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14

Modulation of Synaptic Transmission and Neuronal Excitability: Second Messengers

The Cyclic AMP Pathway Is the Best Understood Second-Messenger Signaling Cascade Initiated by G Protein–Coupled Receptors

The Second-Messenger Pathways Initiated by G Protein–Coupled Receptors Share a Common Molecular Logic

A Family of G Proteins Activates Distinct Second-Messenger Pathways

Hydrolysis of Phospholipids by Phospholipase C Produces Two Important Second Messengers, IP_3 and Diacylglycerol

Receptor Tyrosine Kinases Compose the Second Major Family of Metabotropic Receptors

Several Classes of Metabolites Can Serve as Transcellular Messengers

Hydrolysis of Phospholipids by Phospholipase A_2 Liberates Arachidonic Acid to Produce Other Second Messengers

Endocannabinoids Are Transcellular Messengers That Inhibit Presynaptic Transmitter Release

The Gaseous Second Messenger Nitric Oxide Is a Transcellular Signal That Stimulates Cyclic GMP Synthesis

The Physiological Actions of Metabotropic Receptors Differ From Those of Ionotropic Receptors

Second-Messenger Cascades Can Increase or Decrease the Opening of Many Types of Ion Channels

G Proteins Can Modulate Ion Channels Directly

Cyclic AMP–Dependent Protein Phosphorylation Can Close Potassium Channels

Second Messengers Can Endow Synaptic Transmission with Long-Lasting Consequences

Modulators Can Influence Circuit Function by Altering Intrinsic Excitability or Synaptic Strength

Multiple Neuromodulators Can Converge Onto the Same Neuron and Ion Channels

Why So Many Modulators?

Highlights

The binding of neurotransmitter to postsynaptic receptors produces a postsynaptic potential either directly, by opening ion channels, or indirectly, by altering ion channel activity through changes in the postsynaptic cell's biochemical state. As we saw in Chapters 11 to 13, the type of postsynaptic action depends on the type of receptor. Activation of an *ionotropic receptor* directly opens an ion channel that is part of the receptor macromolecule itself. In contrast, activation of *metabotropic receptors* regulates the opening of ion channels indirectly through biochemical signaling pathways; the metabotropic receptor and the ion channels regulated by the receptor are distinct macromolecules (Figure 14–1).

Whereas the action of ionotropic receptors is fast and brief, metabotropic receptors produce effects that begin slowly and persist for long periods, ranging from hundreds of milliseconds to many minutes. The two types of receptors also differ in their functions. Ionotropic receptors underlie fast synaptic signaling that is the basis of all behaviors, from simple reflexes to complex cognitive processes. Metabotropic receptors

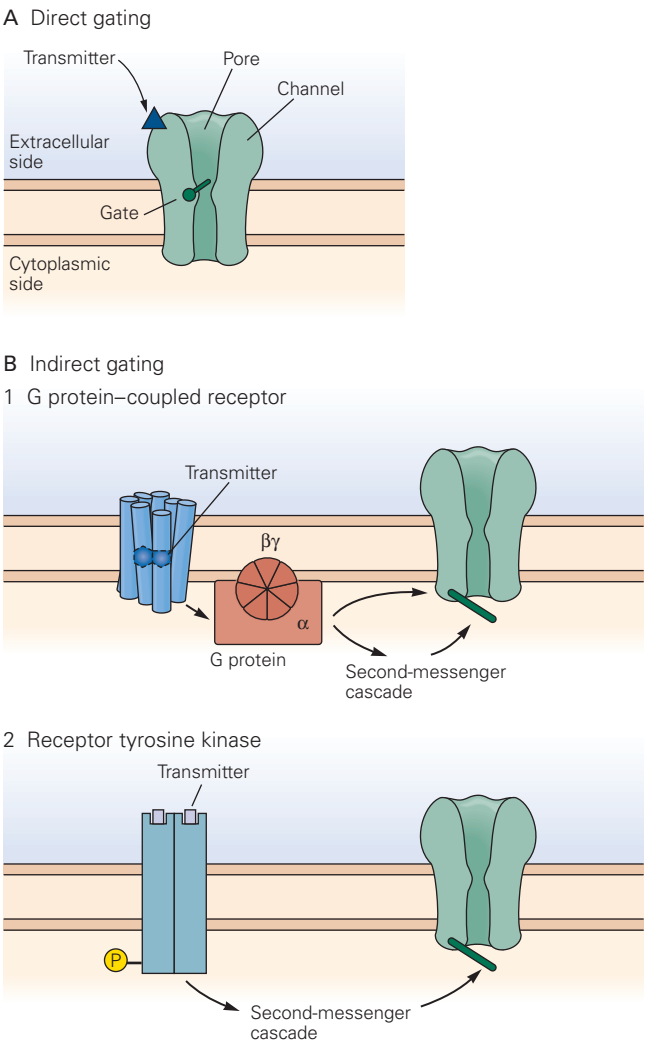

Figure 14–1 Neurotransmitter actions can be divided into two groups according to the way receptor and effector functions are coupled.

A. Direct transmitter actions are produced by the binding of transmitter to *ionotropic receptors*, ligand-gated channels in which the receptor and ion channel are domains within a single macromolecule. The binding of transmitter to the receptor on the extracellular aspect of the receptor-channel protein directly opens the ion channel embedded in the cell membrane.

B. Indirect transmitter actions are caused by binding of transmitter to *metabotropic receptors*, macromolecules that are separate from the ion channels they regulate. There are two families of these receptors. 1. G protein–coupled receptors activate guanosine triphosphate (GTP)-binding proteins that engage a second-messenger cascade or act directly on ion channels. 2. Receptor tyrosine kinases initiate a cascade of protein phosphorylation reactions, beginning with autophosphorylation (P) of the kinase itself on tyrosine residues.

modulate behaviors; they modify reflex strength, activate motor patterns, focus attention, set emotional states, and contribute to long-lasting changes in neural circuits that underlie learning and memory. Metabotropic receptors are responsible for many of the actions of transmitters, hormones, and growth factors. The actions of these neuromodulators can produce remarkable and dramatic changes in neuronal excitability and synaptic strength and, in so doing, can profoundly alter the state of activity in an entire circuit important for behavior.

Ionotropic receptors change the membrane potential quickly. As we have seen, this change is local at first but is propagated as an action potential along the axon if the change in membrane potential is suprathreshold. Activation of metabotropic receptors also begins as a local action that can spread to a wider region of the cell. The binding of a neurotransmitter with a metabotropic receptor activates proteins that in turn activate effector enzymes. The effector enzymes then often produce second-messenger molecules that can diffuse within a cell to activate still other enzymes that catalyze modifications of a variety of target proteins, greatly changing their activities.

There are two major families of metabotropic receptors: G protein–coupled receptors and receptor tyrosine kinases. We first describe the G protein–coupled receptor family and later discuss the receptor tyrosine kinase family.

The G protein–coupled receptors are coupled to an effector by a trimeric guanine nucleotide-binding protein, or G protein (Figure 14–1B). This receptor family comprises α- and β-adrenergic receptors for norepinephrine, muscarinic acetylcholine (ACh) receptors, γ-aminobutyric acid B ($GABA_B$) receptors, certain glutamate and serotonin receptors, all receptors for dopamine, receptors for neuropeptides, odorant receptors, rhodopsin (the protein that reacts to light, initiating visual signals; see Chapter 22), and many others. Many of these receptors are thought to be involved in neurological and psychiatric diseases and are key targets for the actions of important classes of therapeutic drugs.

G protein–coupled receptors activate a variety of effectors. The typical effector is an enzyme that produces a diffusible second messenger. These second messengers in turn trigger a biochemical cascade, either by activating specific protein kinases that phosphorylate the hydroxyl group of specific serine or threonine residues in various proteins or by mobilizing Ca^{2+} ions from intracellular stores, thereby initiating reactions that change the cell's biochemical state. In some instances, the G protein or the second messenger acts directly on an ion channel.

The Cyclic AMP Pathway Is the Best Understood Second-Messenger Signaling Cascade Initiated by G Protein–Coupled Receptors

The adenosine 3′,5′-cyclic monophosphate (cyclic AMP or cAMP) pathway is a prototypic example of a G protein–coupled second-messenger cascade. It was the first second-messenger pathway to be discovered, and our conception of other second-messenger pathways is based on it.

The binding of transmitter to receptors linked to the cAMP cascade first activates a specific G protein, G_s (named for its action to *stimulate* cAMP synthesis). In its resting state, G_s, like all G proteins, is a trimeric protein consisting of an α-, β-, and γ-subunit. The α-subunit is only loosely associated with the membrane and is usually the agent that couples the receptor to its primary effector enzyme. The β- and γ-subunits form a strongly bound complex that is more tightly associated with the membrane. As described later in this chapter, the βγ complex of G proteins can regulate the activity of certain ion channels directly.

In the resting state, the α-subunit binds a molecule of guanosine diphosphate (GDP). Upon the binding of ligand, a G protein–coupled receptor undergoes a conformational change that enables it to bind to the α-subunit, thereby promoting the exchange of GDP with a molecule of guanosine triphosphate (GTP). This leads to a conformational change that causes the α-subunit to dissociate from the βγ complex, thereby activating the α-subunit.

The particular class of α-subunit that is coupled to the cAMP cascade is termed α_s, which stimulates the integral membrane protein adenylyl cyclase to catalyze the conversion of adenosine triphosphate (ATP) to cAMP. When associated with the cyclase, α_s also acts as a GTPase, hydrolyzing its bound GTP to GDP. When GTP is hydrolyzed, α_s becomes inactive. It dissociates from adenylyl cyclase and reassociates with the βγ complex, thereby stopping the synthesis of cAMP (Figure 14–2A). A G_s protein typically remains active for a few seconds before its bound GTP is hydrolyzed.

Once a G protein–coupled receptor binds a ligand, it can interact sequentially with more than one G protein macromolecule. As a result, the binding of relatively few molecules of transmitter to a small number of receptors can activate a large number of cyclase complexes. The signal is further amplified in the next step in the cAMP cascade, the activation of the protein kinase.

The major target of cAMP in most cells is the cAMP-dependent protein kinase (also called protein kinase A or PKA). This kinase, identified and characterized by Edward Krebs and colleagues, is a heterotetrameric enzyme consisting of a dimer of two regulatory (R) subunits and two catalytic (C) subunits. In the absence of cAMP, the R subunits bind to and inhibit the C subunits. In the presence of cAMP, each R subunit binds two molecules of cAMP, leading to a conformational change that causes the R and C subunits to dissociate (Figure 14–2B). Dissociation frees the C subunits to transfer the γ-phosphoryl group of ATP to the hydroxyl groups of specific serine and threonine residues in substrate proteins. The action of PKA is terminated by phosphoprotein phosphatases, enzymes that cleave the phosphoryl group from proteins, producing inorganic phosphate.

Protein kinase A is distantly related through evolution to other serine and threonine protein kinases that we shall consider: the calcium/calmodulin-dependent protein kinases and protein kinase C. These kinases also have regulatory and catalytic domains, but both domains are within the same polypeptide molecule (see Figure 14–4).

In addition to blocking enzymatic activity, the regulatory subunits of PKA also target the catalytic subunits to distinct sites within cells. Human PKA has two types of R subunits, R_I and R_{II}, each with two subtypes: $R_{I\alpha}$, $R_{I\beta}$, $R_{II\alpha}$, and $R_{II\beta}$. The genes for each derive from a common ancestor but have different properties. For example, type II PKA (containing R_{II}-type subunits) is targeted to the membrane by *A kinase attachment proteins* (AKAPs). One type of AKAP targets PKA to the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor by binding both PKA and the postsynaptic density protein PSD-95, which binds to the cytoplasmic tail of the NMDA receptor (Chapter 13). In addition, this AKAP also binds a protein phosphatase, which removes the phosphate group from substrate proteins. By localizing PKA and other signaling components near their substrate, AKAPs form local signaling complexes that increase the specificity, speed, and efficiency of second-messenger cascades. Because AKAPs have only a weak affinity for R_I subunits, most type I PKA is free in the cytoplasm.

Kinases can only phosphorylate proteins on serine and threonine residues that are embedded within a context of specific *phosphorylation consensus sequences* of amino acids. For example, phosphorylation by PKA usually requires a sequence of two contiguous basic amino acids—either lysine or arginine—followed by any amino acid, and then by the serine or threonine residue that is phosphorylated (for example, Arg-Arg-Ala-Thr).

Several important protein substrates for PKA have been identified in neurons. These include voltage-gated

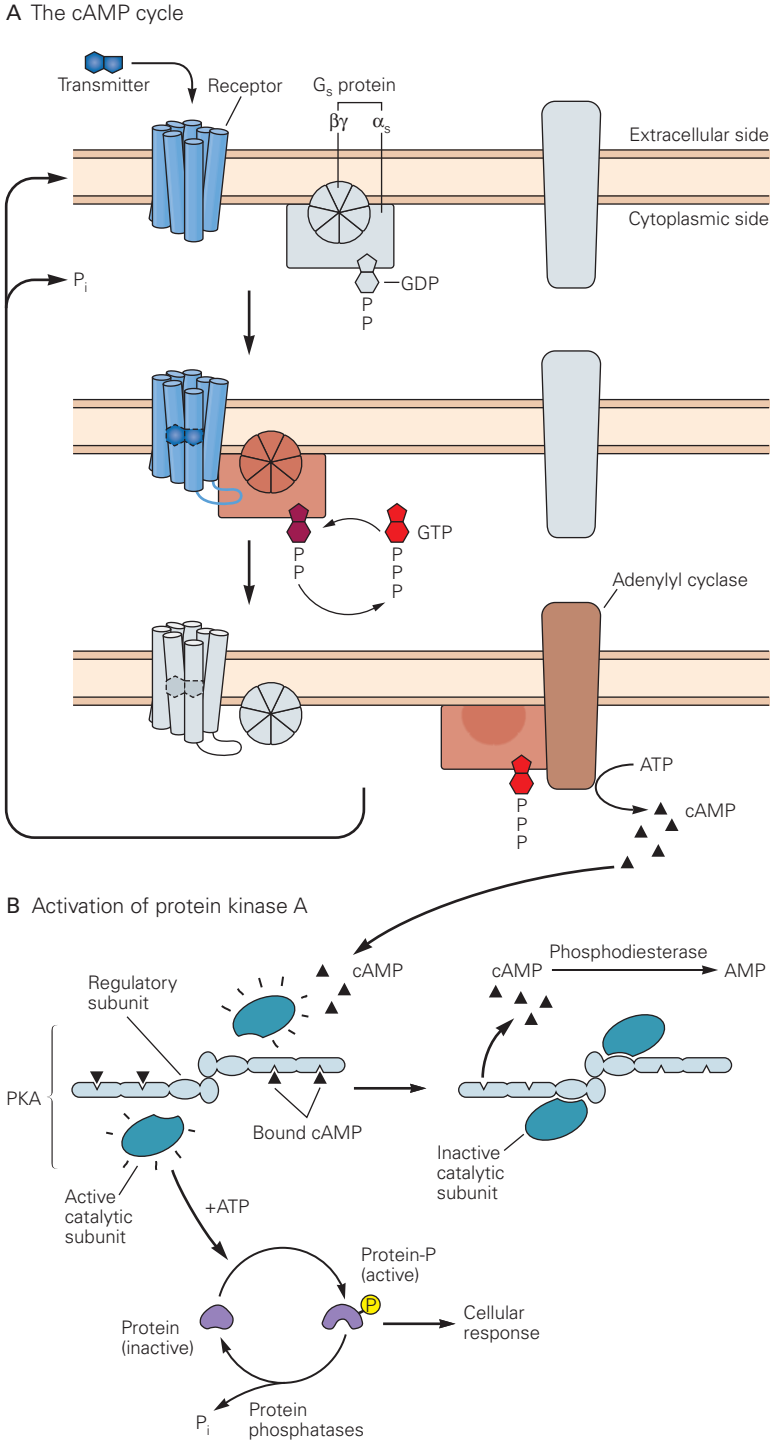

Figure 14–2 Activation of G protein–coupled receptors stimulates cyclic adenosine monophosphate (cAMP) production and protein kinase A. (Adapted from Alberts et al. 1994.)

A. The binding of a transmitter to certain receptors activates the stimulatory G protein (G_s), consisting of α_s-, β-, and γ-subunits. When activated, the α_s-subunit exchanges its bound guanosine diphosphate (**GDP**) for guanosine triphosphate (**GTP**), causing α_s to dissociate from the βγ complex. Next, α_s associates with an intracellular domain of adenylyl cyclase, thereby stimulating the enzyme to produce cAMP from adenosine triphosphate (**ATP**). The hydrolysis of GTP to GDP and inorganic phosphate (P_i) leads to dissociation of α_s from the cyclase and its reassociation with the βγ complex. The cyclase then stops producing the second messenger. As transmitter dissociates from the receptor, the three subunits of the G protein reassociate, and the guanine nucleotide-binding site on the α-subunit is occupied by GDP.

B. Four cAMP molecules bind to the two regulatory subunits of protein kinase A (**PKA**), liberating the two catalytic subunits, which are then free to phosphorylate specific substrate proteins on certain serine or threonine residues, thereby regulating protein function to produce a given cellular response. Two kinds of enzymes regulate this pathway. Phosphodiesterases convert cAMP to adenosine monophosphate (which is inactive), and protein phosphatases remove phosphate groups (**P**) from the substrate proteins, releasing inorganic phosphate, P_i. Phosphatase activity is, in turn, decreased by the protein inhibitor-1 (not shown), when it is phosphorylated by PKA.

and ligand-gated ion channels, synaptic vesicle proteins, enzymes involved in transmitter biosynthesis, and proteins that regulate gene transcription. As a result, the cAMP pathway has widespread effects on the electrophysiological and biochemical properties of neurons. We shall consider some of these actions later in this chapter.

The Second-Messenger Pathways Initiated by G Protein–Coupled Receptors Share a Common Molecular Logic

Approximately 3.5% of genes in the human genome code for G protein–coupled receptors. Although many of these are odorant receptors in olfactory neurons (Chapter 29), many others are receptors for well-characterized neurotransmitters used throughout the nervous system. Despite their enormous diversity, all G protein–coupled receptors consist of a single polypeptide with seven characteristic membrane-spanning regions (serpentine receptors) (Figure 14–3A). Recent results from X-ray crystallography have provided detailed insights into the three-dimensional structure of these receptors in contact with their respective G proteins (Figure 14–3B).

The number of substances that act as second messengers in synaptic transmission is much fewer than the number of transmitters. More than 100 substances serve as transmitters; each can activate several types of receptors present in different cells. The few second messengers that have been well characterized fall into two categories, intracellular and transcellular. Intracellular messengers are molecules whose actions are confined to the cell in which they are produced. Transcellular messengers are molecules that can readily cross the cell membrane and thus can leave the cell in which they are produced to act as intercellular signals, or first messengers, on neighboring cells.

A Family of G Proteins Activates Distinct Second-Messenger Pathways

Approximately 20 types of α-subunits have been identified, 5 types of β-subunits, and 12 types of γ-subunits. G proteins with different α-subunits couple different classes of receptors and effectors and therefore have different physiological actions. For example, the inhibitory *G_i proteins*, which contain the α_i-subunit, inhibit adenylyl cyclase and decrease cAMP levels. Other G proteins ($G_{q/11}$ proteins, which contain α_q- or α_{11}-subunits) activate phospholipase C and probably other signal transduction mechanisms not yet identified. The G_o protein, which contains the α_o-subunit, is expressed at particularly high levels in the brain, but its exact targets are not known. Compared with other organs of the body, the brain contains an exceptionally large variety of G proteins. Even so, because of the limited number of classes of G proteins compared to the much larger number of receptors, one type of G protein can often be activated by different classes of receptors.

The number of known effector targets for G proteins is even more limited than the types of G proteins. Important effectors include certain ion channels that are activated by the βγ complex, adenylyl cyclase in the cAMP pathway, phospholipase C in the diacylglycerol-inositol polyphosphate pathway, and phospholipase A_2 in the arachidonic acid pathway. Each of these effectors (except for the ion channels) initiates changes in specific target proteins within the cell, either by generating second messengers that bind to the target protein or by activating a protein kinase that phosphorylates it.

Hydrolysis of Phospholipids by Phospholipase C Produces Two Important Second Messengers, IP_3 and Diacylglycerol

Many important second messengers are generated through the hydrolysis of phospholipids in the inner leaflet of the plasma membrane. This hydrolysis is catalyzed by three enzymes—phospholipase C, D, and A_2—named for the ester bonds they hydrolyze in the phospholipid. The phospholipases each can be activated by different G proteins coupled to different receptors.

The most commonly hydrolyzed phospholipid is *phosphatidylinositol 4,5-bisphosphate* (PIP_2), which typically contains the fatty acid stearate esterified to the glycerol backbone in the first position and the unsaturated fatty acid arachidonate in the second. Activation of receptors coupled to G_q or G_{11} stimulates *phospholipase C*, which leads to the hydrolysis of PIP_2 (specifically the phosphodiester bond that links the glycerol backbone to the polar head group) and production of two second messengers, *diacylglycerol* (DAG) and *inositol 1,4,5-trisphosphate* (IP_3).

Diacylglycerol, which is hydrophobic, remains in the membrane when formed, where it recruits the cytoplasmic protein kinase C (PKC). Together with DAG and certain membrane phospholipids, PKC forms an active complex that can phosphorylate many protein substrates in the cell, both membrane-associated and cytoplasmic (Figure 14–4A). Activation of some isoforms of PKC requires elevated levels of cytoplasmic Ca^{2+} in addition to DAG.

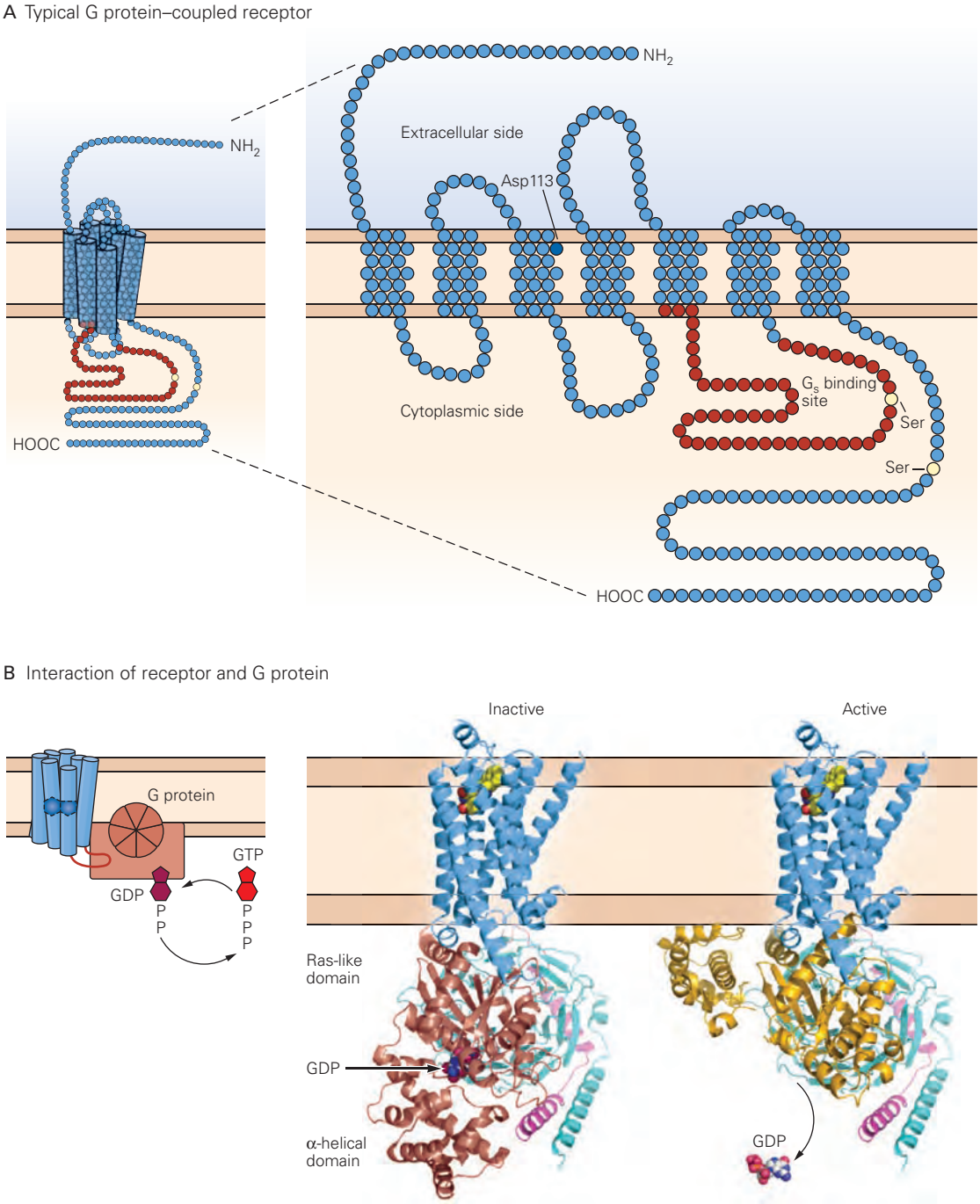

Figure 14–3 G protein–coupled receptors contain seven membrane-spanning domains.

A. The β_2-adrenergic receptor shown here is representative of G protein–coupled receptors, including the β_1-adrenergic and muscarinic acetylcholine (ACh) receptors and rhodopsin. It consists of a single subunit with an extracellular amino terminus, intracellular carboxy terminus, and seven membrane-spanning α-helixes. The binding site for the neurotransmitter lies in a cleft in the receptor formed by the transmembrane helixes. The amino acid residue aspartic acid (**Asp**)-113 participates in binding. The part of the receptor indicated in **brown** associates with G_s protein α-subunits. Two serine (**Ser**) residues in the intracellular carboxy-terminal tail are sites for phosphorylation by specific receptor kinases, which helps inactivate the receptor. (Adapted, with permission, from Frielle et al. 1989.)

B. Models based on X-ray crystal structures of the β_2-adrenergic receptor (**blue**) interacting with the G_s protein in the inactive guanosine diphosphate (**GDP**)-bound state and the active guanosine triphosphate (**GTP**)-bound state. A high-affinity synthetic agonist is bound in the transmembrane region near the extracellular surface of the membrane (space-filling model). The α_s-, β-, and γ-subunits of the inactive G_s protein are shown in **brown**, **cyan**, and **purple**, respectively. In the active state, α_s (**gold**) undergoes a conformational change that enables it to interact with adenylyl cyclase. (Adapted, with permission, from Kobilka 2013. Copyright © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.)

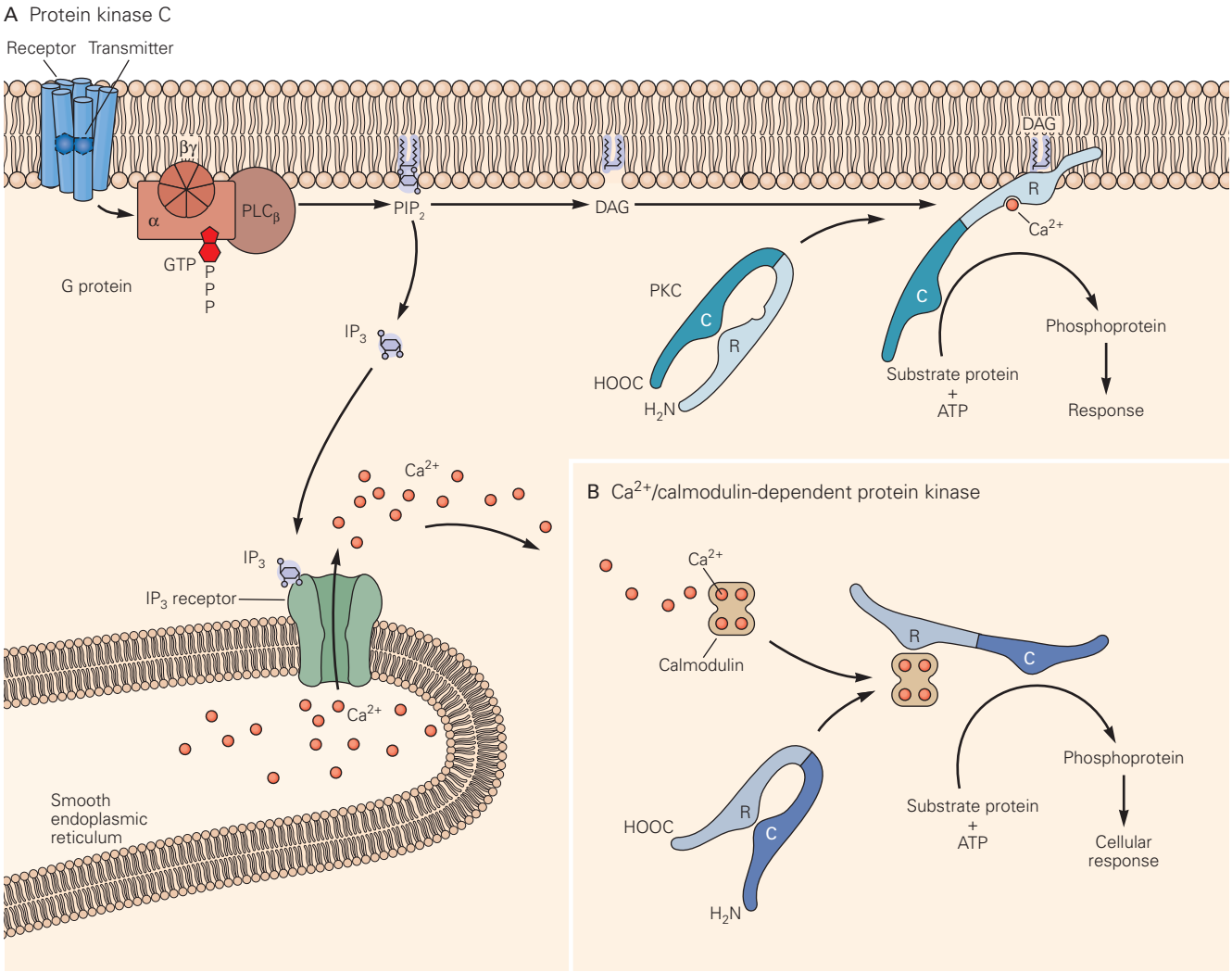

Figure 14–4 Hydrolysis of phospholipids in the cell membrane activates three major second-messenger cascades.

A. The binding of transmitter to a receptor activates a G protein that activates phospholipase C_β (**PLC_β**). This enzyme cleaves phosphatidylinositol 4,5-bisphosphate (**PIP_2**) into the second messengers inositol 1,4,5-trisphosphate (**IP_3**) and diacylglycerol (**DAG**). IP_3 is water soluble and diffuses into the cytoplasm, where it binds to the IP_3 receptor-channel on the smooth endoplasmic reticulum, thereby releasing Ca^{2+} from internal stores. DAG remains in the membrane, where it recruits and activates protein kinase C (**PKC**). Membrane phospholipid is also a necessary cofactor for PKC activation. Some isoforms of PKC also require Ca^{2+} for activation. PKC is composed of a single protein molecule that has both a regulatory domain that binds DAG and a catalytic domain that phosphorylates proteins on serine or threonine residues. In the absence of DAG the regulatory domain inhibits the catalytic domain.

B. The calcium/calmodulin-dependent protein kinase is activated when Ca^{2+} binds to calmodulin and the calcium/calmodulin complex then binds to a regulatory domain of the kinase. The kinase is composed of many similar subunits (only one of which is shown here), each having both regulatory and catalytic functions. The catalytic domain phosphorylates proteins on serine or threonine residues. (**ATP**, adenosine triphosphate; **C**, catalytic subunit; **COOH**, carboxy terminus; **H_2N**, amino terminus; **R**, regulatory subunit.)

The second product of the phospholipase C pathway, IP_3, stimulates the release of Ca^{2+} from intracellular membrane stores in the lumen of the smooth endoplasmic reticulum. The membrane of the reticulum contains a large integral membrane macromolecule, the IP_3 receptor, which forms both a receptor for IP_3 on its cytoplasmic surface and a Ca^{2+} channel that spans the membrane of the reticulum. When this macromolecule binds IP_3, the channel opens, releasing Ca^{2+} into the cytoplasm (Figure 14–4A).

The increase in intracellular Ca^{2+} triggers many biochemical reactions and opens calcium-gated channels

in the plasma membrane. Calcium can also act as a second messenger to trigger the release of additional Ca^{2+} from internal stores by binding to another integral protein in the membrane of the smooth endoplasmic reticulum, the *ryanodine receptor* (so called because it binds the plant alkaloid ryanodine, which inhibits the receptor; in contrast, caffeine opens the ryanodine receptor). Like the IP_3 receptor to which it is distantly related, the ryanodine receptor forms a Ca^{2+} channel that spans the reticulum membrane; however, cytoplasmic Ca^{2+}, not IP_3, opens the ryanodine receptor-channel.

Calcium often acts by binding to the small cytoplasmic protein calmodulin. An important function of the calcium/calmodulin complex is to activate *calcium/calmodulin-dependent protein kinase* (CaM kinase). This enzyme is a complex of many similar subunits, each containing both regulatory and catalytic domains within the same polypeptide chain. When the calcium/calmodulin complex is absent, the C-terminal regulatory domain of the kinase binds and inactivates the catalytic portion. Binding to the calcium/calmodulin complex causes conformational changes of the kinase molecule that unfetter the catalytic domain for action (Figure 14–4B). Once activated, CaM kinase can phosphorylate itself through intramolecular reactions at many sites in the molecule. Autophosphorylation has an important functional effect: It converts the enzyme into a form that is independent of calcium/calmodulin and therefore persistently active, even in the absence of Ca^{2+}.

Persistent activation of protein kinases is a general and important mechanism for maintaining biochemical processes that underlie long-term changes in synaptic function associated with certain forms of memory. In addition to the persistent activation of calcium/calmodulin-dependent protein kinase, PKA can also become persistently active following a prolonged increase in cAMP because of a slow enzymatic degradation of free regulatory subunits through the ubiquitin pathway. The decline in regulatory subunit concentration results in the long-lasting presence of free catalytic subunits, even after cAMP levels have declined, leading to the continued phosphorylation of substrate proteins. PKC can also become persistently active through proteolytic cleavage of its regulatory and catalytic domains or through the expression of a PKC isoform that lacks a regulatory domain. Finally, the duration of phosphorylation can be enhanced by certain proteins that act to inhibit the activity of phosphoprotein phosphatases. One such protein, inhibitor-1, inhibits phosphatase activity only when the inhibitor is itself phosphorylated by PKA.

Receptor Tyrosine Kinases Compose the Second Major Family of Metabotropic Receptors

The *receptor tyrosine kinases* represent a distinct family of receptors from the G protein–coupled receptors. The receptor tyrosine kinases are integral membrane proteins composed of a single subunit with an extracellular ligand-binding domain connected to a cytoplasmic region by a single transmembrane segment. The cytoplasmic region contains a protein kinase domain that phosphorylates both itself (autophosphorylation) and other proteins on tyrosine residues (Figure 14–5A). This phosphorylation results in the activation of a large number of proteins, including other kinases that are capable of acting on ion channels.

Receptor tyrosine kinases are activated when bound by peptide hormones, including epidermal growth factor (EGF), fibroblast growth factor (FGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and insulin. Cells also contain important nonreceptor cytoplasmic tyrosine kinases, such as the protooncogene *src*. These nonreceptor tyrosine kinases are often activated by interactions with receptor tyrosine kinases and are important in regulating growth and development.

Many (but not all) of the receptor tyrosine kinases exist as monomers in the plasma membrane in the absence of ligand. Ligand binding causes two monomeric receptor subunits to form a dimer, thereby activating the intracellular kinase. Each monomer phosphorylates its counterpart at a tyrosine residue, an action that enables the kinase to phosphorylate other proteins. Like the serine and threonine protein kinases, tyrosine kinases regulate the activity of neuronal proteins they phosphorylate, including the activity of certain ion channels. Tyrosine kinases also activate an isoform of phospholipase C, phospholipase Cγ, which like PLCβ cleaves PIP_2 into IP_3 and DAG.

Receptor tyrosine kinases initiate cascades of reactions involving several adaptor proteins and other protein kinases that often lead to changes in gene transcription. The mitogen-activated protein kinases (MAP kinases) are an important group of serine-threonine kinases that can be activated by a signaling cascade initiated by receptor tyrosine kinase. MAP kinases are activated by cascades of protein-kinase reactions (kinase kinases), each cascade specific to one of three types of MAP kinase: extracellular signal-regulated kinase (ERK), p38 MAP kinase, and *c-Jun* N-terminal kinase (JNK). Activated MAP kinases have several important actions. They translocate to the nucleus where they