropic receptors and metabotropic receptors (Figure 13–3). There are three major types of ionotropic glutamate receptors: *AMPA*, *kainate*, and *NMDA*, named according to the types of pharmacological agonists that activate them (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, kainate, and *N*-methyl-D-aspartate, respectively). These receptors are also differentially sensitive to antagonists. The NMDA receptor is selectively blocked by the drug *APV* (2-amino-5-phosphonovaleric acid). The AMPA and kainate receptors are not affected by APV, but both are blocked by the drug *CNQX* (6-cyano-7-nitroquinoxaline-2,3-dione). Because of this shared pharmacological sensitivity, these two types are sometimes called the *non-NMDA receptors*. Another important distinction between NMDA and non-NMDA receptors is that the NMDA receptor channel is highly permeable to Ca^{2+}, whereas most non-NMDA receptors are not. There are several types of metabotropic glutamate receptors, most of which can be activated by *trans*-(1S,3R)-1-amino-1,3-cyclopentanedicarboxylic acid (*ACPD*).

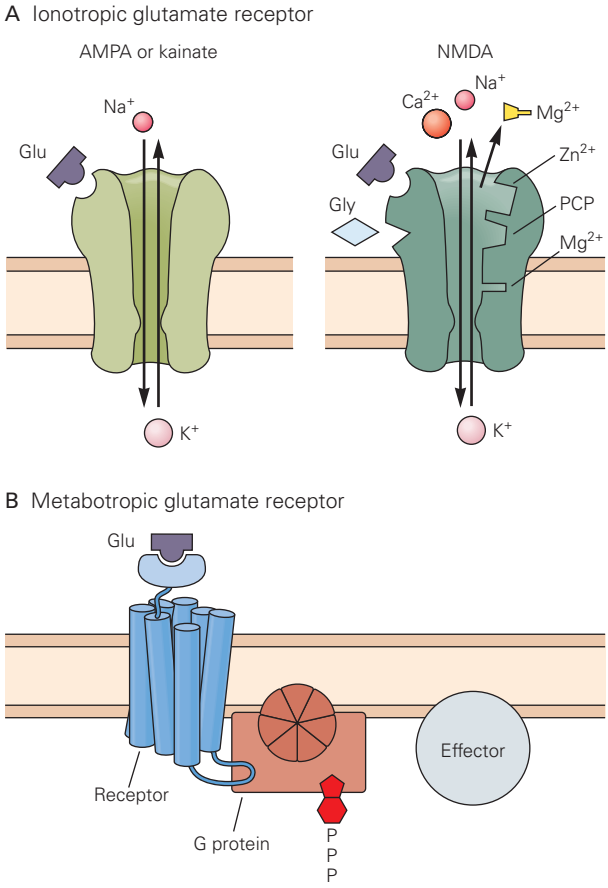

Figure 13–3 Different classes of glutamate receptors regulate excitatory synaptic actions in neurons in the spinal cord and brain.

A. Ionotropic glutamate receptors directly gate ion channels permeable to cations. The AMPA and kainate types bind the glutamate agonists AMPA or kainate, respectively; these receptors contain a channel that is permeable to Na^+ and K^+. The NMDA receptor binds the glutamate agonist NMDA; it contains a channel permeable to Ca^{2+}, K^+, and Na^+. It has binding sites for glutamate, glycine, Zn^{2+}, phencyclidine (**PCP**, or angel dust), MK801 (an experimental drug), and Mg^{2+}, each of which regulates the functioning of the channel differently.

B. Binding of glutamate (**Glu**) to metabotropic glutamate receptors indirectly gates ion channels by activating a GTP-binding protein (**G protein**), which in turn interacts with effector molecules that alter metabolic and ion channel activity (Chapter 11).

The action of all ionotropic glutamate receptors is excitatory or depolarizing because the reversal potential of their ionic current is near zero, causing channel opening to produce a depolarizing inward current at negative membrane potentials. In contrast, metabotropic receptors can produce either excitation or inhibition, depending on the reversal potential of the ionic currents that they regulate and whether they promote channel opening or channel closing.

The Ionotropic Glutamate Receptors Are Encoded by a Large Gene Family

Over the past 30 years, a large variety of genes coding for the subunits of all the major neurotransmitter receptors have been identified. In addition, many of these subunit genes are alternatively spliced, generating further diversity. This molecular analysis demonstrates evolutionary linkages among the structure of receptors that enable us to classify them into three distinct families (Figure 13–4).

The ionotropic glutamate receptor family includes the AMPA, kainate, and NMDA receptors. The genes encoding the AMPA and kainate receptors are more closely related to one another than are the genes encoding the NMDA receptors. Surprisingly, the glutamate receptor family bears little resemblance to the two other gene families that encode ionotropic receptors (one of which encodes the nicotinic ACh, GABA, and glycine receptors, and the other the ATP receptors, as described later).

The AMPA, kainate, and NMDA receptors are tetramers composed of two or more types of related subunits, with all four subunits arranged around a central pore. The AMPA receptor subunits are encoded by four separate genes (*GluA1–GluA4*), whereas the kainate receptor subunits are encoded by five different genes (*GluK1–GluK5*). Autoantibodies to the GluA3 subunit of the AMPA receptor are thought to play an important role in some forms of epilepsy. These antibodies actually mimic glutamate by activating GluA3-containing receptors, resulting in excessive excitation and seizures. NMDA receptors, on the other hand, are encoded by a family consisting of five genes that fall

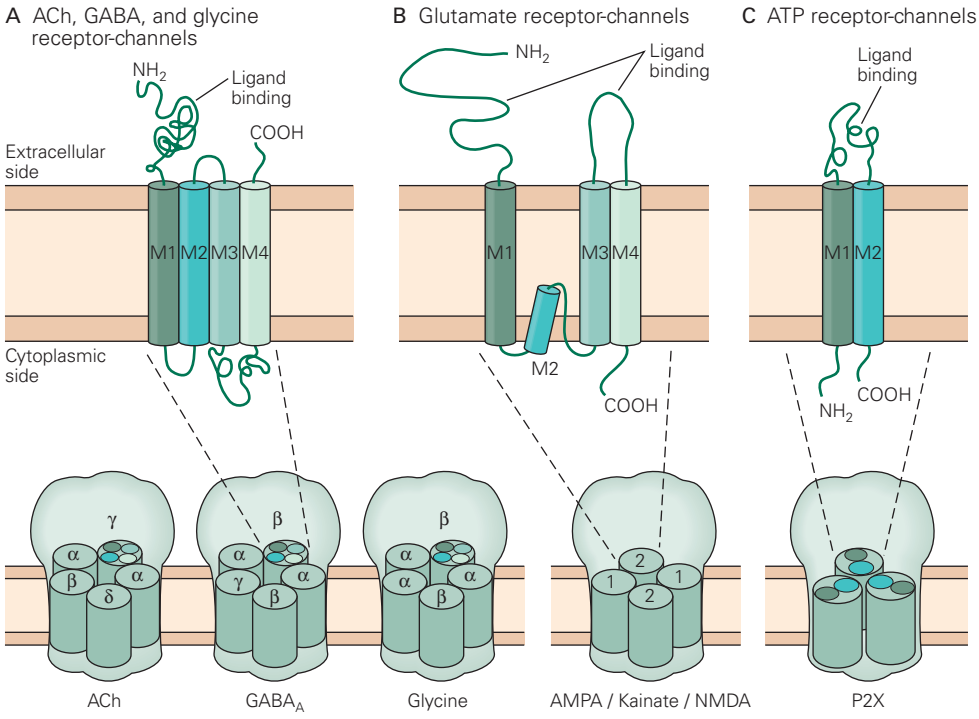

Figure 13–4 The three families of ionotropic receptors.

A. The nicotinic ACh, $GABA_A$, and glycine receptor-channels are all pentamers composed of several types of related subunits. As shown here, the ligand-binding domain is formed by the extracellular amino-terminal region of the protein. Each subunit has a membrane domain with four membrane-spanning α-helixes (M1–M4) and a short extracellular carboxyl terminus. The M2 helix lines the channel pore.

B. The glutamate receptor-channels are tetramers, often composed of two different types of closely related subunits (here denoted **1** and **2**). The subunits have a large extracellular amino terminus, a membrane domain with three membrane-spanning α-helixes (M1, M3, and M4), a large extracellular loop connecting the M3 and M4 helixes, and an intracellular carboxyl terminus. The M2 segment forms a loop that dips into and out of the cytoplasmic side of the membrane, contributing to the selectivity filter of the channel. The glutamate binding site is formed by residues in the extracellular amino terminus and in the M3–M4 extracellular loop.

C. The adenosine triphosphate (**ATP**) receptor-channels (or purinergic P2X receptors) are trimers. Each subunit possesses two membrane-spanning α-helixes (M1 and M2) and a large extracellular loop that binds ATP. The M2 helix lines the pore.

into two groups: The *GluN1* gene encodes one type of subunit, whereas four distinct *GluN2* genes (*A–D*) encode a second type. Each NMDA receptor contains two GluN1 subunits and two GluN2 subunits.

Glutamate Receptors Are Constructed From a Set of Structural Modules

All ionotropic glutamate receptor subunits share a common architecture with similar motifs. Eric Gouaux and colleagues have provided important insights into the structure of the ionotropic glutamate receptors, initially through an X-ray crystallographic model of an AMPA receptor composed of four GluA2 subunits. The subunits have a large extracellular amino-terminal domain, which is followed in the primary amino acid sequence by an extracellular ligand-binding domain and a transmembrane domain (Figures 13–4B and 13–5). The transmembrane domain contains three transmembrane α-helixes (M1, M3, and M4) and a loop (M2) between the M1 and M3 helixes that dips into and out of the cytoplasmic side of the membrane. This M2 loop resembles the pore-lining P loop of K^+ channels and helps form the selectivity filter of the channel (see Figure 8–12).

Both extracellular domains are homologous to bacterial amino acid binding protein domains. The ligand-binding domain is a bi-lobed clamshell-like structure (Figure 13–5A), whereas the amino-terminal domain is homologous to the glutamate-binding domain of metabotropic glutamate receptors but does not bind glutamate. Instead, in the ionotropic glutamate receptors, this domain is involved in subunit assembly, the modulation of receptor function by ligands other than glutamate, and/or the interaction with other synaptic proteins to regulate synapse development.

The ligand-binding domain is formed by two distinct regions in the linear sequence of the protein. One region comprises the end of the amino-terminal domain up to the M1 transmembrane helix; the second region is formed by the large extracellular loop connecting the M3 and M4 helixes (Figure 13–5A). In the ionotropic receptors, the binding of a molecule of glutamate within the clamshell triggers the closure of the lobes of the clamshell; competitive antagonists also bind to the clamshell but fail to trigger clamshell closure. This suggests that the conformational change associated with clamshell closure is important for opening the ion channel.

In addition to the core subunits that form the receptor-channel, AMPA receptors contain additional (or auxiliary) subunits that regulate receptor trafficking to the membrane and function. One important class of auxiliary subunits comprises the *transmembrane AMPA receptor regulatory proteins* (TARPs). A TARP subunit has four transmembrane domains, and its association with the pore-forming AMPA receptor subunits enhances the surface membrane trafficking, synaptic localization, and gating of the AMPA receptors. The first TARP family member to be identified was stargazin, which was isolated through a genetic screen in the *stargazer* mutant mouse, so named because these animals have a tendency to tip their heads backward and stare upward. Loss of stargazin leads to a complete loss of AMPA receptors from cerebellar granule cells, which results in cerebellar ataxia and frequent seizures. Other members of the TARP family are similarly required for AMPA receptor trafficking to the surface membrane in other types of neurons.

High-resolution cryo-electron microscopy has revealed the structure of TARP subunits in association with the AMPA receptor subunits (Figure 13–5D,E). These studies suggest that interactions between a TARP subunit and the ligand-binding domain clamshell of an AMPA receptor can stabilize the receptor in the glutamate-bound open state, thereby enhancing the channel open time, single-channel conductance, and affinity for glutamate.

Given the homology among the various subtypes of glutamate receptors, it is not surprising that the overall structure of the kainate and NMDA receptors is similar to that of the homomeric GluA2 receptor. However, there are some important differences that give rise to the distinct physiological functions of the different receptors. The high permeability of the NMDA receptor-channels to Ca^{2+} has been localized to a single amino acid residue in the pore-forming M2 loop. All NMDA receptor subunits contain the neutral residue asparagine at this position in the pore. In most types of AMPA receptor subunits, the residue at this position is the uncharged amino acid glutamine; in the GluA2 subunit, however, the corresponding M2 residue is arginine, a positively charged basic amino acid. Inclusion of even a single GluA2 subunit prevents the AMPA receptor-channel from conducting Ca^{2+} (Figure 13–6B), most likely as a result of strong electrostatic repulsion by the arginine. The opening of AMPA receptor-channels in cells that lack the GluA2 subunit can produce a significant Ca^{2+} influx because the pores of these receptors lack the positively charged arginine residue.

Interestingly, the DNA of the *GluA2* gene does not encode an arginine residue at this position in the M2 loop but rather codes for a glutamine residue. After transcription, the codon for glutamine in the *GluA2* mRNA is replaced with one for arginine through an enzymatic process termed RNA editing (Figure 13–6A). The importance of this RNA editing was investigated using a genetically modified mouse whose *GluA2* gene was engineered so that the relevant nucleotide in the

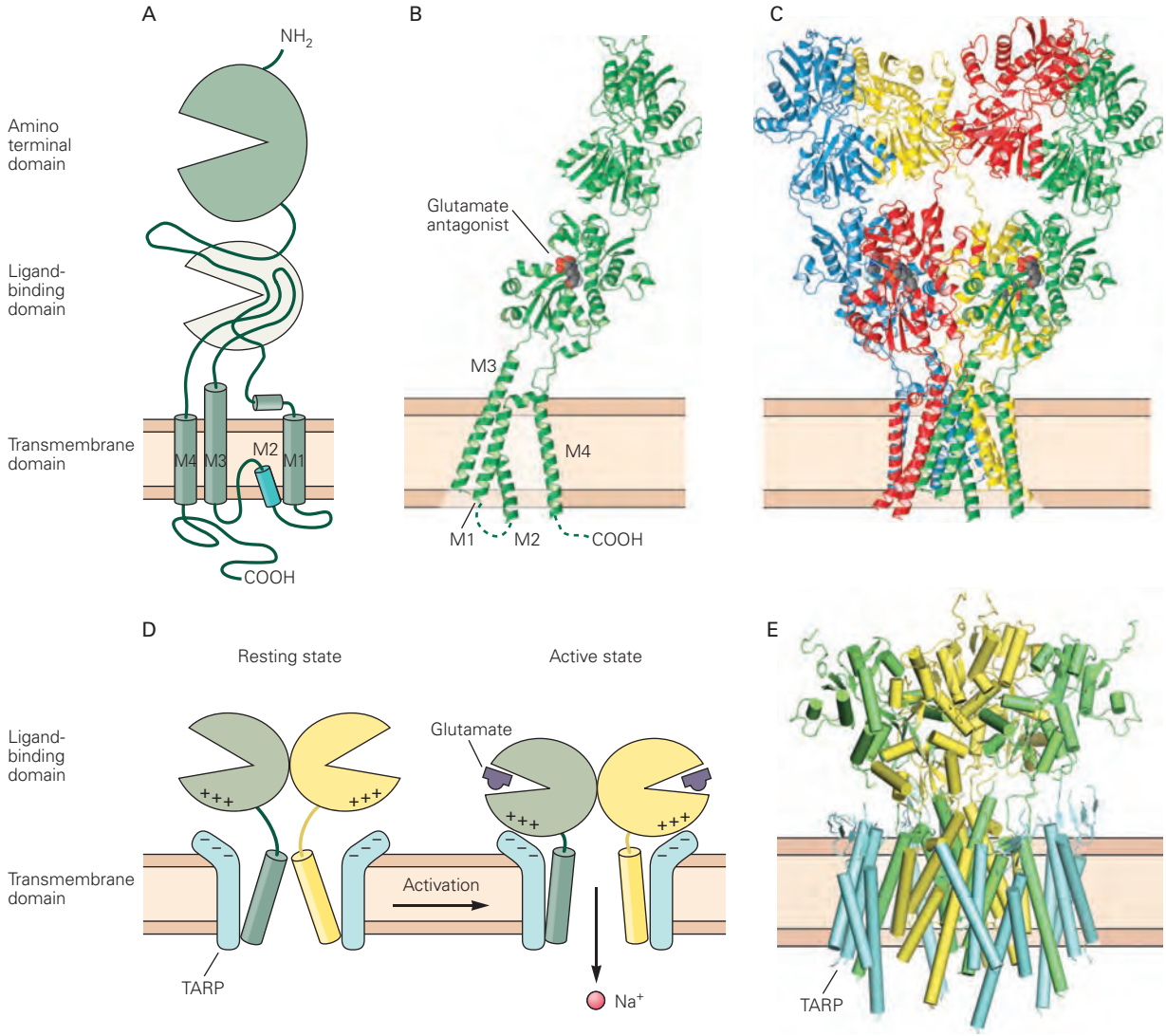

Figure 13–5 Atomic structure of an ionotropic glutamate receptor.

A. Schematic organization of the ionotropic glutamate receptors. The receptors contain a large extracellular amino terminus, a transmembrane domain containing three membrane-spanning α-helixes (M1, M3, and M4), and a loop that dips into the cytoplasmic side of the membrane (M2). The ligand-binding domain is formed by the extracellular region of the receptor on the amino-terminal side of the M1 segment and by the extracellular loop connecting M3 and M4. These two regions intertwine to form a clamshell-like structure that binds glutamate and various pharmacological agonists and competitive antagonists. A similar structure is formed at the extreme amino terminus of the receptor. In ionotropic glutamate receptors, this amino-terminal domain does not bind glutamate but is thought to modulate receptor function and synapse development. (Reproduced, with permission, from Armstrong et al. 1998.)

B. Three-dimensional X-ray crystal structure of a single AMPA receptor GluA2 subunit. This side view shows the amino-terminal, ligand-binding, and transmembrane domains (compare to panel A). The M1, M3, and M4 transmembrane α-helixes are indicated, as is a short α-helix in the M2 loop. A molecule of a competitive antagonist of glutamate bound to the ligand-binding domain is shown (**red space-filling representation**). The cytoplasmic loops connecting the membrane α-helixes were not resolved in the structure and have been drawn as **dashed lines**. (Reproduced, with permission, from Sobolevsky, Rosconi, and Gouaux 2009.)

C. This side view shows the structure of a receptor assembled from four identical GluA2 subunits (the subunits are colored differently for illustrative purposes). The subunits associate through their extracellular domains as a pair of dimers (two-fold symmetry). In the amino-terminal domain, one dimer is formed by the **blue** and **yellow** subunits, the other dimer by the **red** and **green** subunits. In the ligand-binding domain, the subunits change partners. In one dimer, the blue subunit associates with the red subunit, whereas in the other dimer, the yellow subunit associates with the green subunit. In the transmembrane region, the subunits associate as a four-fold symmetric tetramer. The significance of this highly unusual subunit arrangement is not fully understood. (Reproduced, with permission, from Sobolevsky, Rosconi, and Gouaux 2009.)

D. Cartoon side view of auxiliary TARP subunits (**blue**) associated with pore-forming GluA2 subunits. For simplicity, only the transmembrane and ligand-binding domain of two of the four GluA2 subunits is shown. Two of four TARP subunits are also shown. Binding of glutamate causes the clamshell-like ligand-binding domain to close, leading to a conformational change in the transmembrane domain that opens the pore. An electrostatic interaction between TARP and GluA2 stabilizes the receptor in the open state. (Adapted, with permission, from Mayer 2016. Copyright © 2016 Elsevier Ltd.)

E. Three-dimensional structure of the TARP-GluA2 complex. The α-helixes are shown as cylinders. The four TARP subunits are shown in blue. Transmembrane and ligand-binding domains of GluA2 subunits are shown in **yellow** and **green**. (Adapted, with permission, from Mayer 2016. Copyright © 2016 Elsevier Ltd.)

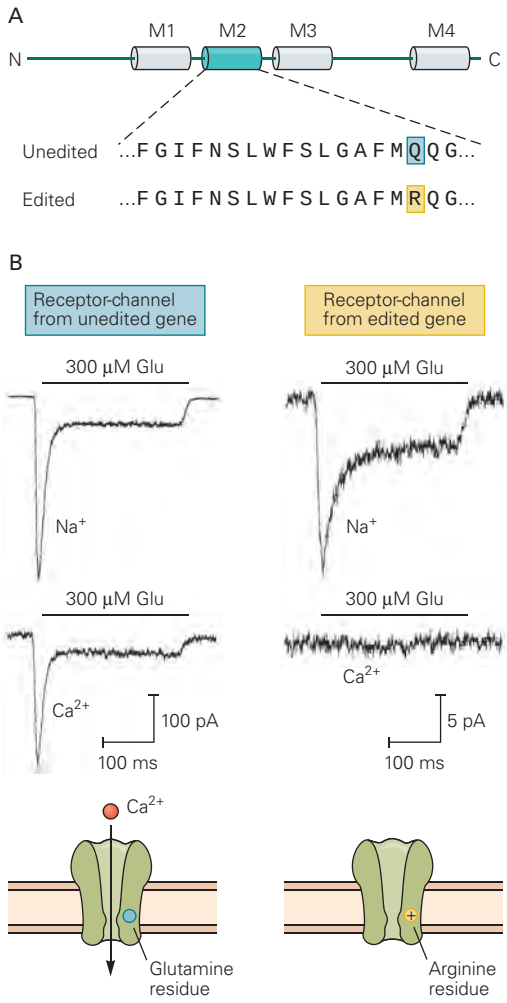

Figure 13–6 Determinants of calcium ion permeability of the AMPA receptor-channel.

A. Comparison of amino acid sequences in the M2 region of the AMPA receptor-channel coded by the *GluA2* gene before and after RNA editing. The unedited transcript codes for the polar residue glutamine (**Q**, the single-letter amino acid notation), whereas the edited transcript codes for the positively charged residue arginine (**R**). In adults, the GluA2 protein exists almost exclusively in the edited form.

B. AMPA receptor-channels expressed from unedited transcripts conduct Ca^{2+} (*left traces*), whereas those expressed from edited transcripts do not (*right traces*). The traces show currents elicited by glutamate with either extracellular Na^+ (*top*) or Ca^{2+} (*bottom*) as the predominant permeant cation. (Reproduced, with permission, from Sakmann 1992. Copyright © 1992 Elsevier.)

glutamine codon could no longer be changed to arginine. Such mice develop seizures and die within a few weeks after birth, presumably because the high Ca^{2+} permeability of all the AMPA receptors results in an excess of intracellular Ca^{2+}.

NMDA and AMPA Receptors Are Organized by a Network of Proteins at the Postsynaptic Density

How are the different glutamate receptors localized and arranged at excitatory synapses? Like most ionotropic receptors, glutamate receptors are normally clustered at postsynaptic sites in the membrane, precisely opposed to glutamatergic presynaptic terminals. The vast majority of excitatory synapses in the mature nervous system contain both NMDA and AMPA receptors, whereas in early development, synapses containing only NMDA receptors are common. The pattern of receptor localization and expression at individual synapses depends on a large number of regulatory proteins that constitute the postsynaptic density and help organize the three-dimensional structure of the postsynaptic cell membrane.

The postsynaptic density (PSD) is a remarkably stable structure, permitting its biochemical isolation, purification, and characterization. Electron microscopic studies of intact and isolated PSDs provide a strikingly detailed view of their structure (Figure 13–7A). By using gold-labeled antibodies, it is possible to identify specific protein components of the postsynaptic membrane, including the location and number of glutamate receptors. A typical PSD is around 350 nm in diameter and contains about 20 NMDA receptors, which tend to be localized near the center of the PSD, and 10 to 50 AMPA receptors, which are less centrally localized. The metabotropic glutamate receptors are located on the periphery, outside the main area of the PSD. All three receptor types interact with a wide array of cytoplasmic and membrane proteins to ensure their proper localization (Figure 13–7C).

One of the most prominent proteins in the PSD important for the clustering of glutamate receptors is PSD-95 (PSD protein of 95 kD molecular weight). PSD-95 is a membrane-associated protein that contains three repeated regions—the so-called PDZ domains—important for protein–protein interactions. (The PDZ domains are named after the three proteins in which they were first identified: PSD-95, the DLG tumor suppressor protein in *Drosophila*, and a protein termed ZO-1.) The PDZ domains bind to specific sequences at the carboxy terminus of a number of proteins. In PSD-95, the PDZ domains bind the NMDA receptor and Shaker-type voltage-gated K^+ channels, thereby localizing and concentrating these channels at postsynaptic sites. PSD-95 also interacts with the postsynaptic membrane protein neuroligin, which contacts the presynaptic membrane protein neurexin in the synaptic cleft, an interaction important for synapse development. Mutations in neuroligin are thought to contribute to some cases of autism.

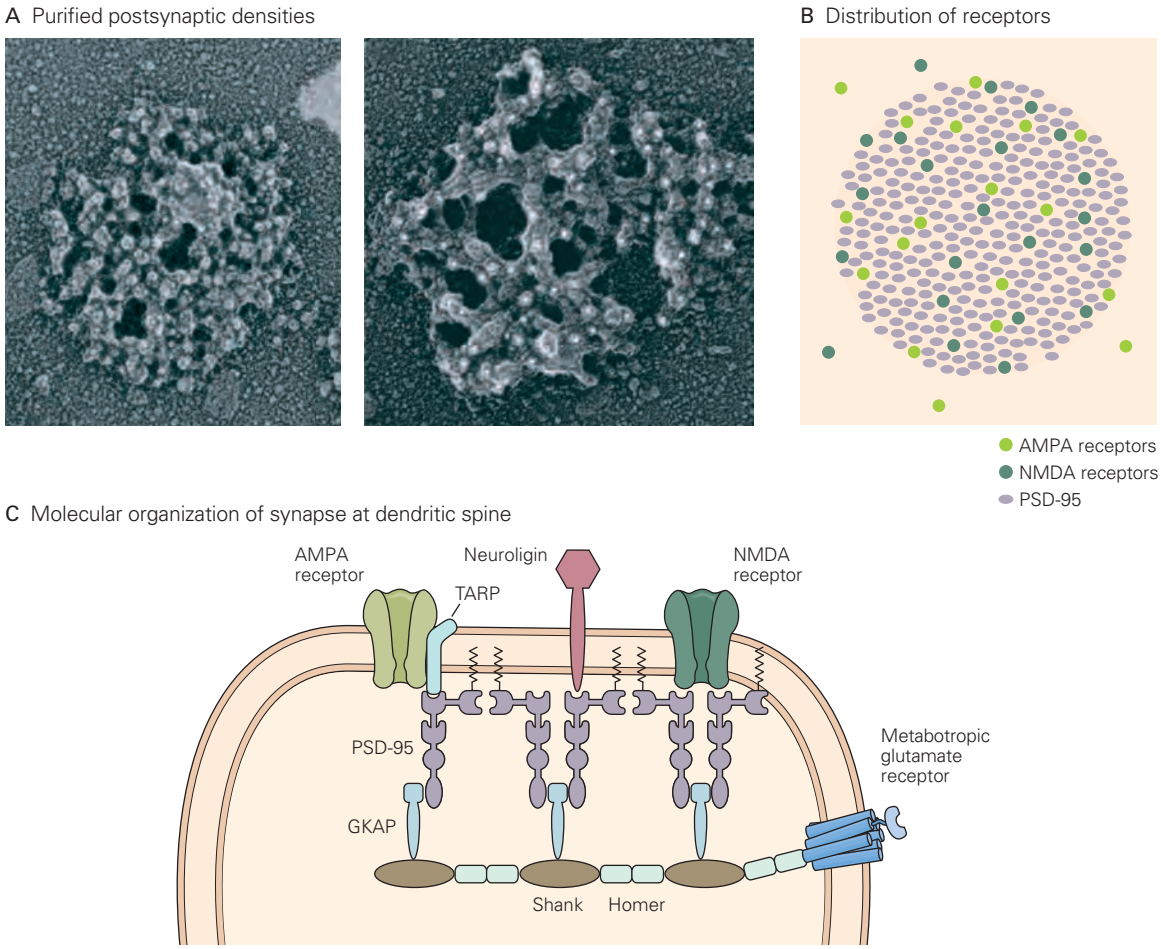

Figure 13–7 The postsynaptic cell membrane is organized into a macromolecular complex at excitatory synapses. Proteins containing PDZ domains help organize the distribution of AMPA and NMDA glutamate receptors at the postsynaptic density. (Reproduced, with permission, from Sheng and Hoogenrad 2007. Micrographs provided by Thomas S. Reese and Xiaobing Chen; National Institutes of Health, USA.)

A. Electron microscope images of biochemically purified post-synaptic densities, showing organization of the protein network. The membrane lipid bilayer is no longer present. *Left:* View of postsynaptic density from what would normally be the outside of the cell. This image consists of the extracellular domains of various receptors and membrane proteins. *Right:* View of a postsynaptic density from what would normally be the cytoplasmic side of the membrane. **White dots** show immunolabeled guanylate kinase anchoring protein, an important component of the postsynaptic density.

B. The distribution of NMDA receptors, AMPA receptors, and PSD-95, a prominent postsynaptic density protein, at a synapse.

C. The network of receptors and their interacting proteins in the postsynaptic density. PSD-95 contains three PDZ domains at its amino terminus and two other protein-interacting motifs at its carboxyl terminus, an SH3 domain and guanylate kinase (GK) domain. Certain PDZ domains of PSD-95 bind to the carboxyl terminus of the GluN2 subunit of the NMDA receptor. PSD-95 does not directly interact with AMPA receptors but binds to the carboxyl terminus of the TARP family of membrane proteins, which interact with the AMPA receptors as auxiliary subunits. PSD-95 also acts as a scaffold for various cytoplasmic proteins by binding to GK-associated protein (**GKAP**), which interacts with Shank, a large protein that associates into a meshwork linking the various components of the postsynaptic density. PSD-95 also interacts with the cytoplasmic region of neuroligin. The metabotropic glutamate receptor is localized on the periphery of the synapse where it interacts with the protein Homer, which in turn binds to Shank.

Although PSD-95 does not directly bind to AMPA receptors, it does interact with the TARP subunits. The proper localization of AMPA receptors in the postsynaptic membrane depends on the interaction between the carboxy terminus of the TARP subunit and PSD-95. AMPA receptors also bind to a distinct PDZ domain protein called GRIP, and metabotropic glutamate receptors interact with yet another PDZ domain protein called Homer. In addition to interacting with receptors, proteins with PDZ domains interact with

many other cellular proteins, including proteins that bind to the actin cytoskeleton, providing a scaffold around which a complex of postsynaptic proteins is constructed. Indeed, a biochemical analysis of the PSD has identified dozens of proteins that participate in NMDA or AMPA receptor complexes.

NMDA Receptors Have Unique Biophysical and Pharmacological Properties

The NMDA receptor has several interesting properties that distinguish it from AMPA receptors. As mentioned earlier, NMDA receptors have a distinctively high permeability to Ca^{2+}. In addition, the NMDA receptor is unique among ligand-gated channels thus far characterized because its opening depends on membrane voltage as well as transmitter binding.

The voltage dependence is caused by a mechanism that is quite different from that employed by the voltage-gated channels that generate the action potential. In the latter, changes in membrane potential are translated into conformational changes in the channel by an intrinsic voltage sensor. In the NMDA receptors, however, depolarization removes an extrinsic plug from the channel. At the resting membrane potential (–65 mV), extracellular Mg^{2+} binds tightly to a site in the pore of the channel, blocking ionic current. But when the membrane is depolarized (for example, by the opening of AMPA receptor-channels), Mg^{2+} is expelled from the channel by electrostatic repulsion, allowing Na^+, K^+, and Ca^{2+} to flow (Figure 13–8). The NMDA receptor has the further interesting property of being inhibited by the hallucinogenic drug *phencyclidine* (PCP, also known as angel dust) and the experimental compound MK801. Both drugs bind to a site in the pore of the channel that is distinct from the Mg^{2+} binding site (Figure 13–3A).

At most glutamatergic central synapses, the postsynaptic membrane contains both NMDA and AMPA receptors. The relative contributions of current through

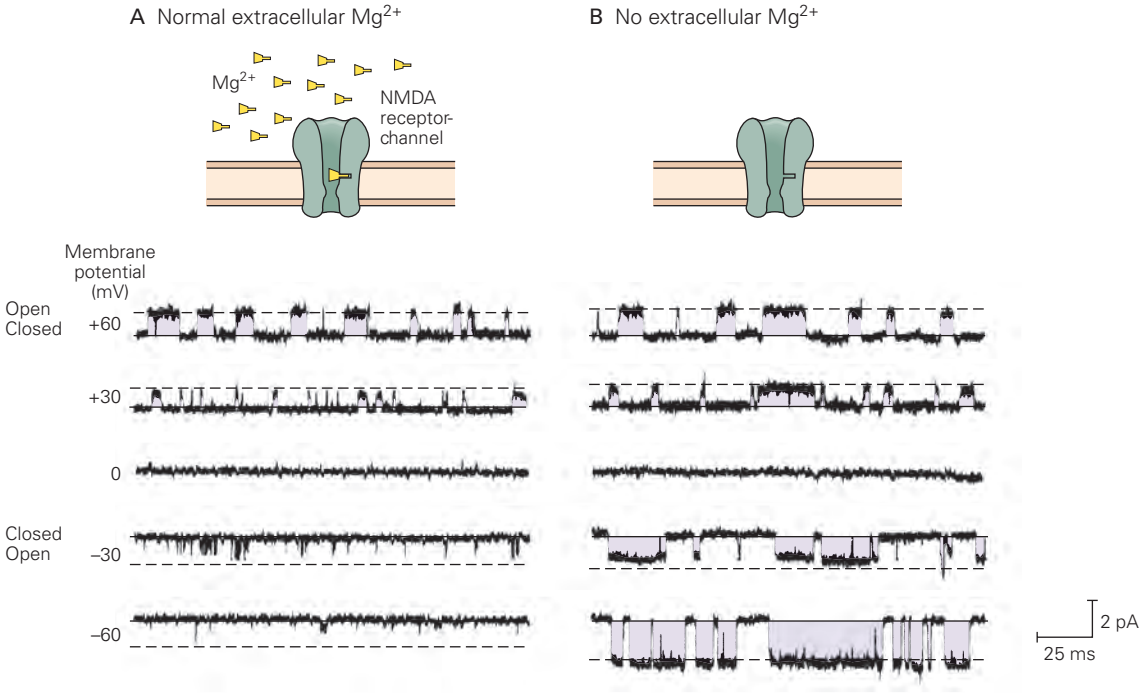

Figure 13–8 Opening of individual NMDA receptor-channels depends on membrane potential in addition to glutamate. These patch-clamp recordings are from individual NMDA receptor-channels (from rat hippocampal cells in culture). **Downward** deflections indicate pulses of inward (negative) current; **upward** deflections indicate outward (positive) current. (Reproduced, with permission, from J. Jen and C.F. Stevens.)

A. When Mg^{2+} is present in normal concentration in the extracellular solution (1.2 mM), the channel is largely blocked at the resting potential (–60 mV). At negative membrane potentials, only brief, flickering, inward currents are seen upon channel opening because of the Mg^{2+} block. Substantial depolarization to voltages positive to the reversal potential of 0 mV (to +30 mV or +60 mV) relieves the Mg^{2+} block, permitting longer-lasting pulses of outward current through the channel.

B. When Mg^{2+} is removed from the extracellular solution, the opening and closing of the channel do not depend on voltage. The channel is open at the resting potential of –60 mV, and the synaptic current reverses near 0 mV, like the total synaptic current (see Figure 13–9B).

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.