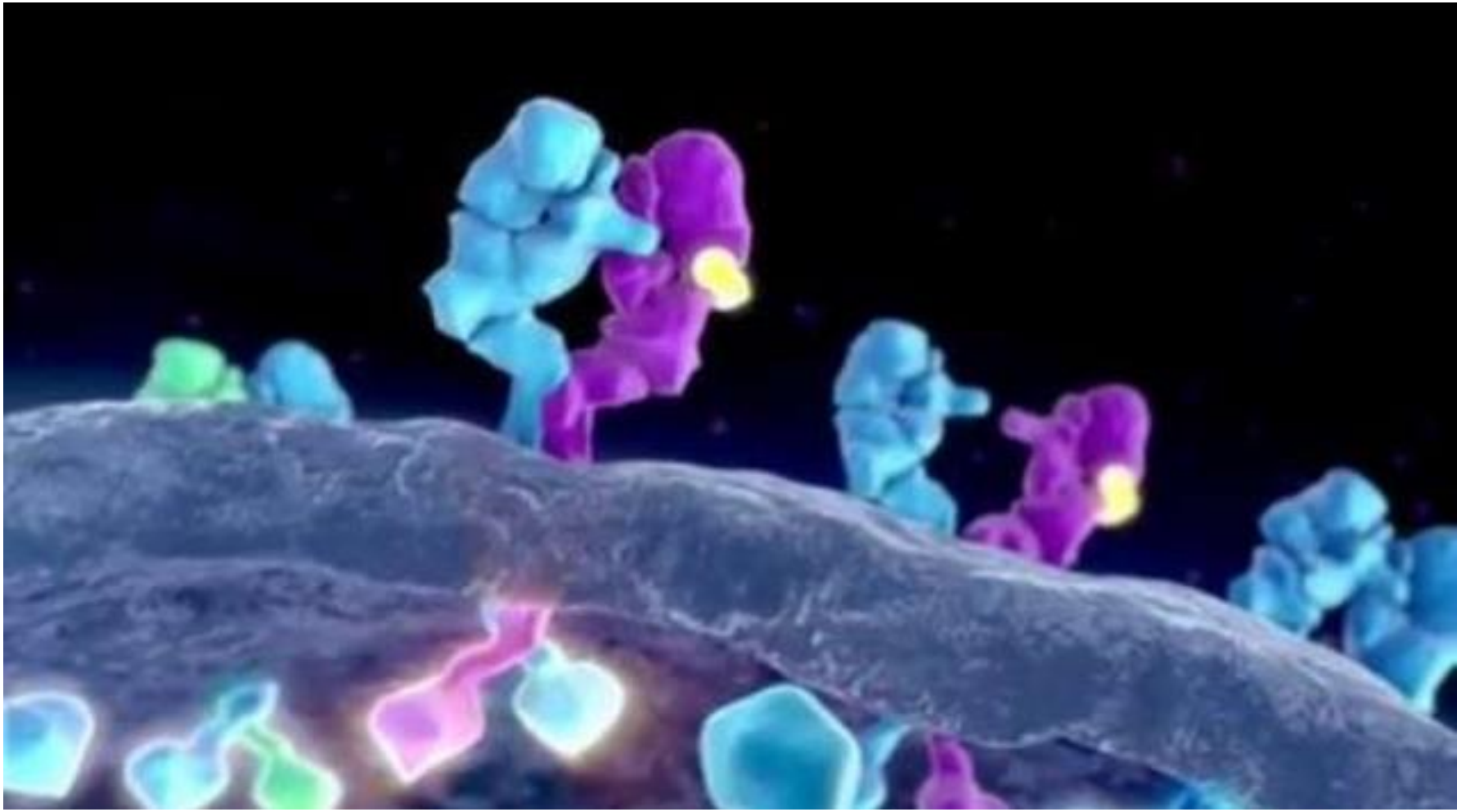
Biosignaling



❖The ability of cells to receive and act on signals from beyond the plasma membrane is fundamental to life.

❖Bacterial cells receive constant input from membrane proteins that act as information receptors, sampling the surrounding medium for pH, osmotic strength, the availability of food, oxygen, and light, and the presence of noxious chemicals, predators, or competitors for food.

❖These signals elicit appropriate responses, such as motion toward food or away from toxic substances or the formation of dormant spores in a nutrient-depleted medium.

❖In multicellular organisms, cells with different functions exchange a wide variety of signals.

❖Plant cells respond to growth hormones and to variations in sunlight.

❖Animal cells exchange information about the concentrations of ions and glucose in extracellular fluids, the interdependent metabolic activities taking place in different tissues, and, in an embryo, the correct placement of cells during development.

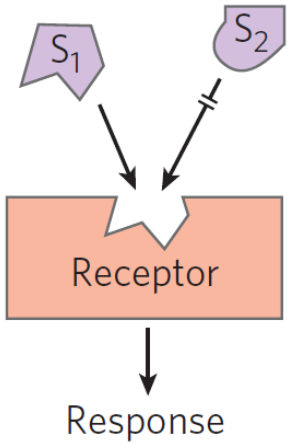
❖In all these cases, the signal represents information that is detected by specific receptors and converted to a cellular response, which always involves a chemical process.

❖This conversion of information into a chemical change, signal transduction, is a universal property of living cells.

❖Signal transductions are remarkably specific and exquisitely sensitive.

❖**Specificity** is achieved by precise molecular complementarity between the signal and receptor molecules, mediated by the same kinds of weak (noncovalent) forces that mediate enzyme-substrate and antigen-antibody interactions.

(a) Specificity
Signal molecule fits binding site on its complementary receptor; other signals do not fit.



❖Multicellular organisms have an additional level of specificity, because the receptors for a given signal, or the intracellular targets of a given signal pathway, are present only in certain cell types.

❖Thyrotropin-releasing hormone, for example, triggers responses in the cells of the anterior pituitary but not in hepatocytes, which lack receptors for this hormone.

❖Epinephrine alters glycogen metabolism in hepatocytes but not in adipocytes; in this case, both cell types have receptors for the hormone, but whereas hepatocytes contain glycogen and the glycogen-metabolizing enzyme that is stimulated by epinephrine, adipocytes contain neither.

❖Adipocytes respond to epinephrine by releasing fatty acids from triacylglycerols and exporting them to other tissues.

❖Three factors account for the extraordinary sensitivity of signal transduction:

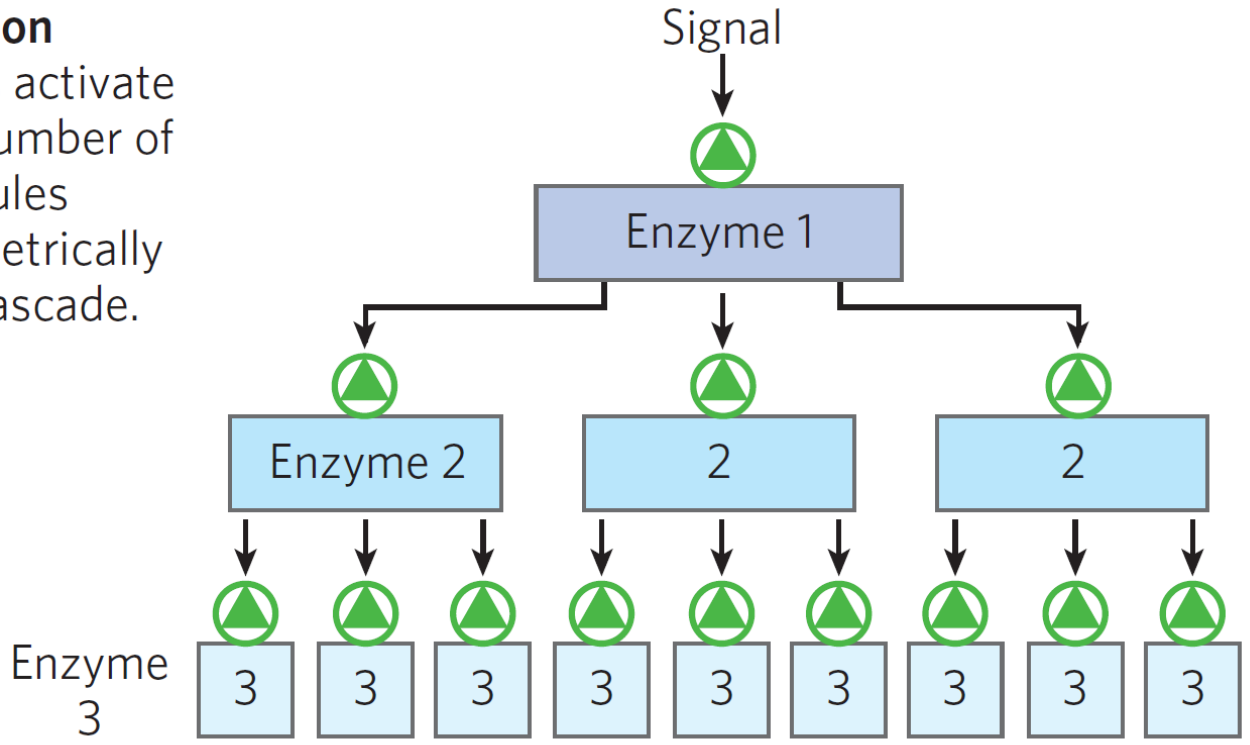
- the high affinity of receptors for signal molecules,
- cooperativity (often but not always) in the ligand-receptor interaction, and
- amplification of the signal by enzyme cascades.

❖The **affinity** between signal (ligand) and receptor can be expressed as the dissociation constant Kd, commonly 10^{-10} M or less—meaning that the receptor detects picomolar concentrations of a signal molecule.

❖Cooperativity in receptor-ligand interactions results in large changes in receptor activation with small changes in ligand concentration.

❖**Amplification** results when an enzyme associated with a signal receptor is activated and, in turn, catalyzes the activation of many molecules of a second enzyme, each of which activates many molecules of a third enzyme, and so on, in a so-called enzyme cascade.

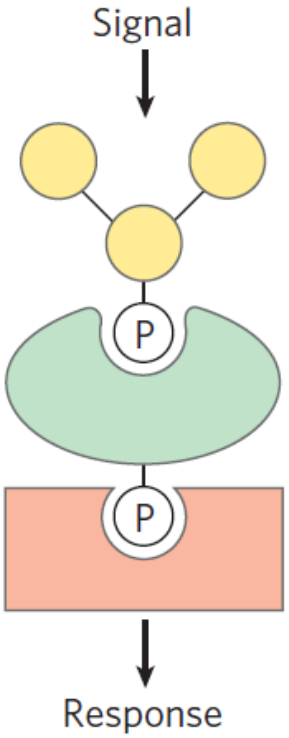
(b) Amplification
When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.



❖**Modularity** of interacting signaling proteins allows a cell to mix and match a set of signaling molecules to create complexes with different functions or cellular locations.

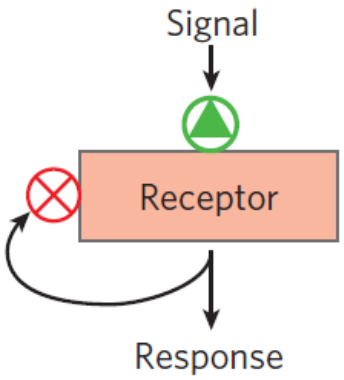
❖The sensitivity of receptor systems is subject to modification.

(c) Modularity
Proteins with multivalent affinities form diverse signaling complexes from interchangeable parts. Phosphorylation provides reversible points of interaction.

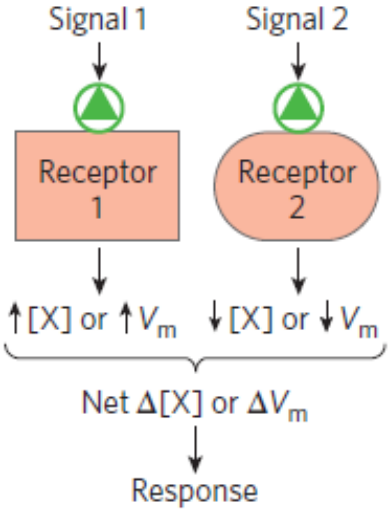


❖When a signal is present continuously, **desensitization** of the receptor system results; when the stimulus falls below a certain threshold, the system again becomes sensitive.

(d) Desensitization/Adaptation
Receptor activation triggers a feedback circuit that shuts off the receptor or removes it from the cell surface.



(e) Integration
When two signals have opposite effects on a metabolic characteristic such as the concentration of a second messenger X, or the membrane potential V_m, the regulatory outcome results from the integrated input from both receptors.



❖A final noteworthy feature of signal-transducing systems is **integration**, the ability of the system to receive multiple signals and produce a unified response appropriate to the needs of the cell or organism.

❖Different signaling pathways converse with each other at several levels, generating complex cross talk that maintains homeostasis in the cell and the organism.

❖Çeşitli sinyal sistemleri incelendiğinde bazı ortak özelliklere sahip oldukları görülebilir; bir sinyal reseptör ile etkileşime geçer, aktif hale geçen reseptör hücresel mekanizmaları başlatır ve bir ikincil haberci veya hücresel protein aktivistiesinde değişiklik meydana getirir, hücrenin metabolik aktivitesi değişir ve sinyal iletimi sona erer.

❖To illustrate these general features of signaling systems, we will look at examples of six basic receptor types:

❖1. G protein–coupled receptors that indirectly activate (through GTP-binding proteins, or G proteins) enzymes that generate intracellular second messengers. This type of receptor is illustrated by the β-adrenergic receptor system that detects epinephrine (adrenaline).

❖2. Receptor tyrosine kinases, plasma membrane receptors that are also enzymes. When one of these receptors is activated by its extracellular ligand, it catalyzes the phosphorylation of several cytosolic or plasma membrane proteins. The insulin receptor is one example; the receptor for epidermal growth factor (EGFR) is another.

❖3. Receptor guanylyl cyclases, which are also plasma membrane receptors with an enzymatic cytoplasmic domain.

❖The intracellular second messenger for these receptors, cyclic guanosine monophosphate (cGMP), activates a cytosolic protein kinase that phosphorylates cellular proteins and thereby changes their activities.

❖4. Gated ion channels of the plasma membrane that open and close (hence the term “gated”) in response to the binding of chemical ligands or changes in transmembrane potential.

❖These are the simplest signal transducers. The acetylcholine receptor ion channel is an example of this mechanism.

❖5. Adhesion receptors that interact with macromolecular components of the extracellular matrix (such as collagen) and convey instructions to the cytoskeletal system about cell migration or adherence to the matrix.

❖Integrins illustrate this general type of transduction mechanism.

❖6. Nuclear receptors that bind specific ligands (such as the hormone estrogen) and alter the rate at which specific genes are transcribed and translated into cellular proteins.

❖Steroid hormones function through mechanisms intimately related to the regulation of gene expression.

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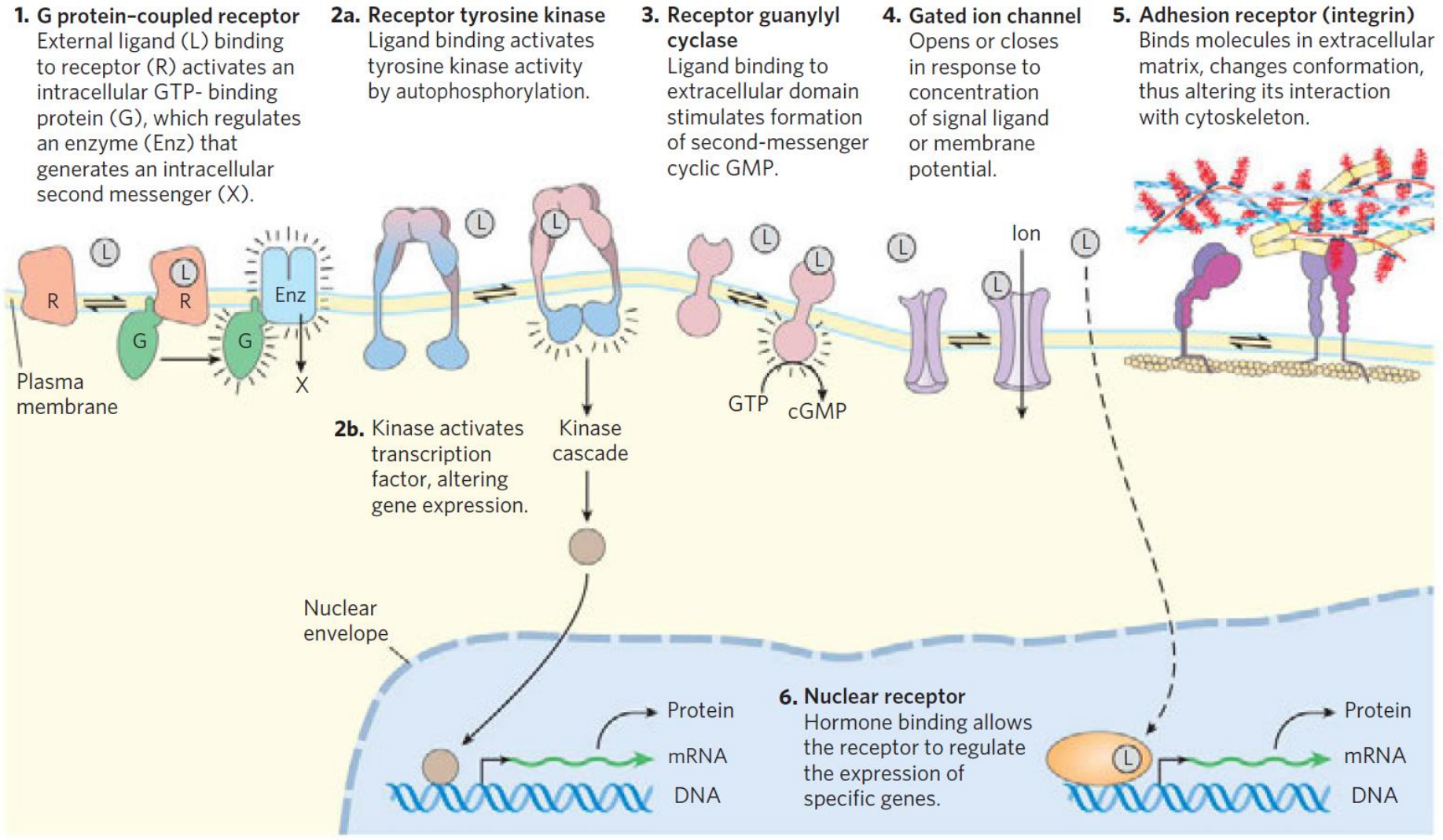


❖G Protein–Coupled Receptors and Second Messengers

❖As their name implies, G protein–coupled receptors (GPCRs) are receptors that are closely associated with a member of the guanosine nucleotide–binding protein (G protein) family.

❖Three essential components define signal transduction through GPCRs: a plasma membrane receptor with seven transmembrane helical segments, a G protein that cycles between active (GTPbound) and inactive (GDP-bound) forms, and an effector enzyme (or ion channel) in the plasma membrane that is regulated by the activated G protein.

❖The G protein, stimulated by the activated receptor, exchanges bound GDP for GTP, then dissociates from the occupied receptor and binds to the nearby effector enzyme, altering its activity. The activated enzyme then generates a second messenger that affects downstream targets.

❖The human genome encodes about 350 GPCRs for detecting hormones, growth factors, and other endogenous ligands, and perhaps 500 that serve as olfactory (smell) and gustatory (taste) receptors.

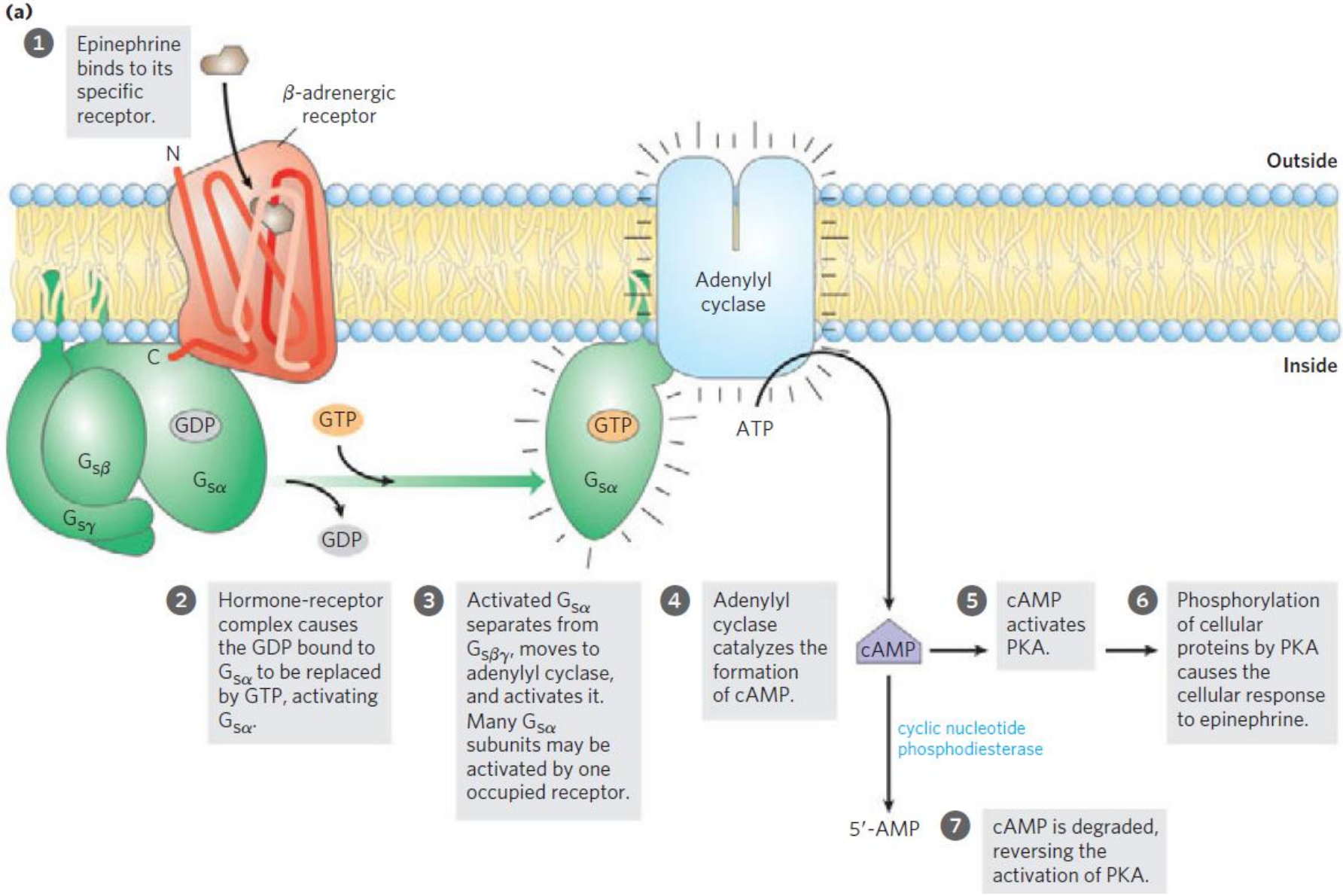

(a)
1 Epinephrine binds to its specific receptor.
β-adrenergic receptor
N
C
Outside
Inside
Adenylyl cyclase
GDP
GTP
Gsβ
Gsα
Gsγ
GTP
Gsα
GDP
ATP
2 Hormone-receptor complex causes the GDP bound to Gsα to be replaced by GTP, activating Gsα.
3 Activated Gsα separates from Gsβγ, moves to adenylyl cyclase, and activates it. Many Gsα subunits may be activated by one occupied receptor.
4 Adenylyl cyclase catalyzes the formation of cAMP.
cAMP
5 cAMP activates PKA.
6 Phosphorylation of cellular proteins by PKA causes the cellular response to epinephrine.
cyclic nucleotide phosphodiesterase
5′-AMP
7 cAMP is degraded, reversing the activation of PKA.

TABLE 12–3 Some Signals That Use cAMP as Second Messenger

Corticotropin (ACTH)
Corticotropin-releasing hormone (CRH)
Dopamine [D_1, D_2]
Epinephrine (β-adrenergic)
Follicle-stimulating hormone (FSH)
Glucagon
Histamine [H_2]
Luteinizing hormone (LH)
Melanocyte-stimulating hormone (MSH)
Odorants (many)
Parathyroid hormone
Prostaglandins E_1, E_2 (PGE_1, PGE_2)
Serotonin [5-HT-1a, 5-HT-2]
Somatostatin
Tastants (sweet, bitter)
Thyroid-stimulating hormone (TSH)

❖A second broad class of GPCRs are coupled through a G protein to a plasma membrane phospholipase C (PLC) that is specific for the membrane phospholipids phosphatidylinositol 4,5-bisphosphate, or PIP2.

❖When one of the hormones that acts by this mechanism binds its specific receptor in the plasma membrane, the receptor-hormone complex catalyzes GTP-GDP exchange on an associated G protein, Gq, activating it in much the same way that the β-adrenergic receptor activates Gs.

❖The activated Gq activates the PIP2-specific PLC, which catalyzes the production of two potent second messengers, diacylglycerol and inositol 1,4,5-trisphosphate, or IP3.

TABLE 12–4 Some Signals That Act through Phospholipase C, IP_3, and Ca^{2+}

Acetylcholine [muscarinic M_1]	Gastrin-releasing peptide	Platelet-derived growth factor (PDGF)
α_1-Adrenergic agonists	Glutamate	Serotonin [5-HT-1c]
Angiogenin	Gonadotropin-releasing hormone (GRH)	Thyrotropin-releasing hormone (TRH)
Angiotensin II	Histamine [H_1]	Vasopressin
ATP [P_{2x}, P_{2y}]	Light (*Drosophila*)	
Auxin	Oxytocin	

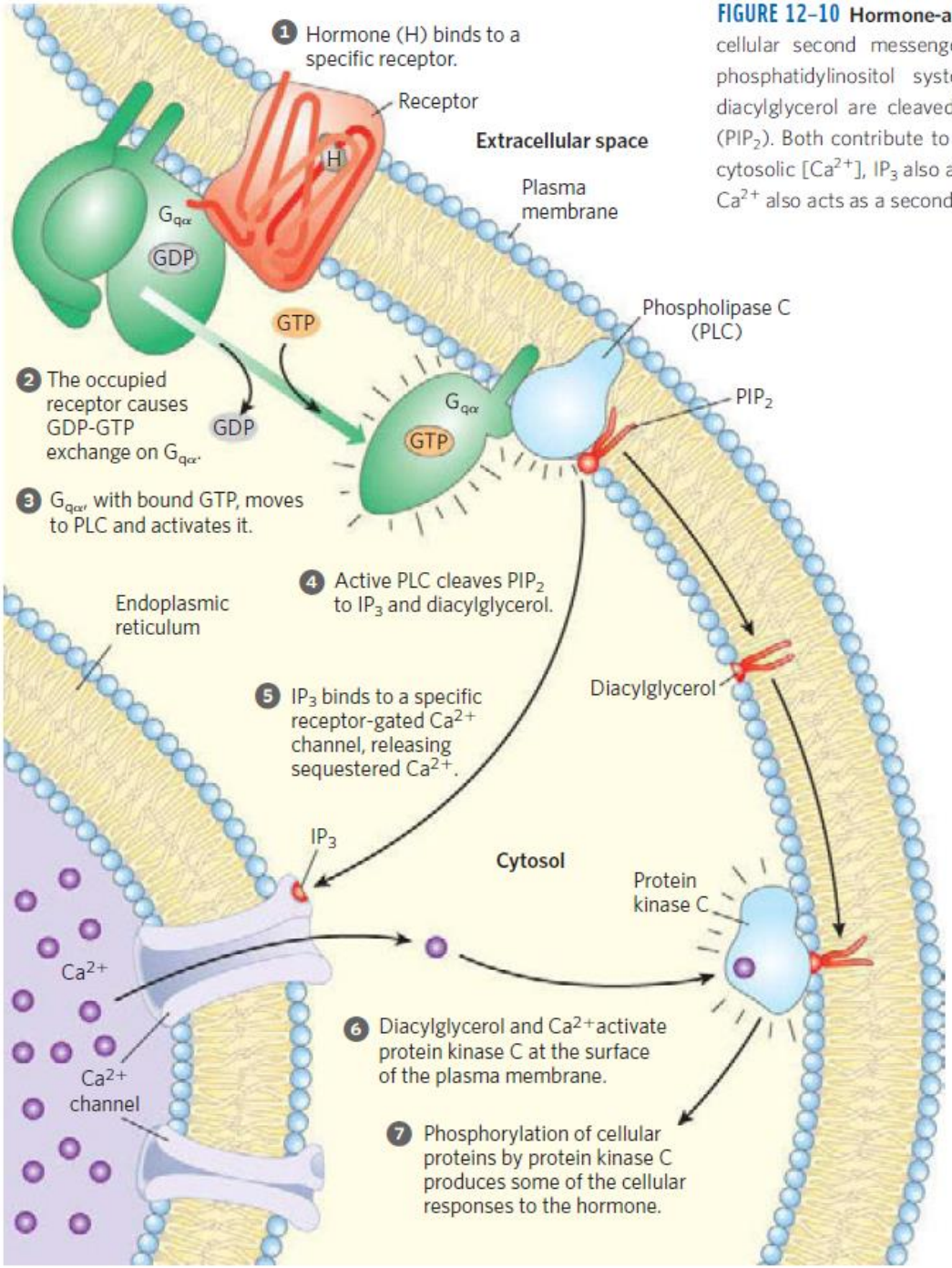


FIGURE 12–10 Hormone-activated phospholipase C and IP_3. Two intracellular second messengers are produced in the hormone-sensitive phosphatidylinositol system: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol are cleaved from phosphatidylinositol 4,5-bisphosphate (PIP_2). Both contribute to the activation of protein kinase C. By raising cytosolic [Ca^{2+}], IP_3 also activates other Ca^{2+}-dependent enzymes; thus Ca^{2+} also acts as a second messenger.

❖Receptor Tyrosine Kinases

❖The receptor tyrosine kinases (RTKs), a large family of plasma membrane receptors with intrinsic protein kinase activity, transduce extracellular signals by a mechanism fundamentally different from that of GPCRs.

❖RTKs have a ligand-binding domain on the extracellular face of the plasma membrane and an enzyme active site on the cytoplasmic face, connected by a single transmembrane segment.

❖The cytoplasmic domain is a protein kinase that phosphorylates Tyr residues in specific target proteins—a Tyr kinase.

❖The receptors for insulin and epidermal growth factor are prototypes for this group.

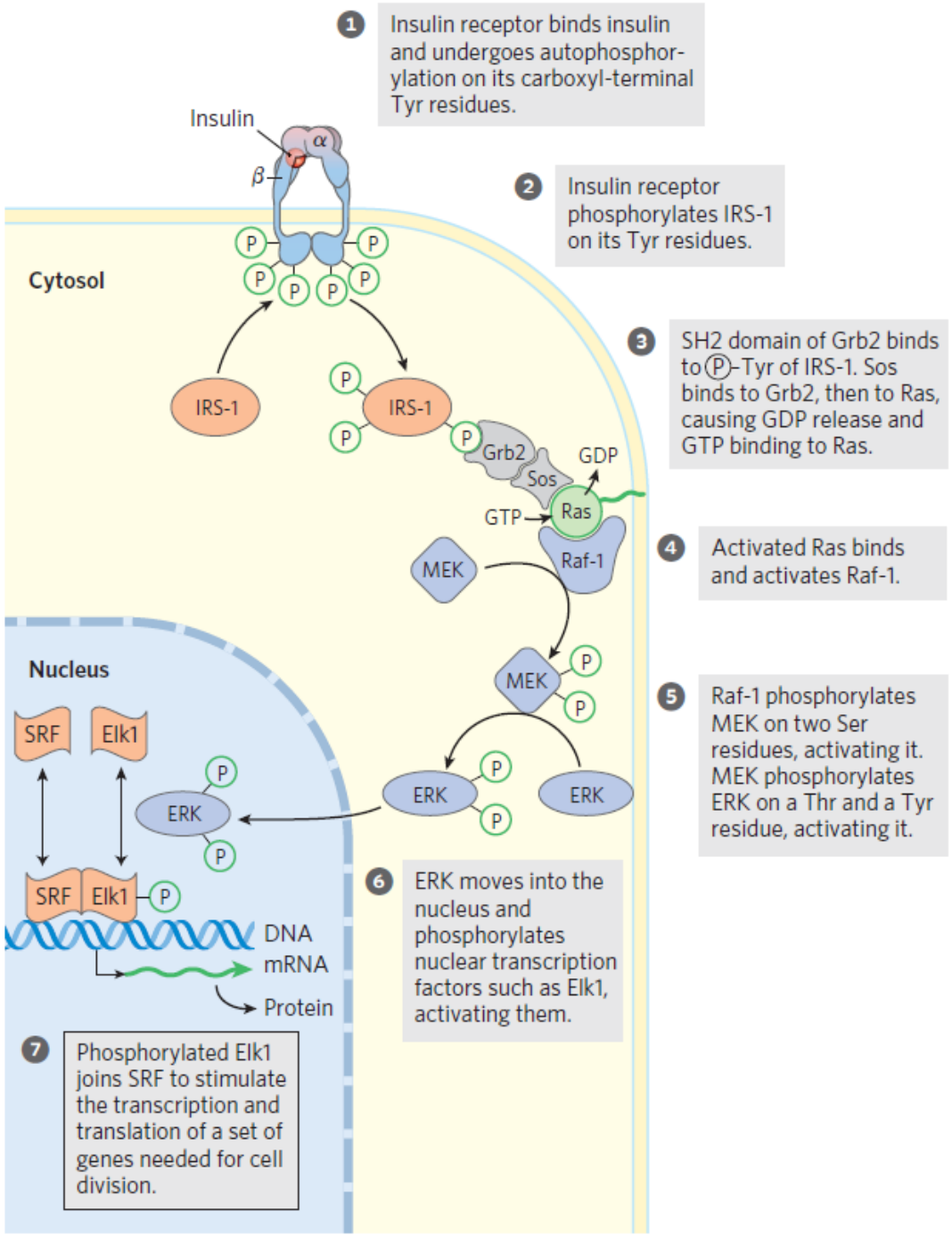


FIGURE 12–15 Regulation of gene expression by insulin through a MAP kinase cascade. The insulin receptor (INSR) consists of two α subunits on the outer face of the plasma membrane and two β subunits that traverse the membrane and protrude from the cytosolic face. Binding of insulin to the α subunits triggers a conformational change that allows the autophosphorylation of Tyr residues in the carboxyl-terminal domain of the β subunits. Autophosphorylation further activates the Tyr kinase domain, which then catalyzes phosphorylation of other target proteins. The signaling pathway by which insulin regulates the expression of specific genes consists of a cascade of protein kinases, each of which activates the next. INSR is a Tyr-specific kinase; the other kinases (all shown in blue) phosphorylate Ser or Thr residues. MEK is a dual-specificity kinase, which phosphorylates both a Thr and a Tyr residue in ERK (*extracellular regulated kinase*); MEK is mitogen-activated, ERK-activating kinase; SRF is serum response factor.

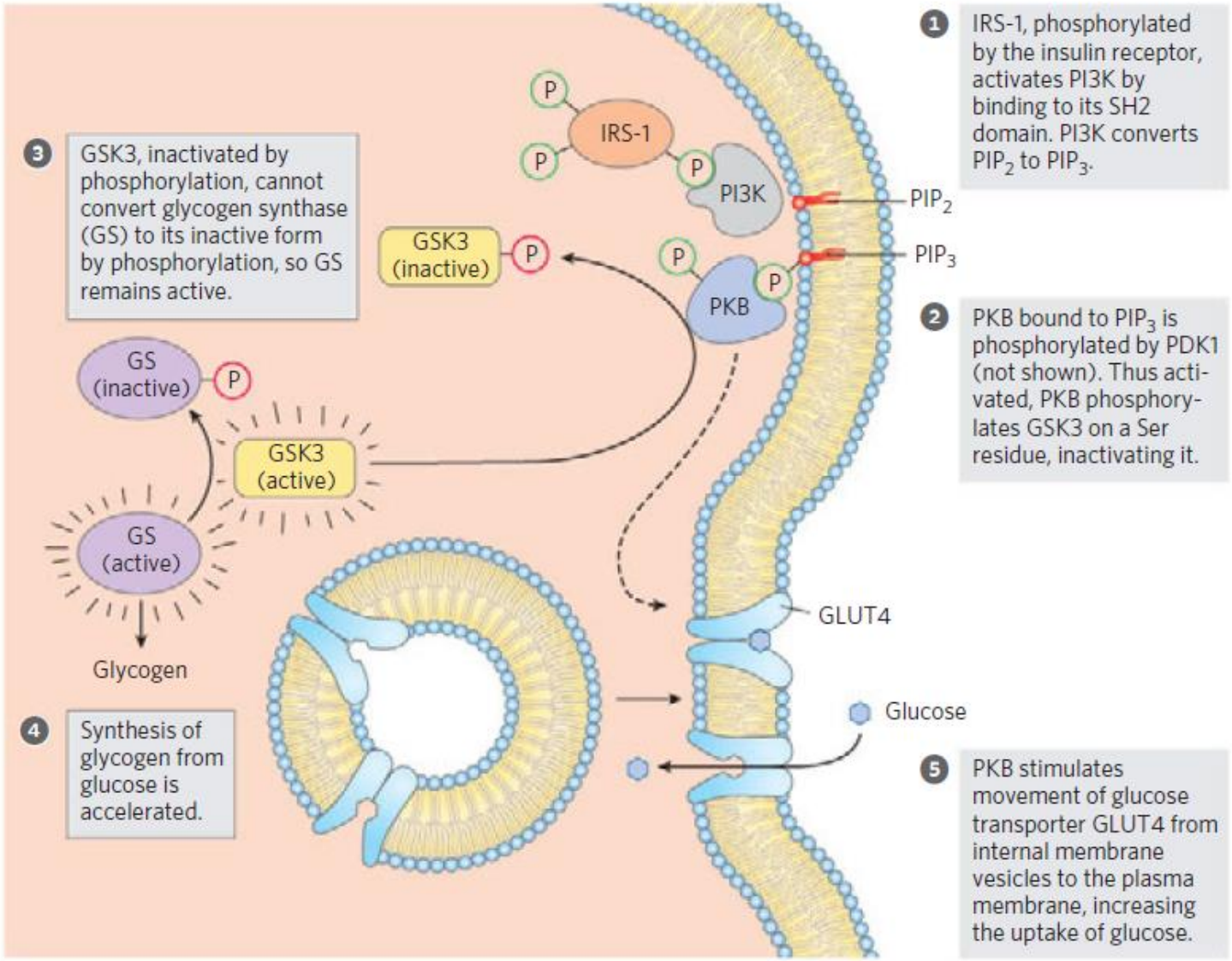


FIGURE 12–16 Insulin action on glycogen synthesis and GLUT4 movement to the plasma membrane. The activation of PI3 kinase (PI3K) by phosphorylated IRS-1 signals (through protein kinase B, PKB) movement of the glucose transporter GLUT4 to the plasma membrane, and the activation of glycogen synthase.

❖Receptor Guanylyl Cyclases, cGMP, and Protein Kinase G

❖Guanylyl cyclases are receptor enzymes that, when activated, convert GTP to the second messenger cyclic GMP (cGMP).

❖Many of the actions of cGMP in animals are mediated by cGMP-dependent protein kinase, also called protein kinase G (PKG).

❖On activation by cGMP, PKG phosphorylates Ser and Thr residues in target proteins.

❖Cyclic GMP carries different messages in different tissues. In the kidney and intestine it triggers changes in ion transport and water retention; in cardiac muscle (a type of smooth muscle) it signals relaxation; in the brain it may be involved both in development and in adult brain function.

❖Guanylyl cyclase in the kidney is activated by the peptide hormone atrial natriuretic factor (ANF), which is released by cells in the cardiac atrium when the heart is stretched by increased blood volume.

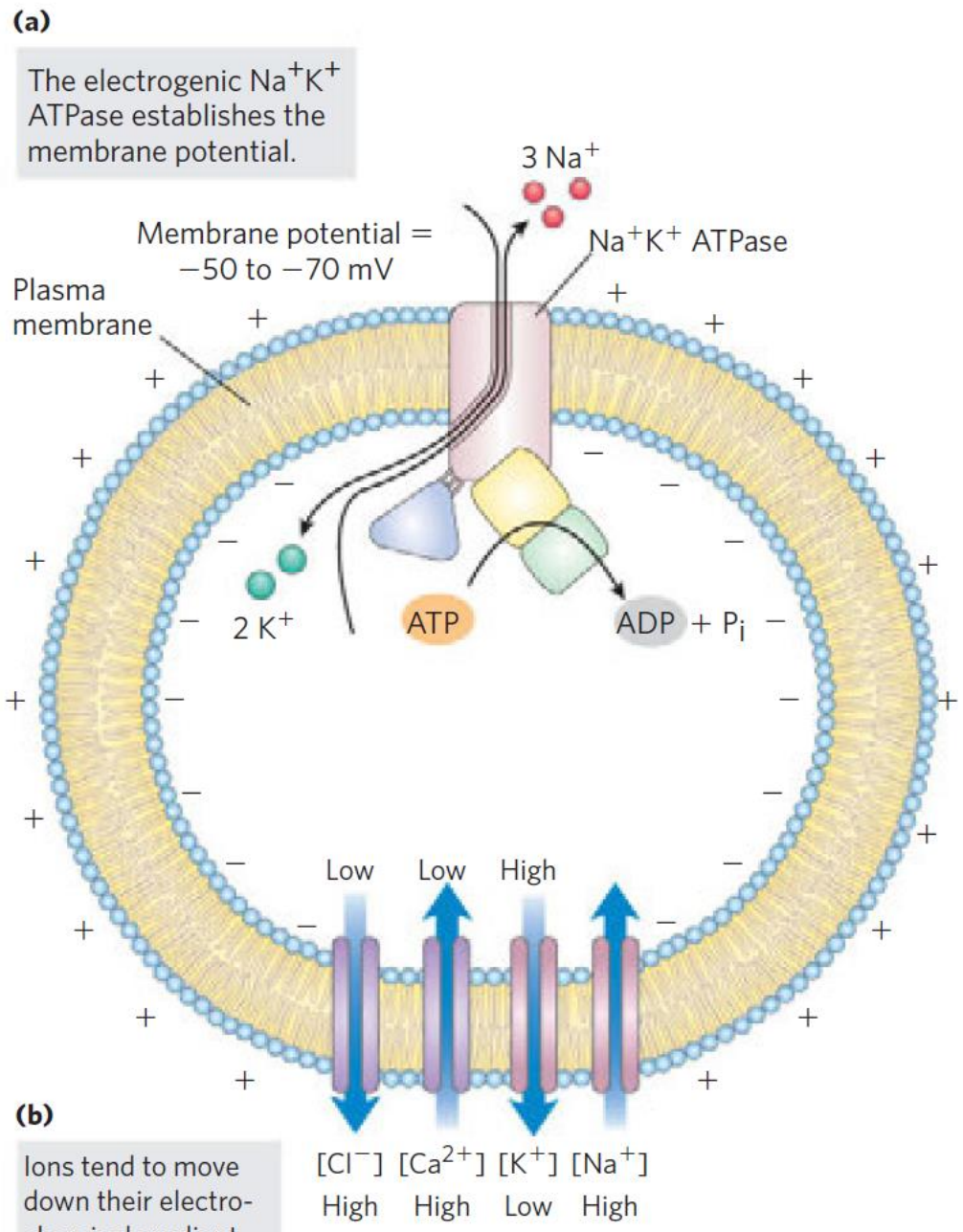
❖Gated Ion Channels

❖Certain cells in multicellular organisms are “excitable”: they can detect an external signal, convert it into an electrical signal (specifically, a change in membrane potential), and pass it on.

❖Excitable cells play central roles in nerve conduction, muscle contraction, hormone secretion, sensory processes, and learning and memory.

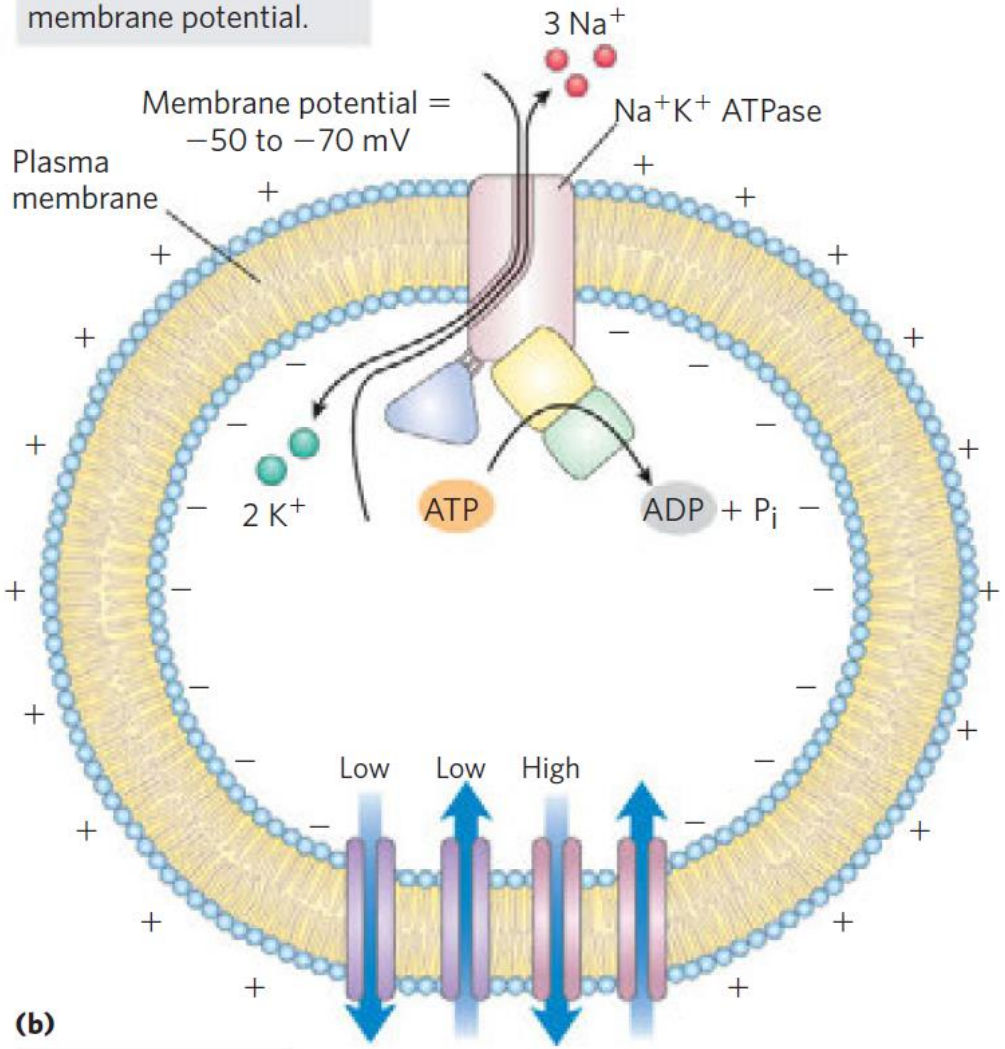
❖The excitability of sensory cells, neurons, and myocytes depends on ion channels, signal transducers that provide a regulated path for the movement of inorganic ions such as Na, K, Ca2, and Cl across the plasma membrane in response to various stimuli.

❖These ion channels are “gated”: they may be open or closed, depending on whether the associated receptor has been activated by the binding of its specific ligand (a neurotransmitter, for example) or by a change in the transmembrane electrical potential.


(a)
The electrogenic Na^+K^+ ATPase establishes the membrane potential.
3 Na^+
Membrane potential = −50 to −70 mV
Na^+K^+ ATPase
Plasma membrane
2 K^+
ATP
ADP + P_i
Low
Low
High
(b)
Ions tend to move down their electro-chemical gradient across the polarized membrane.
[Cl^-] High
[Ca^{2+}] High
[K^+] Low
[Na^+] High

(a)

The electrogenic Na^+K^+ ATPase establishes the membrane potential.



(b)

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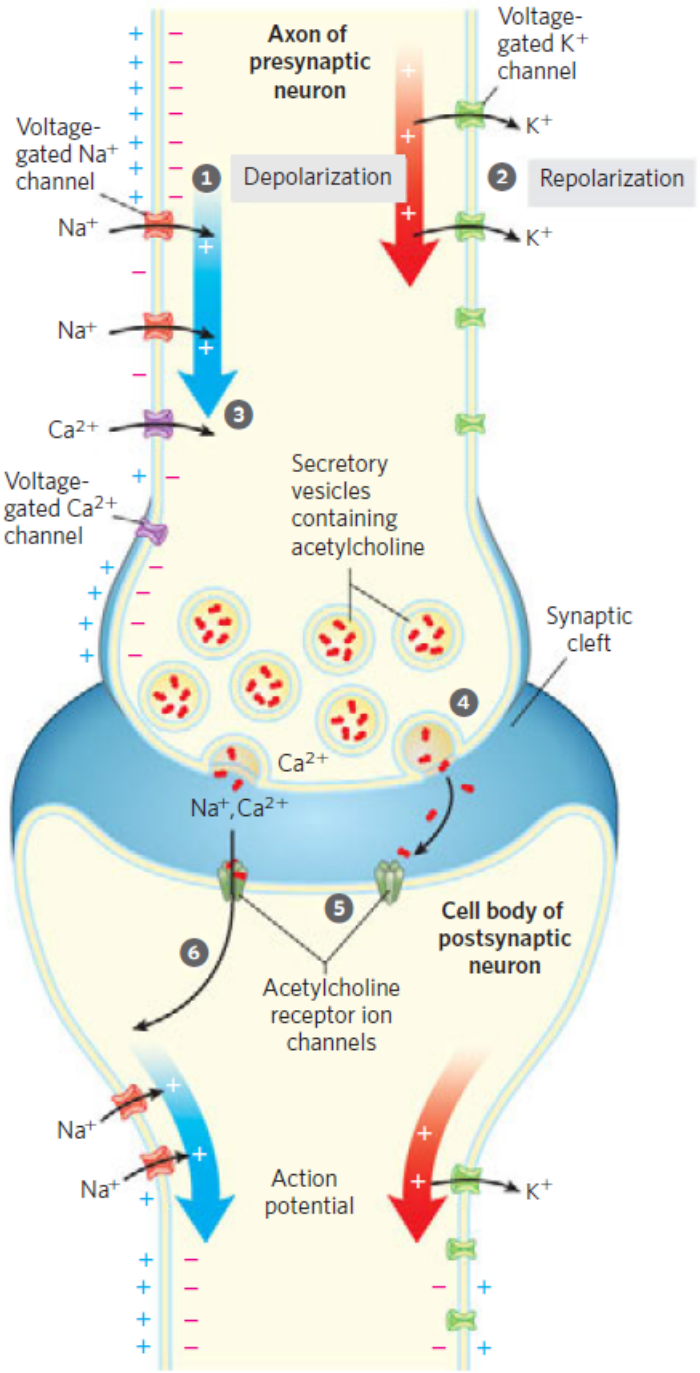
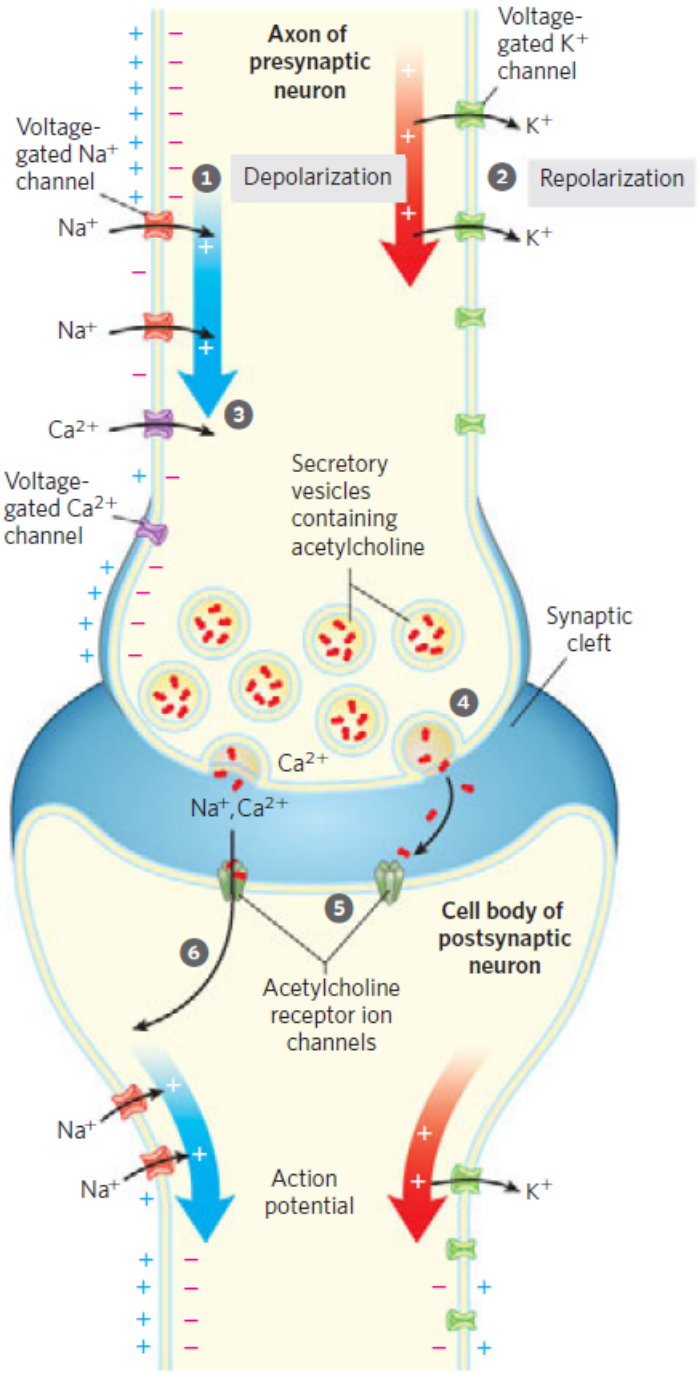


FIGURE 12–26 Role of voltage-gated and ligand-gated ion channels in neural transmission. Initially, the plasma membrane of the presynaptic neuron is polarized (inside negative) through the action of the electrogenic Na^+K^+ ATPase, which pumps out 3 Na^+ for every 2 K^+ pumped in (see Fig. 12–25). ❶ A stimulus to this neuron (not shown) causes an action potential to move along the axon (blue arrow), away from the cell body. The opening of a voltage-gated Na^+ channel allows Na^+ entry, and the resulting local depolarization causes the adjacent Na^+ channel to open, and so on. The directionality of movement of the action potential is ensured by the brief refractory period that follows the opening of each voltage-gated Na^+ channel. ❷ A split second after the action potential passes a point in the axon, voltage-operated K^+ channels open, allowing K^+ exit that brings about repolarization of the membrane (red arrow), to make it ready for the next action potential. (For clarity, Na^+ channels and K^+ channels are drawn on opposite sides of the axon; both types of channels are uniformly distributed in the axonal membrane.) ❸ When the wave of depolarization reaches the axon tip, voltage-gated Ca^{2+} channels open, allowing Ca^{2+} entry. ❹ The resulting increase in internal $[Ca^{2+}]$ triggers exocytic release of the neurotransmitter acetylcholine into the synaptic cleft. ❺ Acetylcholine binds to a receptor on the postsynaptic neuron (or myocyte), causing its ligand-gated ion channel to open. ❻ Extracellular Na^+ and Ca^{2+} enter through this channel, depolarizing the postsynaptic cell. The electrical signal has thus passed to the cell body of the postsynaptic neuron (or myocyte) and will move along its axon to a third neuron (or a myocyte) by this same sequence of events.



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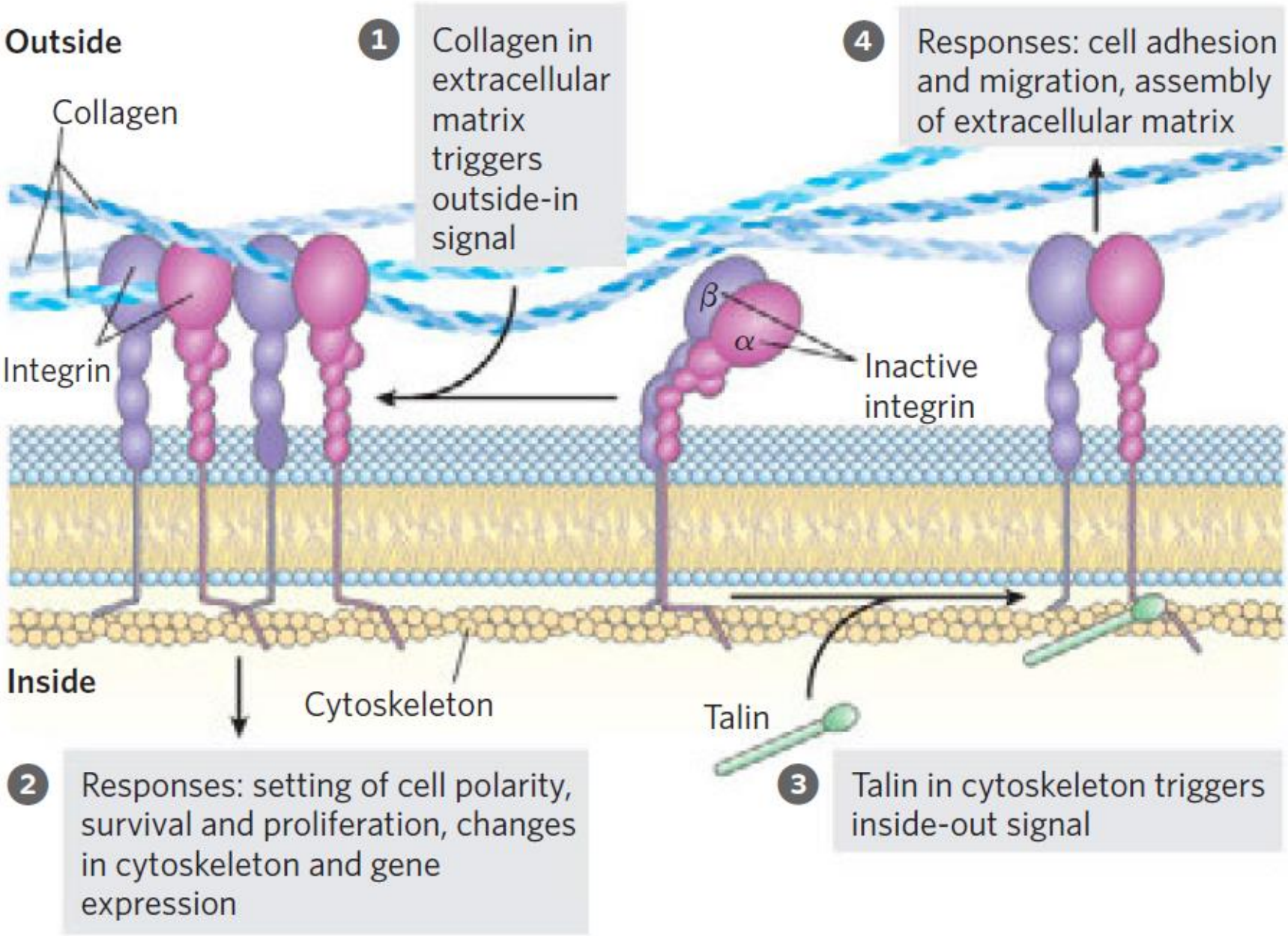
❖Integrins: Bidirectional Cell Adhesion Receptors

❖Integrins are proteins of the plasma membrane that mediate the adhesion of cells to each other and to the extracellular matrix, and carry signals in both directions across the membrane.

❖The mammalian genome encodes 18 different α subunits and 8 different β subunits, which are found in a range of combinations with various ligand-binding specificities in various tissues.

❖Each of the 24 different integrins found thus far seems to have a unique function.

❖Because they can inform cells about the extracellular neighborhood, integrins play crucial roles in processes that require selective cell-cell interactions, such as embryonic development, blood clotting, immune cell function, normal differentiation, and tumor growth and metastasis.


Outside
1 Collagen in extracellular matrix triggers outside-in signal
4 Responses: cell adhesion and migration, assembly of extracellular matrix
Collagen
Integrin
β
α
Inactive integrin
Inside
Cytoskeleton
Talin
2 Responses: setting of cell polarity, survival and proliferation, changes in cytoskeleton and gene expression
3 Talin in cytoskeleton triggers inside-out signal

❖**Regulation of Transcription by Nuclear Hormone Receptors**

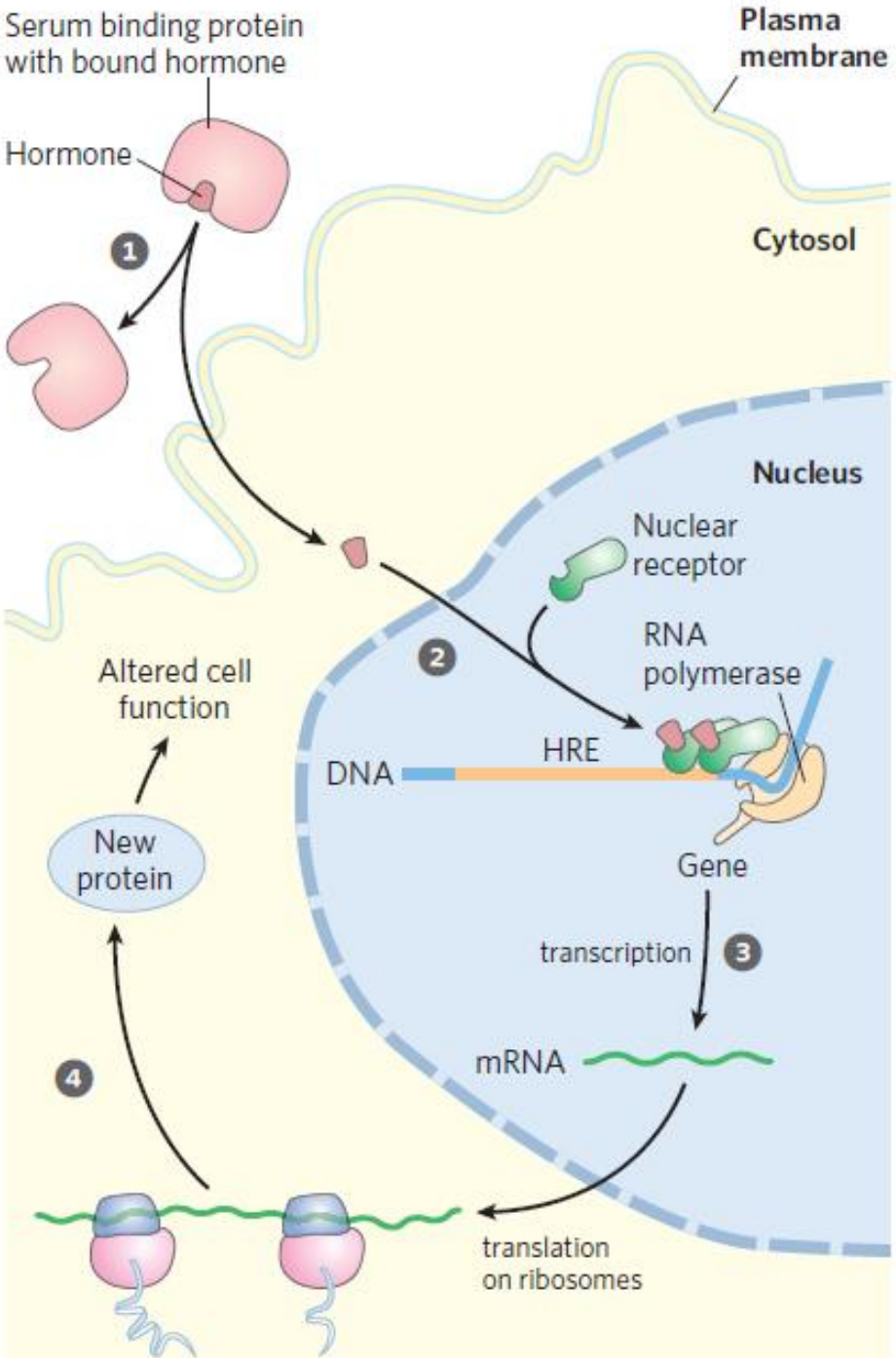
❖The steroid, retinoic acid (retinoid), and thyroid hormones form a large group of hormones (receptor ligands) that exert at least part of their effects by a mechanism fundamentally different from that of other hormones: they act in the nucleus to alter gene expression.

❖Steroid hormones (estrogen, progesterone, and cortisol, for example), too hydrophobic to dissolve readily in the blood, are transported on specific carrier proteins from their point of release to their target tissues.

❖In target cells, these hormones pass through the plasma membrane by simple diffusion and bind to specific receptor proteins in the nucleus.

❖Steroid hormone receptors with no bound ligand (aporeceptors) often act to suppress the transcription of target genes.

❖Hormone binding triggers changes in the conformation of a receptor protein so that it becomes capable of interacting with specific regulatory sequences in DNA called hormone response elements (HREs), thus altering gene expression.



1. Hormone, carried to the target tissue on serum binding proteins, diffuses across the plasma membrane and binds to its specific receptor protein in the nucleus.

2. Hormone binding changes the conformation of the receptor; it forms homo- or hetero-dimers with other hormone-receptor complexes and binds to specific regulatory regions called hormone response elements (HREs) in the DNA adjacent to specific genes.

3. Receptor attracts coactivator or corepressor protein(s) and, with them, regulates transcription of the adjacent gene(s), increasing or decreasing the rate of mRNA formation.

4. Altered levels of the hormone-regulated gene product produce the cellular response to the hormone.

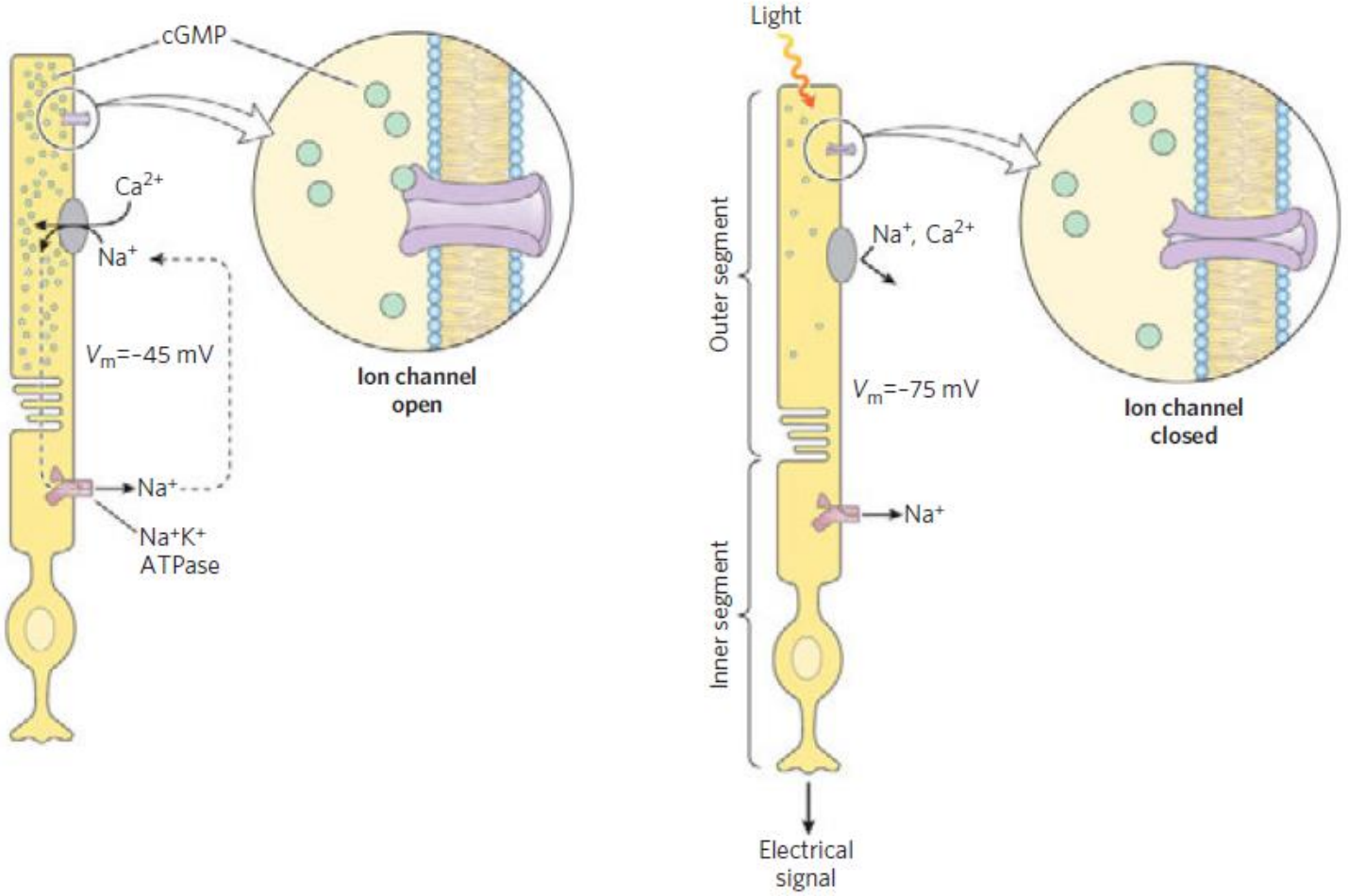
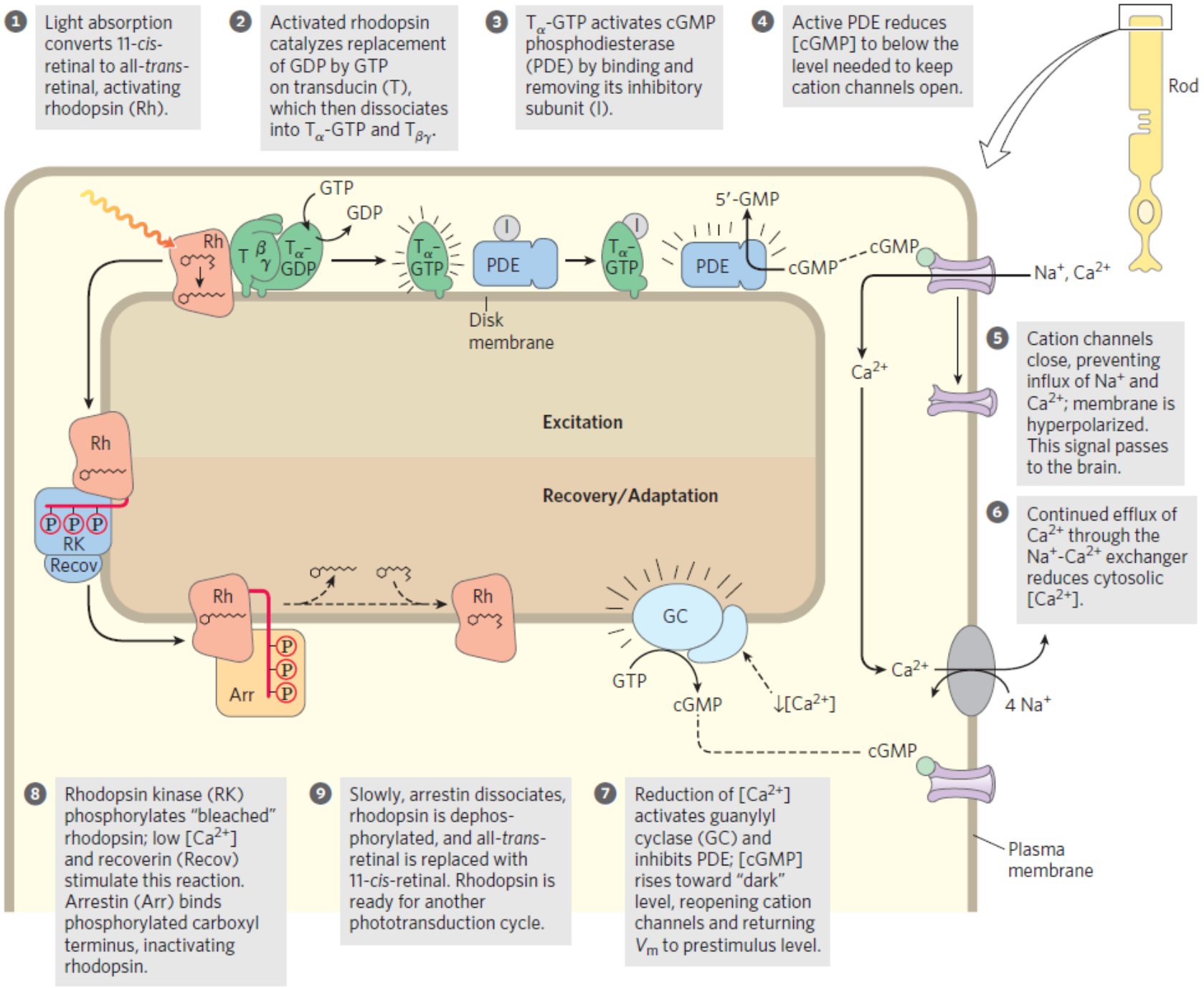
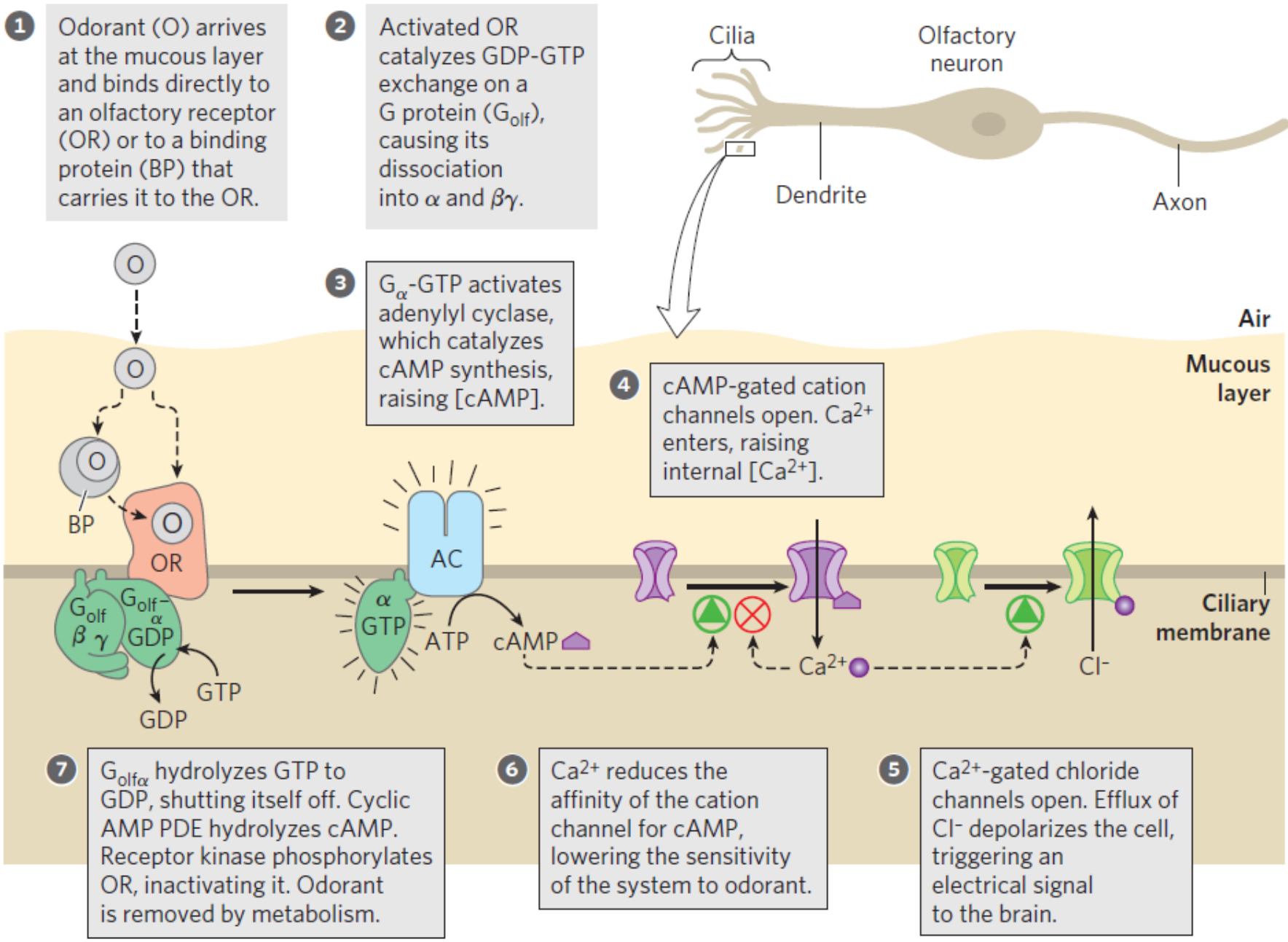


FIGURE 12–37 Light-induced hyperpolarization of rod cells. The rod cell consists of an outer segment, filled with stacks of membranous disks (not shown) containing the photoreceptor rhodopsin, and an inner segment that contains the nucleus and other organelles (not shown). The inner segment forms a synapse with interconnecting neurons (Fig. 12–36). Cones have a similar structure. ATP in the inner segment powers the Na^+K^+ ATPase, which creates a transmembrane electrical potential by pumping 3 Na^+ out for every 2 K^+ pumped in. The membrane potential is reduced by the inflow of Na^+ and Ca^{2+} through cGMP-gated cation channels in the outer-segment plasma membrane. When rhodopsin absorbs light, it triggers degradation of cGMP (green dots) in the outer segment, causing closure of the ion channel. Without cation influx through this channel, the cell becomes hyperpolarized. This electrical signal is passed to the brain through the ranks of neurons shown in Figure 12–36.


1 Light absorption converts 11-cis-retinal to all-trans-retinal, activating rhodopsin (Rh).
2 Activated rhodopsin catalyzes replacement of GDP by GTP on transducin (T), which then dissociates into T_α-GTP and $T_{\beta\gamma}$.
3 T_α-GTP activates cGMP phosphodiesterase (PDE) by binding and removing its inhibitory subunit (I).
4 Active PDE reduces [cGMP] to below the level needed to keep cation channels open.
Rod
Rh
GTP
GDP
T
T_α-GDP
T_α-GTP
I
PDE
5′-GMP
cGMP
Na+, Ca2+
Disk membrane
Excitation
Recovery/Adaptation
Ca2+
5 Cation channels close, preventing influx of Na+ and Ca2+; membrane is hyperpolarized. This signal passes to the brain.
6 Continued efflux of Ca2+ through the Na+-Ca2+ exchanger reduces cytosolic [Ca2+].
RK
Recov
Arr
GC
4 Na+
↓[Ca2+]
Plasma membrane
8 Rhodopsin kinase (RK) phosphorylates "bleached" rhodopsin; low [Ca2+] and recoverin (Recov) stimulate this reaction. Arrestin (Arr) binds phosphorylated carboxyl terminus, inactivating rhodopsin.
9 Slowly, arrestin dissociates, rhodopsin is dephosphorylated, and all-trans-retinal is replaced with 11-cis-retinal. Rhodopsin is ready for another phototransduction cycle.
7 Reduction of [Ca2+] activates guanylyl cyclase (GC) and inhibits PDE; [cGMP] rises toward "dark" level, reopening cation channels and returning V_m to prestimulus level.


1 Odorant (O) arrives at the mucous layer and binds directly to an olfactory receptor (OR) or to a binding protein (BP) that carries it to the OR.
2 Activated OR catalyzes GDP-GTP exchange on a G protein (G_{olf}), causing its dissociation into α and $\beta\gamma$.
3 G_{α}-GTP activates adenylyl cyclase, which catalyzes cAMP synthesis, raising [cAMP].
4 cAMP-gated cation channels open. Ca^{2+} enters, raising internal [Ca^{2+}].
5 Ca^{2+}-gated chloride channels open. Efflux of Cl^- depolarizes the cell, triggering an electrical signal to the brain.
6 Ca^{2+} reduces the affinity of the cation channel for cAMP, lowering the sensitivity of the system to odorant.
7 $G_{olf\alpha}$ hydrolyzes GTP to GDP, shutting itself off. Cyclic AMP PDE hydrolyzes cAMP. Receptor kinase phosphorylates OR, inactivating it. Odorant is removed by metabolism.
Cilia
Olfactory neuron
Dendrite
Axon
Air
Mucous layer
Ciliary membrane
O
BP
OR
G_{olf} β γ
G_{olf} α GDP
GTP
GDP
AC
α GTP
ATP
cAMP
Ca^{2+}
Cl^-

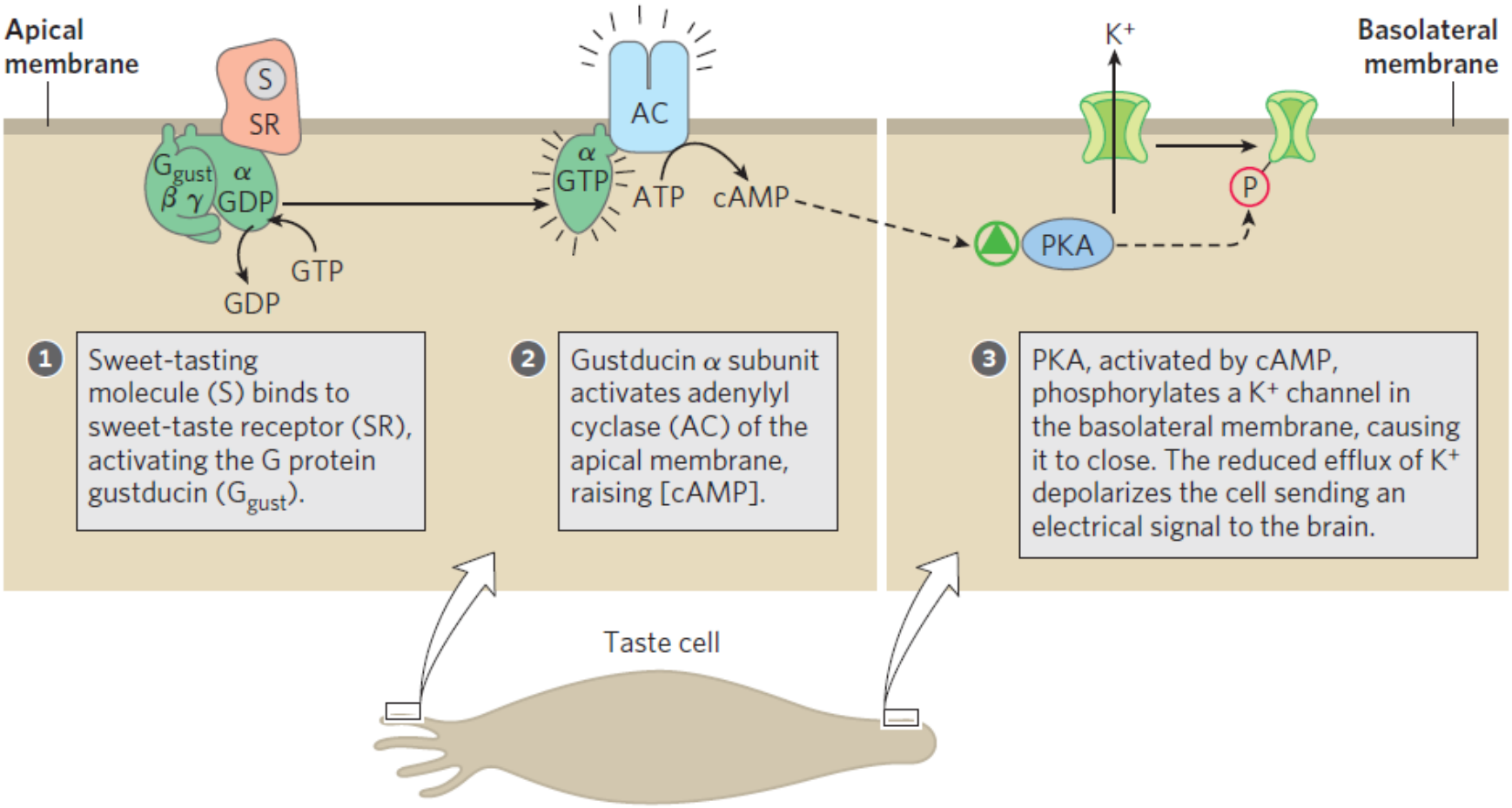


FIGURE 12–42 **Transduction mechanism for sweet tastants.**