Physiology of cells I.

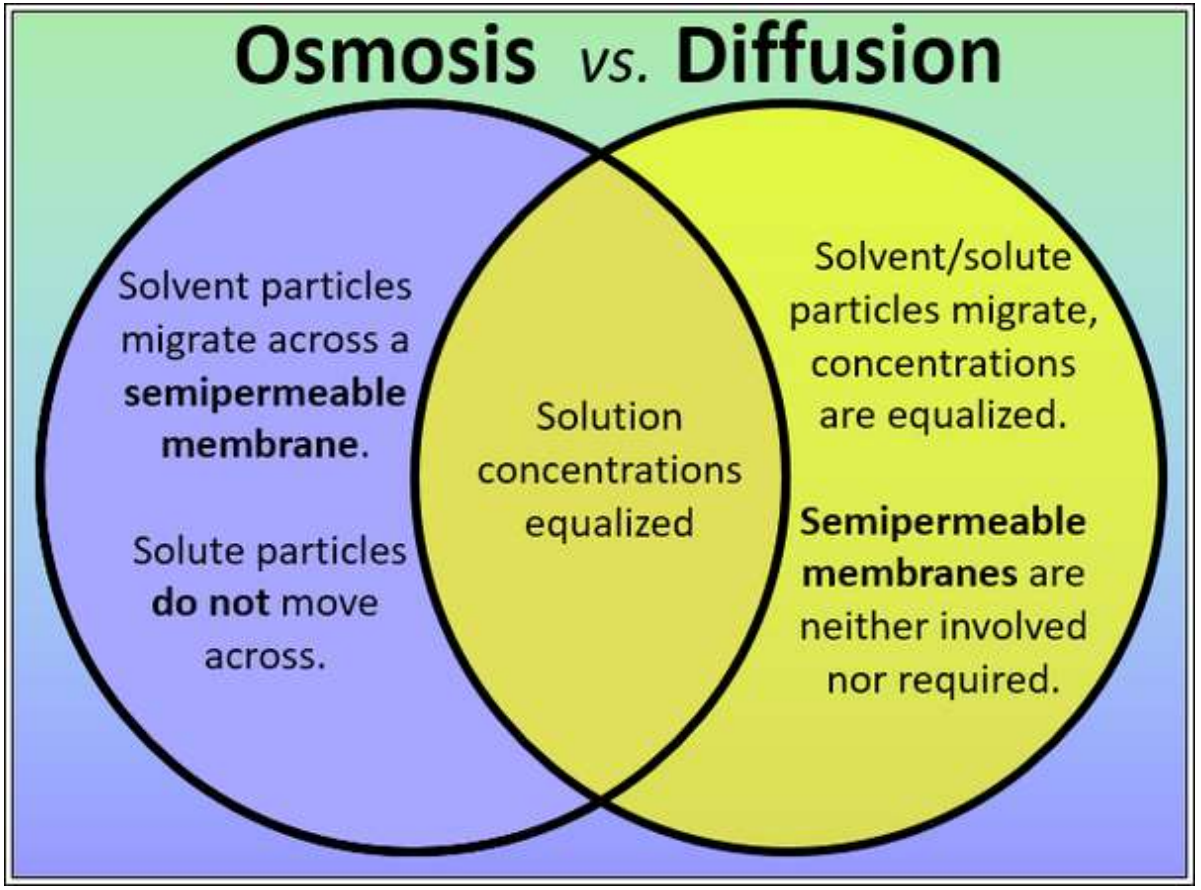
Compendium of physiology

Foundation of physiology

- What is physiology?
- Physiological genomics is the link between the organ and the gene
- Cells live in a highly protected milieu intérieur
- Homeostatic mechanisms — operating through sophisticated feedback control mechanisms — are responsible for maintaining the constancy of the milieu intérieur
  - Homeostasis
  - Negative feedback mechanisms

Structure of cell membranes

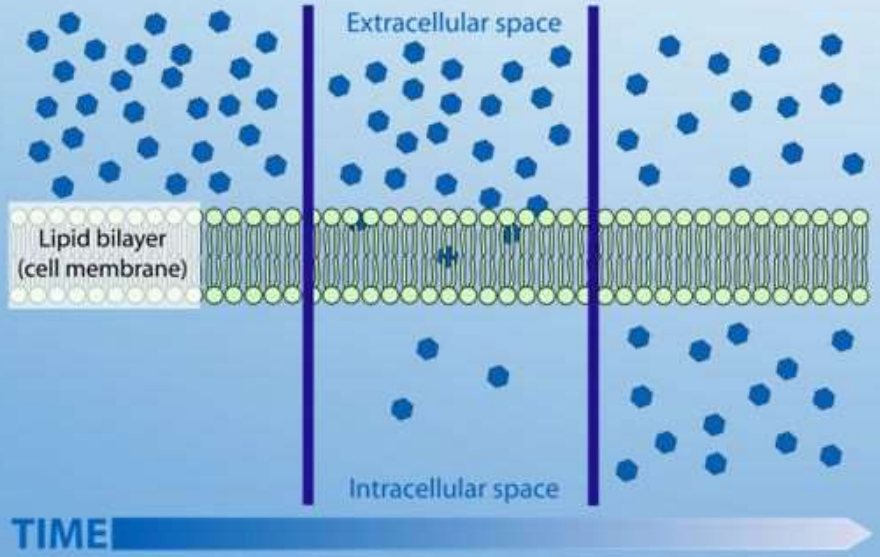
- The surface of the cell is defined by a membrane
  - Impermeable – large molecules
  - Selectively permeable – ions and metabolites
  - Active transport - accumulation against concentration gradient
- The cell membrane is composed primarily of phospholipids



DIFFUSION AND OSMOSIS
(PASSIVE TRANSPORT)

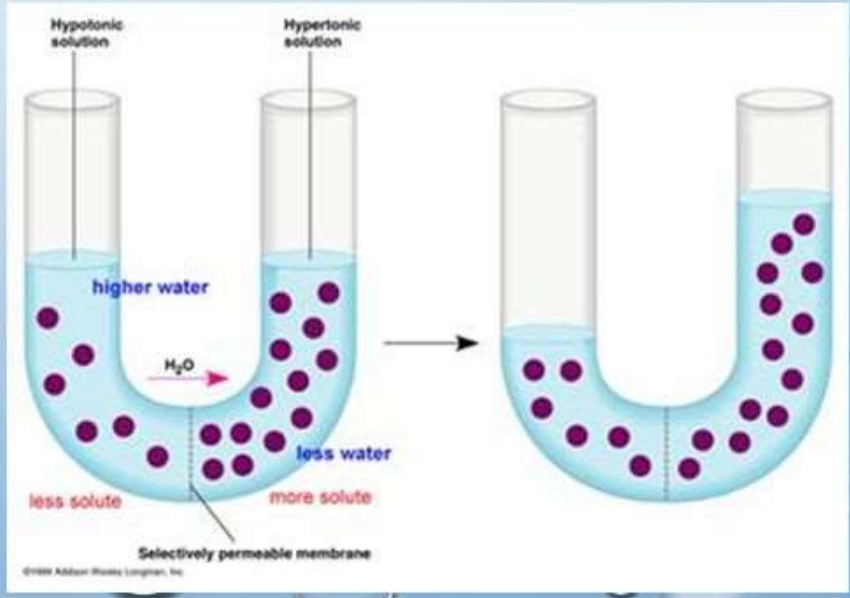
DIFFUSION

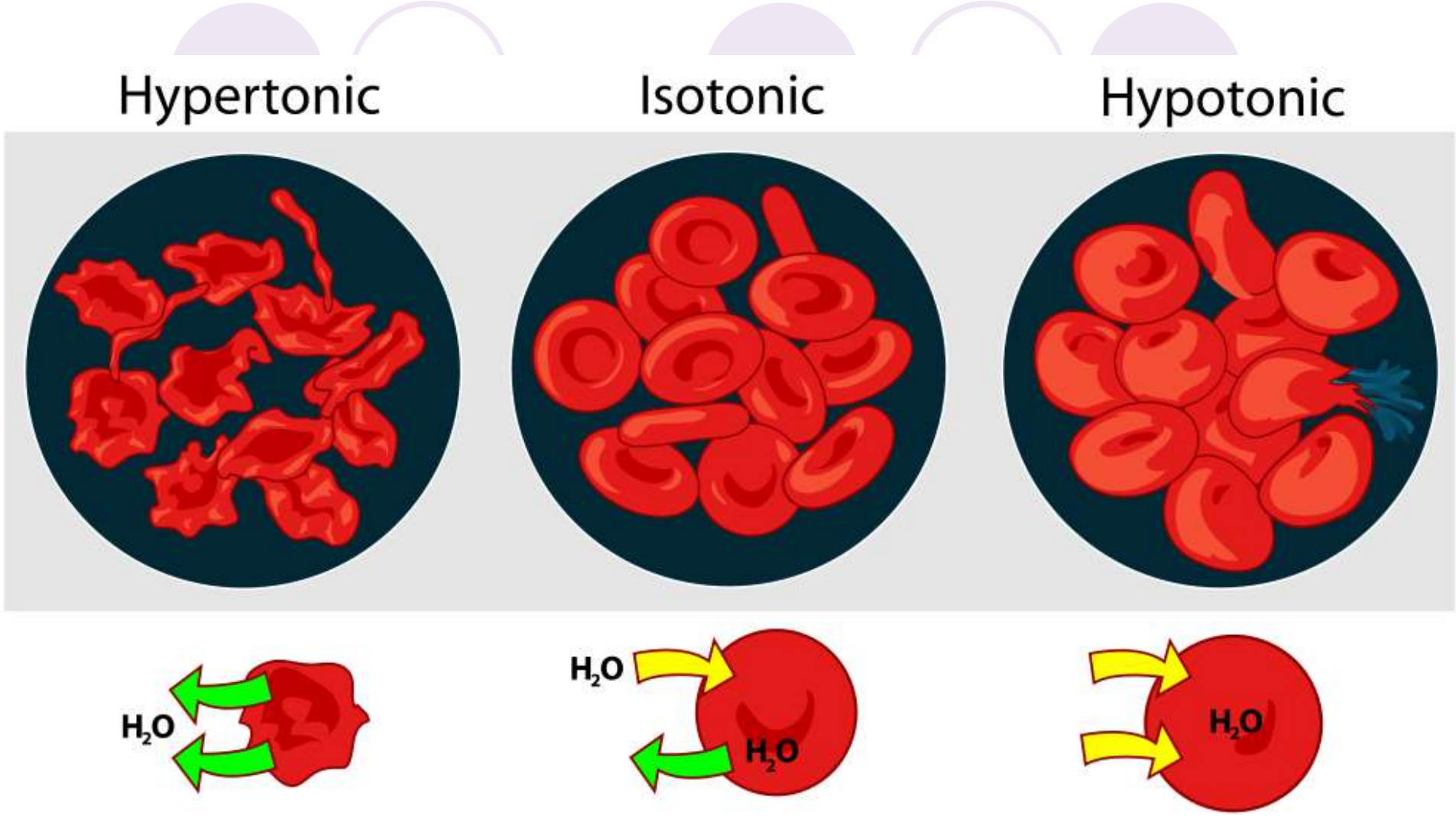
- MOVEMENT OF **MOLECULES** FROM HIGH CONCENTRATION TO LOW CONCENTRATION

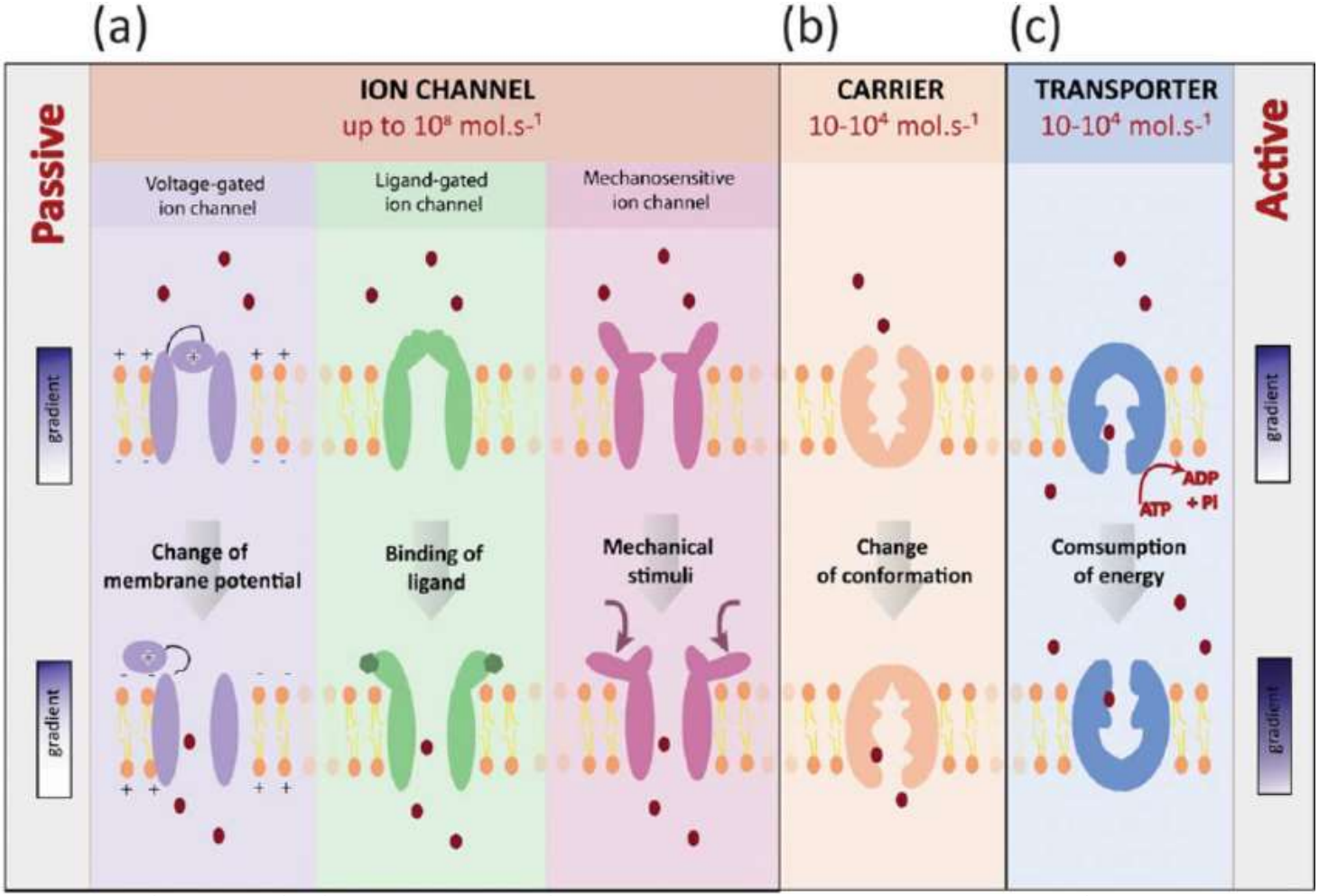


OSMOSIS

- MOVEMENT OF **WATER** THROUGH A SEMIPERMEABLE MEMBRANE FROM AREAS OF HIGHER TO LOWER CONCENTRATION




Hypertonic
Isotonic
Hypotonic
H_2O
H_2O
H_2O
H_2O



Types of membrane proteins mediating translocation across cell membrane : passive transport across ion channels (a) or carriers (b) are driven by a chemical gradient. Ion channels are classified into three groups according to their mechanism of opening: voltage-gated ion channels open after membrane depolarization, ligand-gated ion channels following a ligand binding, whereas mechanosensitive channels open upon mechanic stimulation. (c) Active transport by transporters allow a transport against a chemical gradient thanks to the consumption of energy, e.g. by ATP hydrolysis.

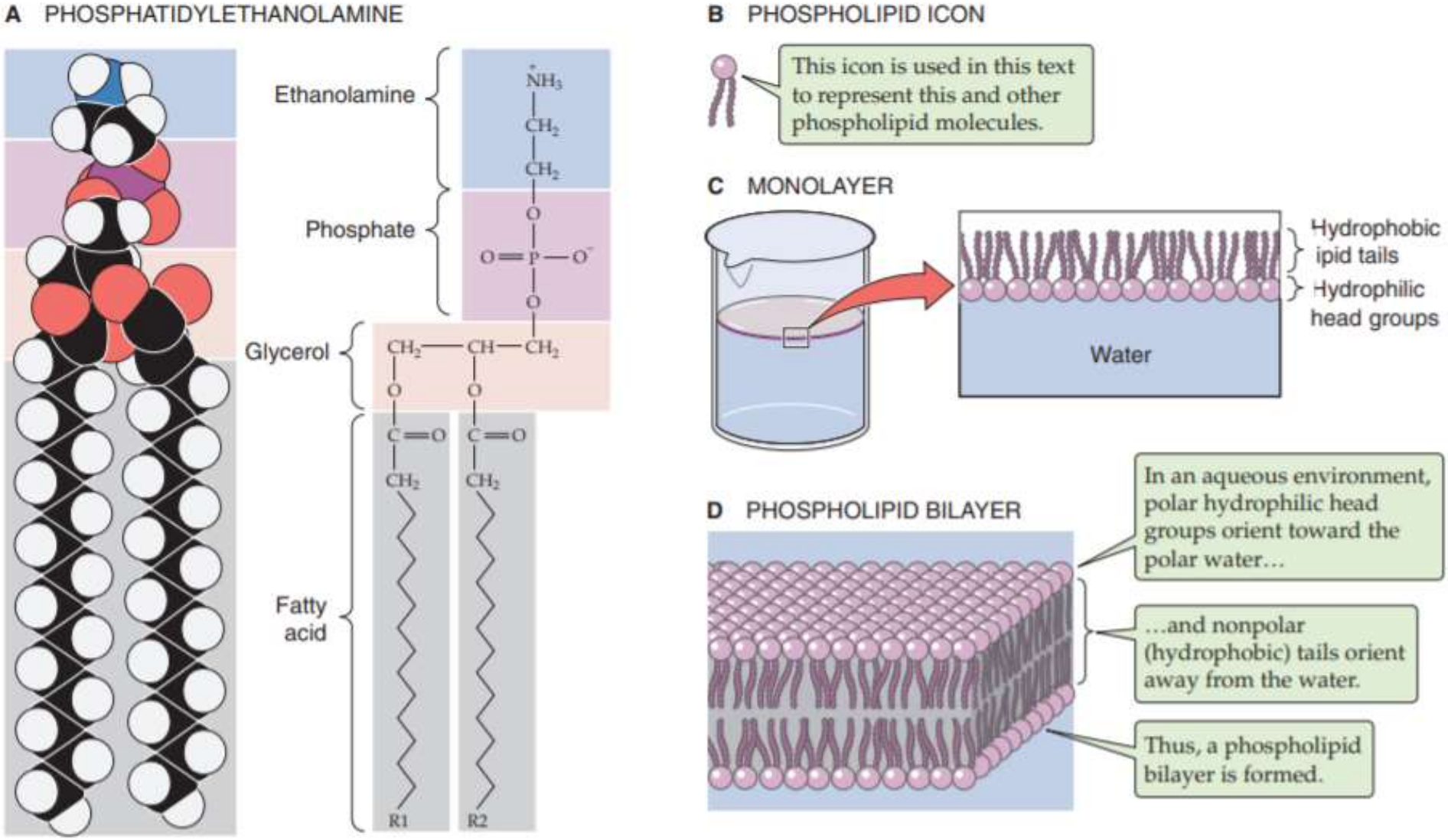


Figure 2-1 Phospholipids.

Structure of cell membranes

- Phospholipids form complex structures in aqueous solution
- The diffusion of individual lipids within a leaflet of a bilayer is determined by the chemical makeup of its constituents
  - phosphatidylinositols
  - phosphatidylserines
  - phosphatidylcholines
  - sphingolipids (derivatives of sphingosine),
    - sphingomyelins
    - glycosphingolipids such as the galactocerebrosides
    - Gangliosides
  - Cholesterol

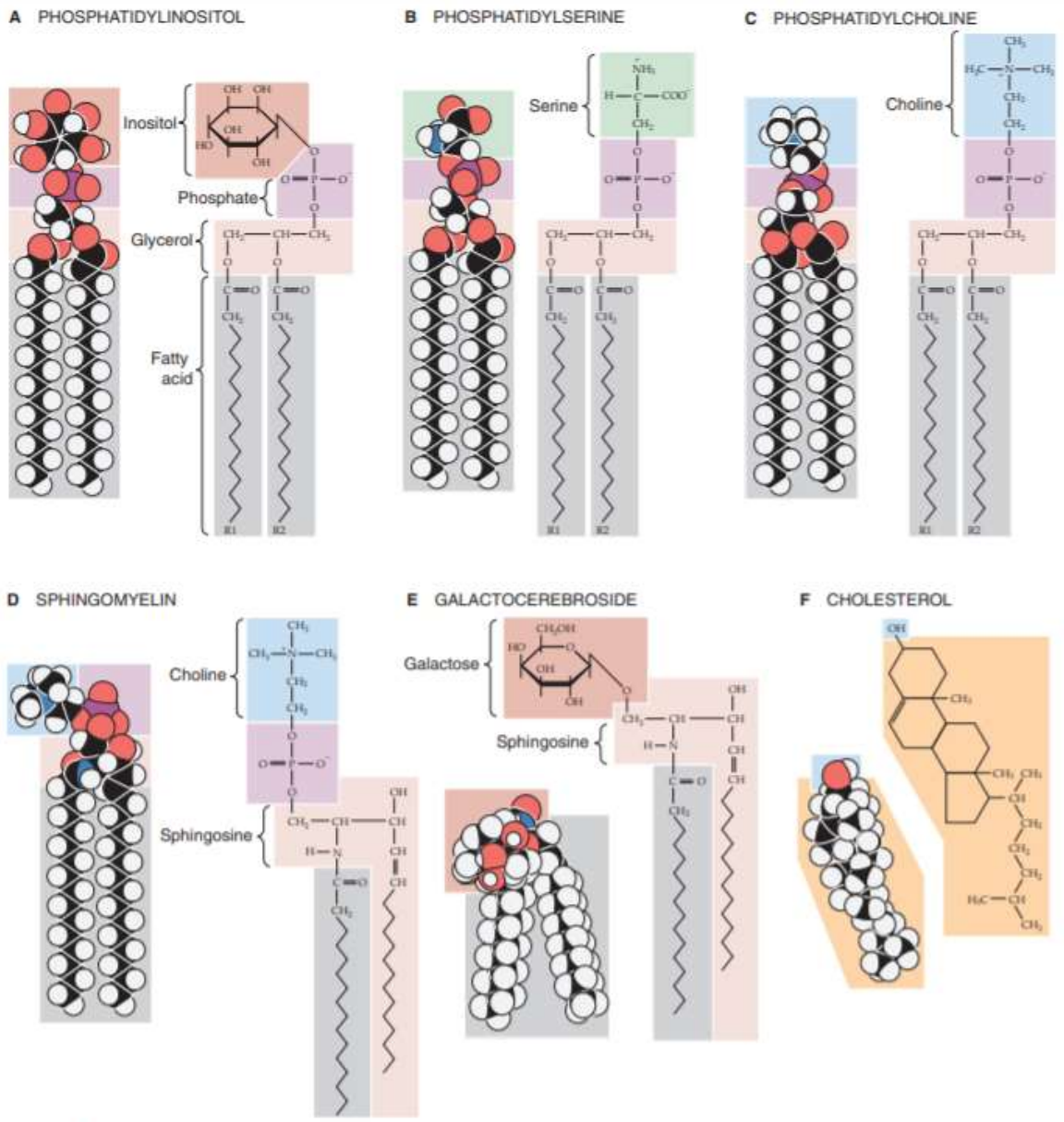
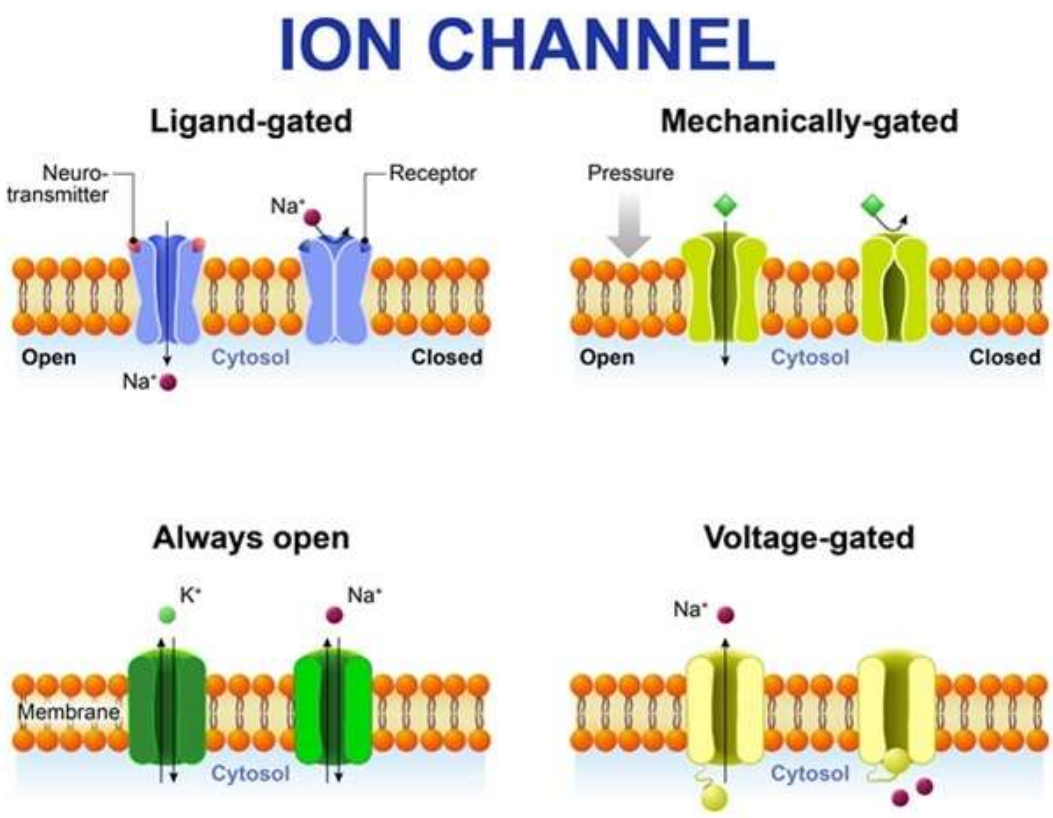


Figure 2-2 Structures of some common membrane lipids.

Phospholipid bilayer membranes are impermeable to charged molecules

- Ions (-)
- Large water-soluble molecules (-)
- Uncharged polar molecules (O2, CO2, NH3, water) (+)



Membrane proteins can be integrally or peripherally associated with the plasma membrane

- Peripherally associated membrane proteins
- Integral membrane proteins
- Transmembrane proteins
- Glycophospholipid-linked proteins
- Some membrane proteins are mobile in the plane of the bilayer

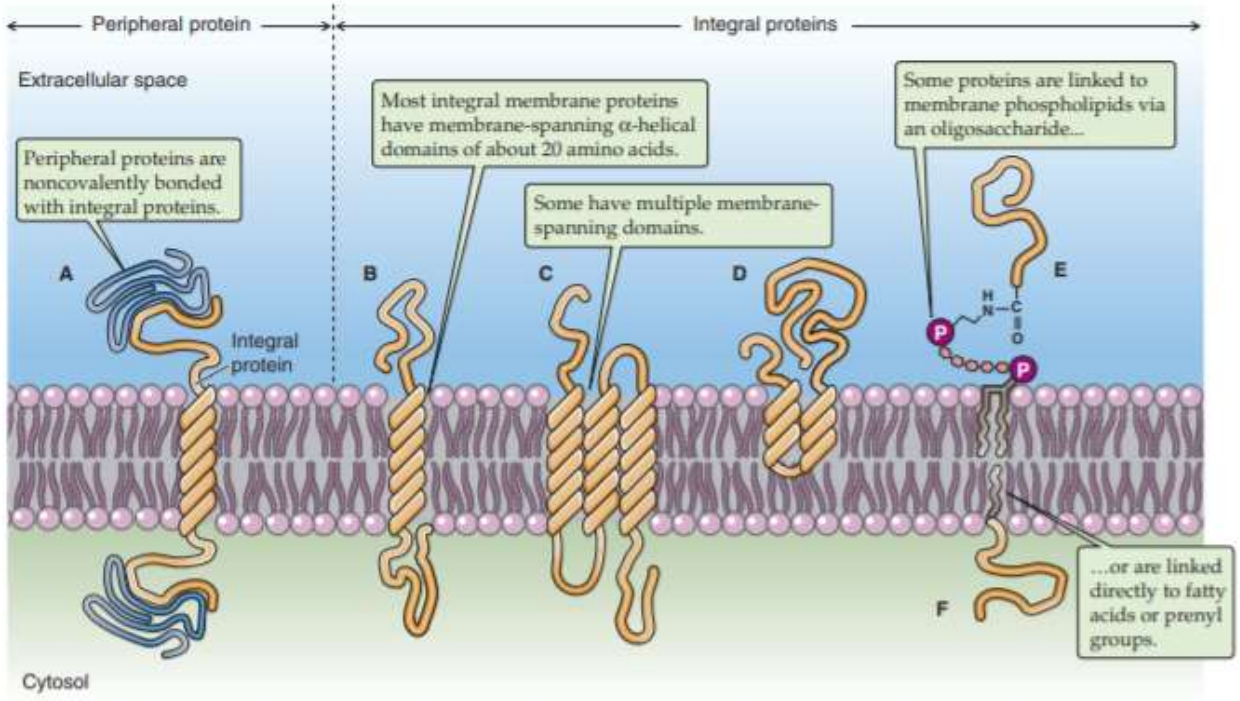


Figure 2-5 Classes of membrane proteins. In **E,** protein is coupled by a GPI linkage.

Function of membrane proteins

- Integral membrane proteins can serve as receptors
- Integral membrane proteins can serve as adhesion molecules
- Integral membrane proteins can carry out the transmembrane movement of water-soluble substances
- Integral membrane proteins can participate in intracellular signaling
- Peripheral membrane proteins participate in intracellular signaling and can form a submembranous cytoskeleton

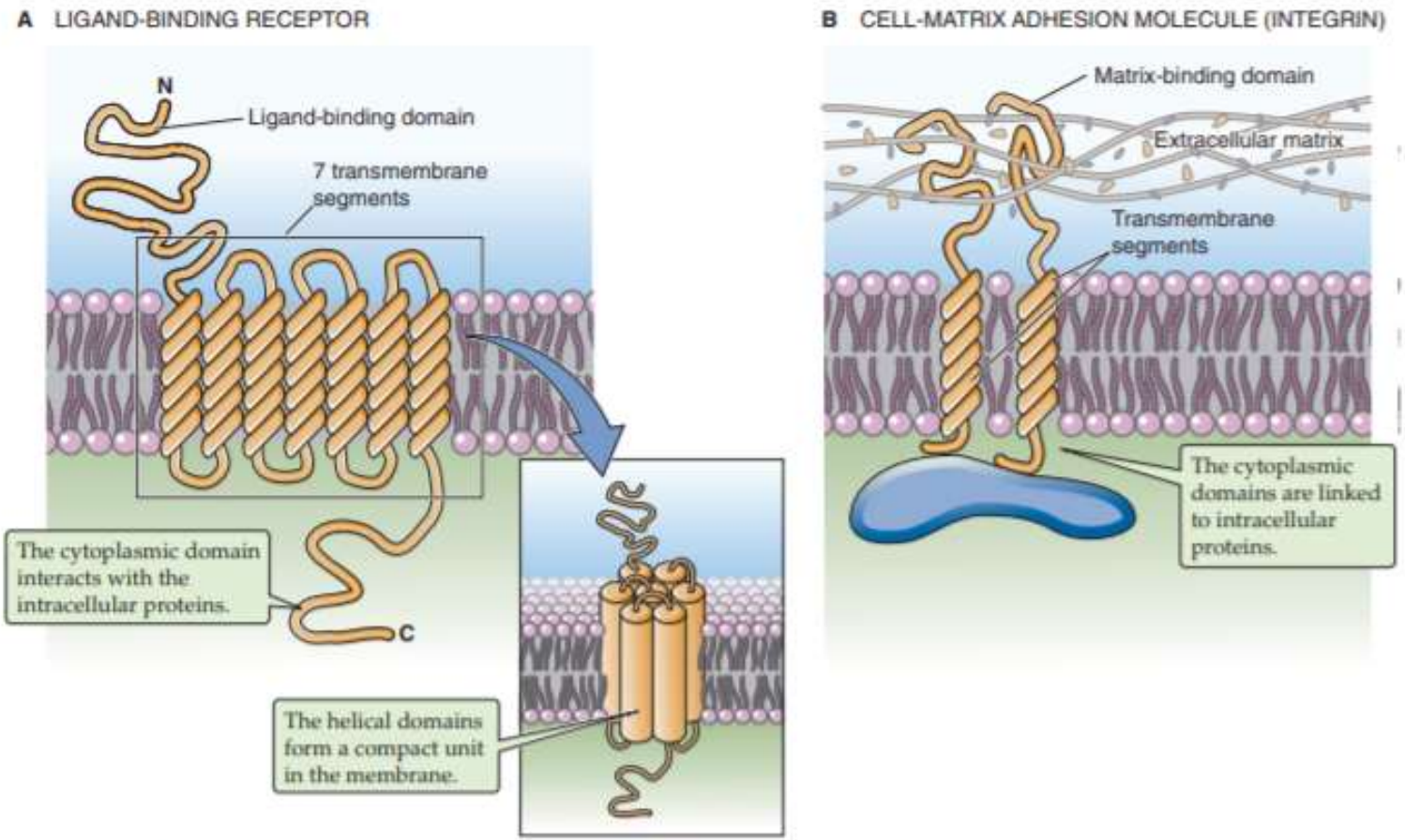


Figure 2-7 Integral membrane proteins that transmit signals from the outside to the inside of a cell. **A,** The ligand may be a hormone, a growth factor, a neurotransmitter, an odorant, or another local mediator. **B,** An integrin is an adhesion molecule that attaches the cell to the extracellular matrix.

Cellular components and cytoskeleton

- The cell is composed of discrete organelles that subserve distinct functions
- The nucleus stores, replicates, and reads the cell's genetic information
- Lysosomes digest material that is derived from the interior and exterior of the cell
- The mitochondrion is the site of oxidative energy production
- The cytoplasm is not amorphous but is organized by the cytoskeleton
- Intermediate filaments provide cells with structural support
- Microtubules provide structural support and provide the basis for several types of subcellular motility
- Thin fi laments (actin) and thick filaments (myosin) are present in almost every cell type

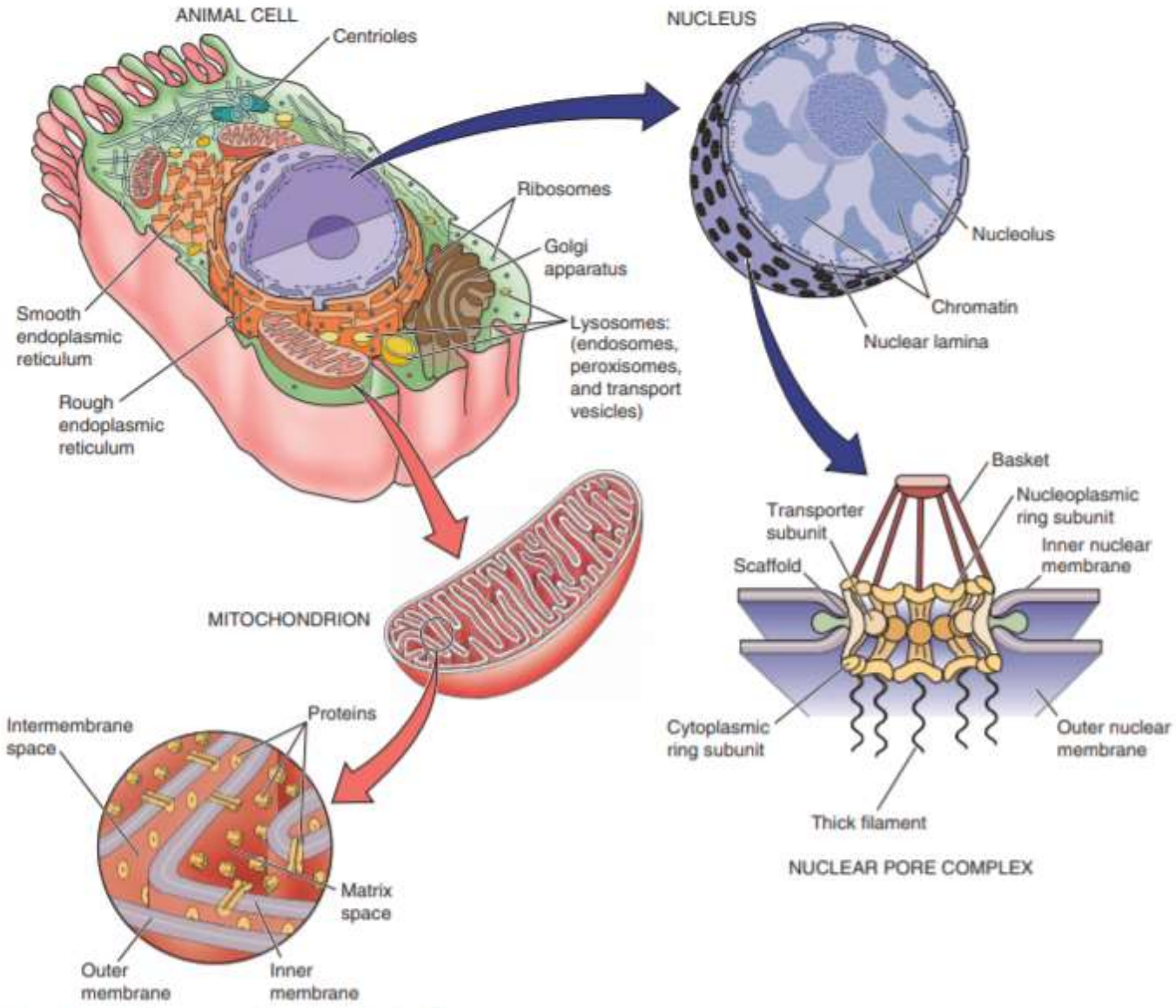


Figure 2-10 Ultrastructure of a typical animal cell.

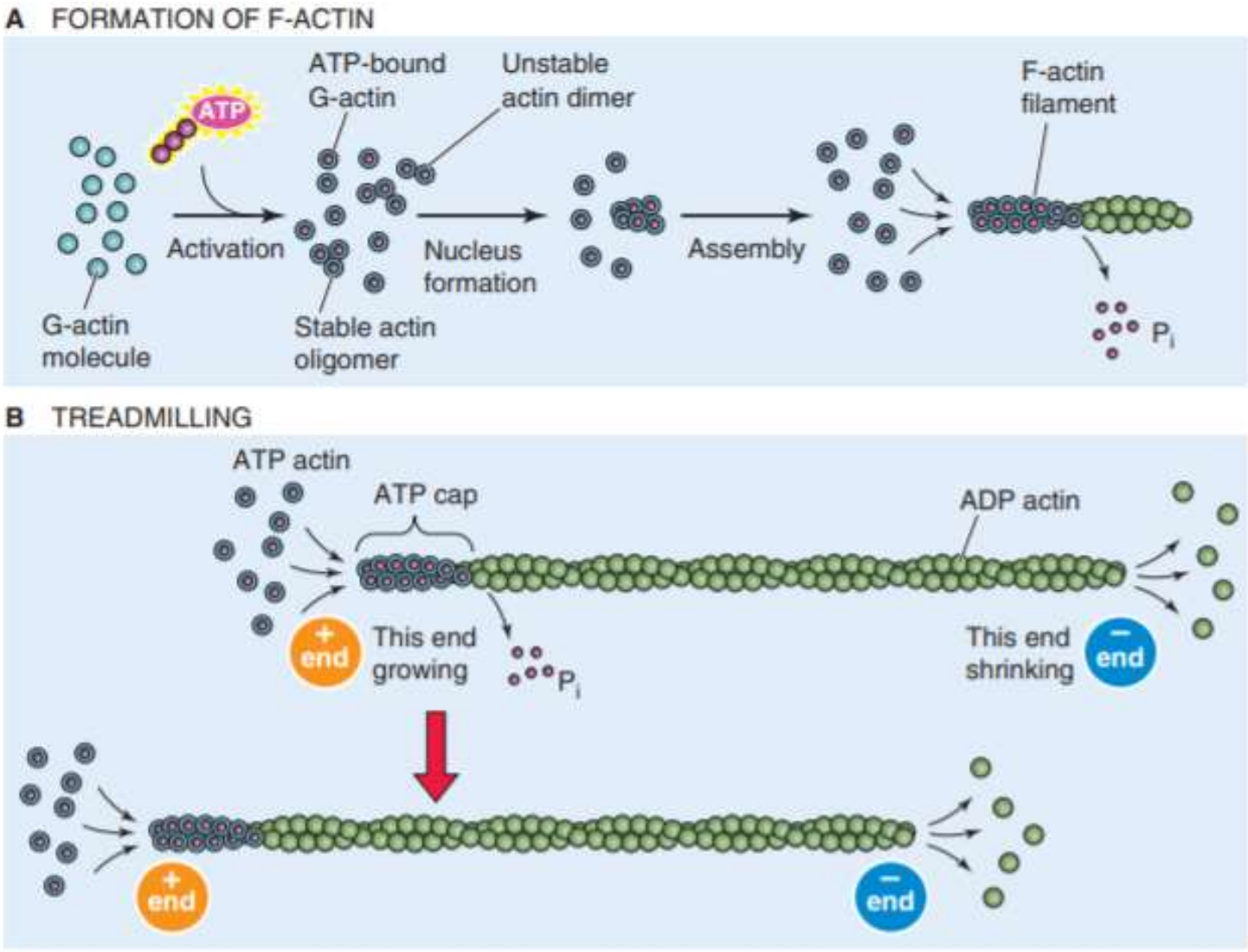


Figure 2-12 Thin filaments. **A,** Single molecules of G-actin form F-actin filaments. **B,** F-actin can grow at the plus end while shrinking at the minus end, with no change in length.

Synthesis and recycling of membrane proteins

- Secretory and membrane proteins are synthesized in association with the rough endoplasmic reticulum
- Simultaneous protein synthesis and translocation through the rough endoplasmic reticulum membrane requires signal recognition and protein translocation machinery
- Newly synthesized secretory and membrane proteins undergo post-translational modification and folding in the lumen of the rough endoplasmic reticulum
- Secretory and membrane proteins follow the secretory pathway through the cell
- Carrier vesicles control the traffic between the organelles of the secretory pathway
- Specialized protein complexes, such as clathrin and coatamers, mediate the formation and fusion of vesicles in the secretory pathway
- Cells internalize extracellular material through the process of endocytosis

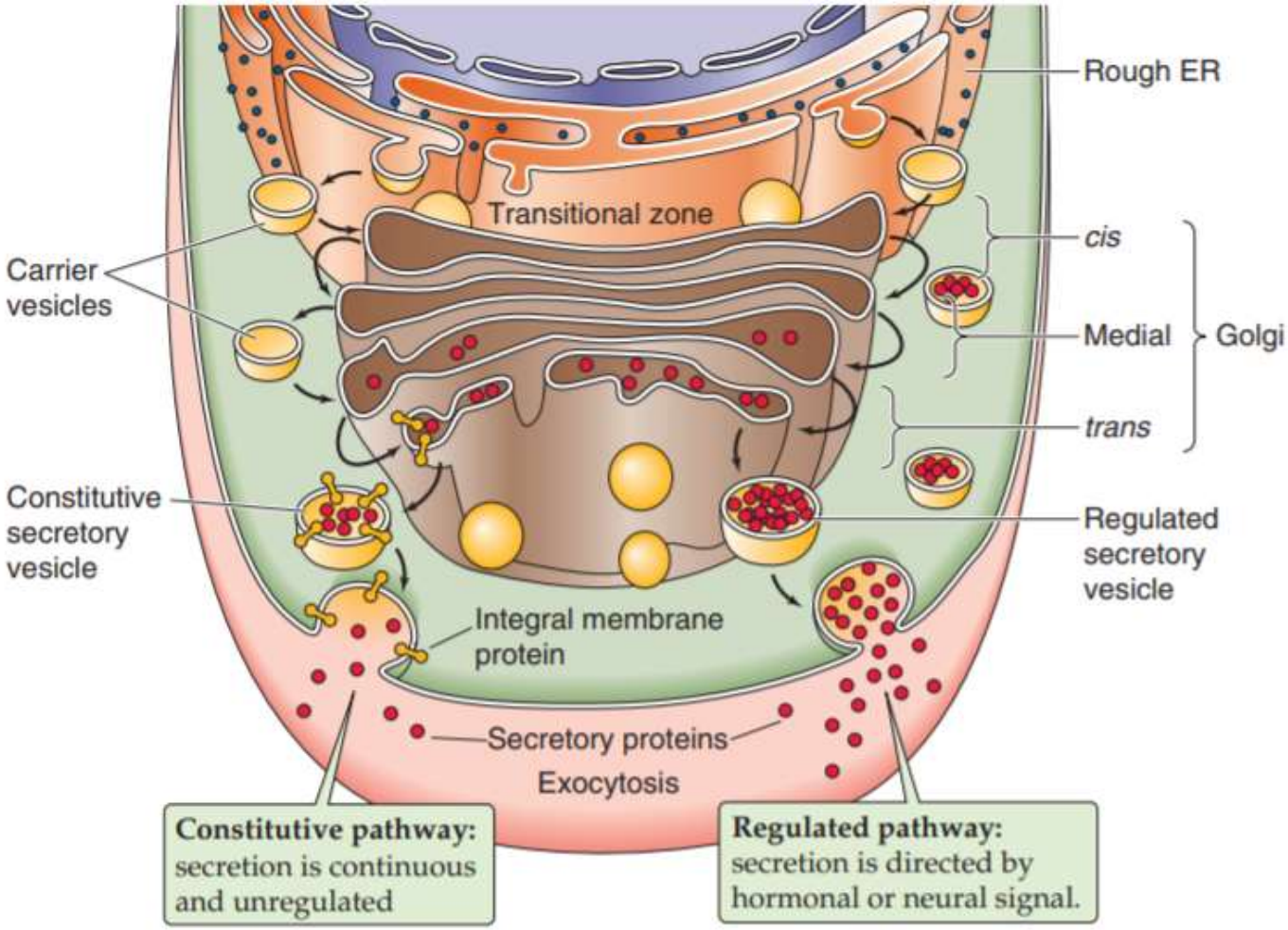


Figure 2-18 The secretory pathway. After their synthesis in the rough ER, secretory and membrane proteins destined for the plasma membrane move through the Golgi stacks and secretory vesicles. In the constitutive pathway, vesicles fuse spontaneously with the plasma membrane. In the regulated pathway, the vesicles fuse only when triggered by a signal such as a hormone.

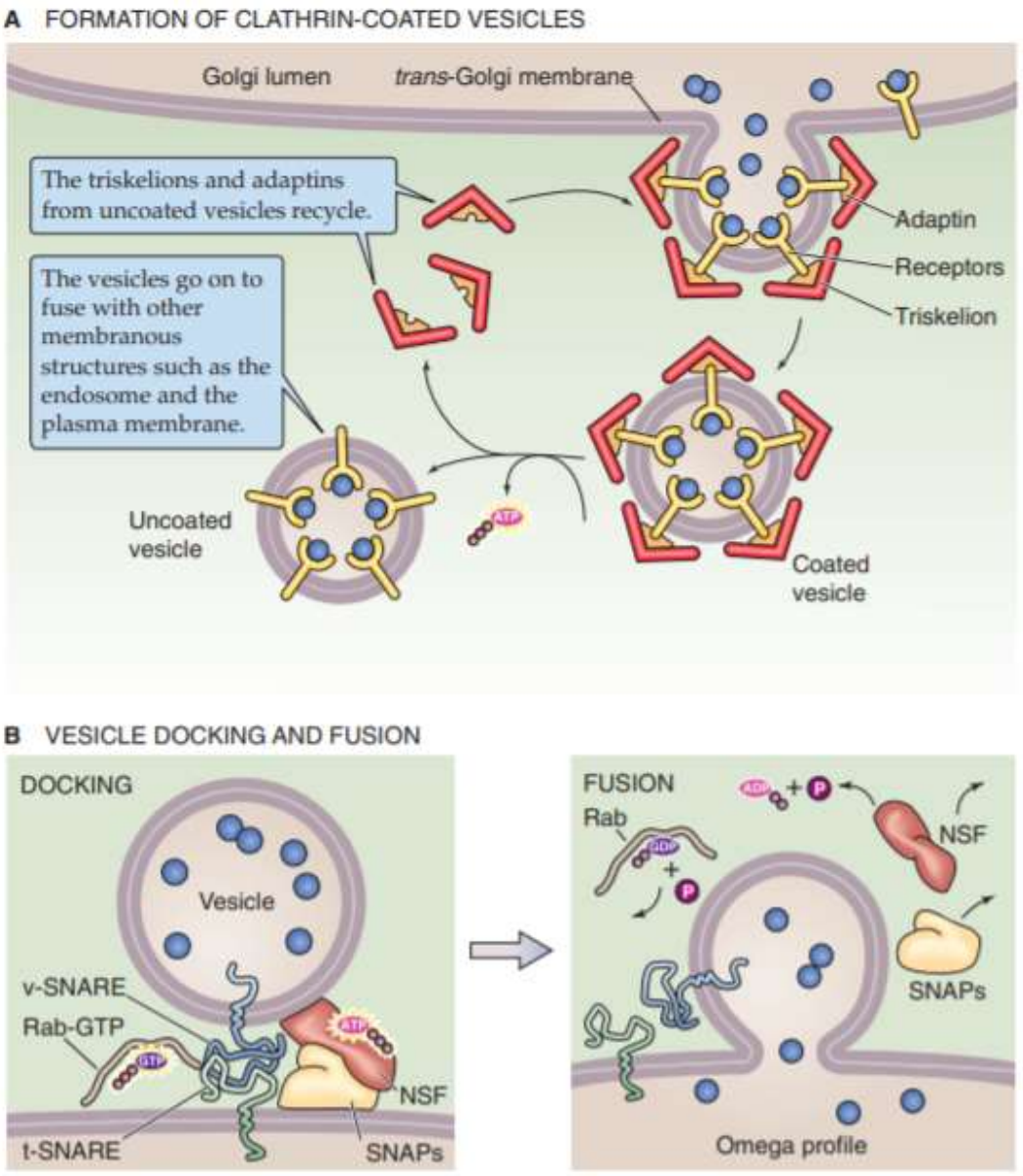


Figure 2-19 Vesicle formation and fusion. **A,** Clathrin mediates the formation of secretory vesicles that bud off from the *trans* Golgi as well as the internalization of membrane from the cell surface during the process of endocytosis. **B,** A complex of proteins forms a bridge between the vesicle and the target membranes. ATP provides the fuel for fusion. The Rab appears to be a molecular switch. NSF, *N*-ethylmaleimide–sensitive factor; SNAP, soluble NSF attachment protein; SNARE, SNAP receptor.

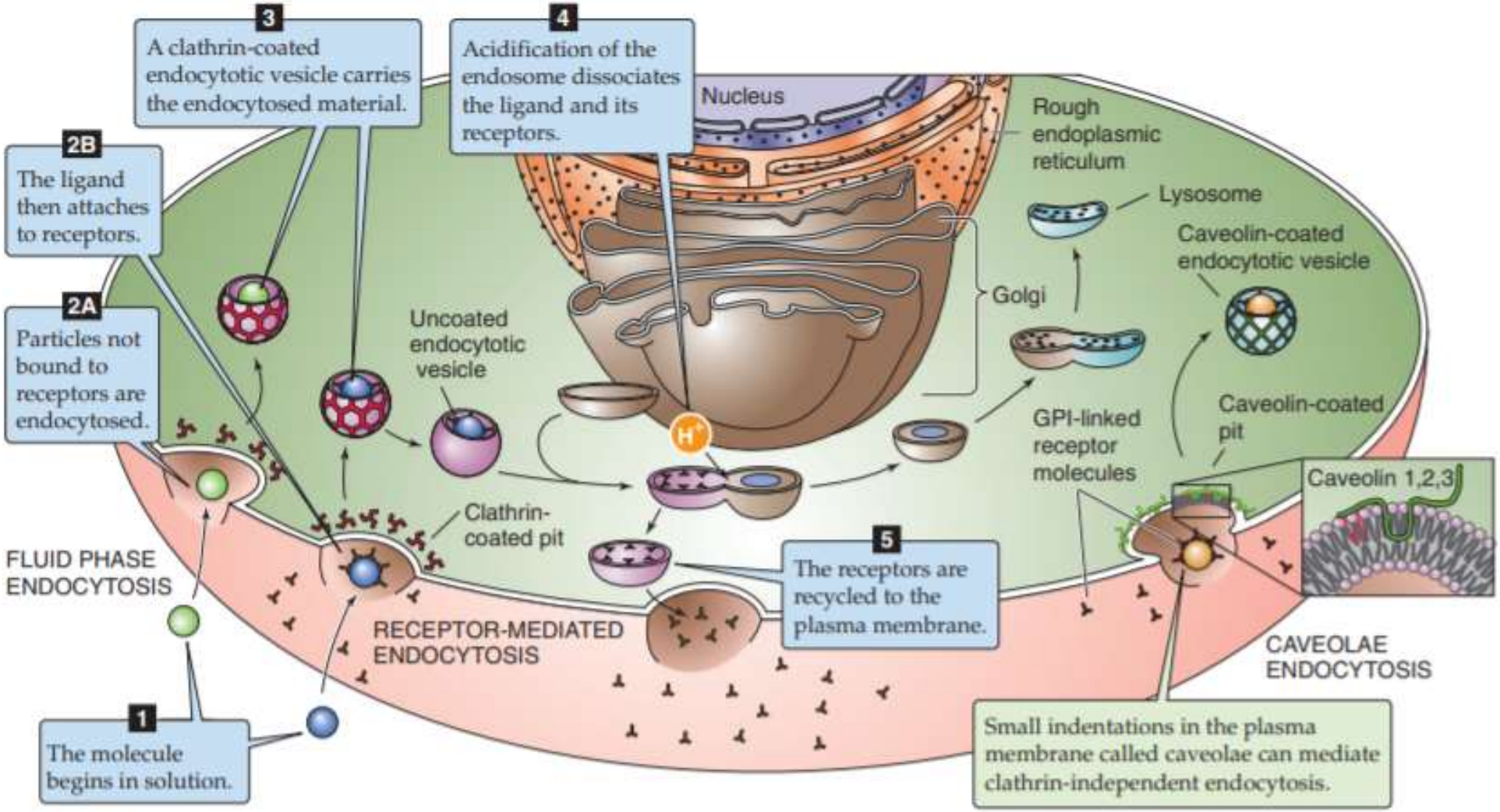


Figure 2-22 Endocytosis.

Signal transduction

- Cells can communicate with one another by chemical signals
  - Hormones and chemical signals
  - Endocrine, paracrine, autocrine
- Soluble chemical signals interact with target cells by binding to surface or intracellular receptors

1. **Ligand-gated ion channels.** Integral membrane proteins, these hybrid receptor/channels are involved in signaling between electrically excitable cells. The binding of a neurotransmitter such as ACh to its receptor—which in fact is merely part of the channel—results in transient opening of the channel, thus altering the ion permeability of the cell.
2. **G protein–coupled receptors.** These integral plasma membrane proteins work indirectly—through an intermediary—to activate or to inactivate a separate membrane-associated enzyme or channel. The intermediary is a heterotrimeric guanosine triphosphate (GTP)–binding complex called a G protein.
3. **Catalytic receptors.** When activated by a ligand, these integral plasma membrane proteins are either enzymes themselves or part of an enzymatic complex.
4. **Nuclear receptors.** These proteins, located in the cytosol or nucleus, are ligand-activated transcription factors. These receptors link extracellular signals to gene transcription.

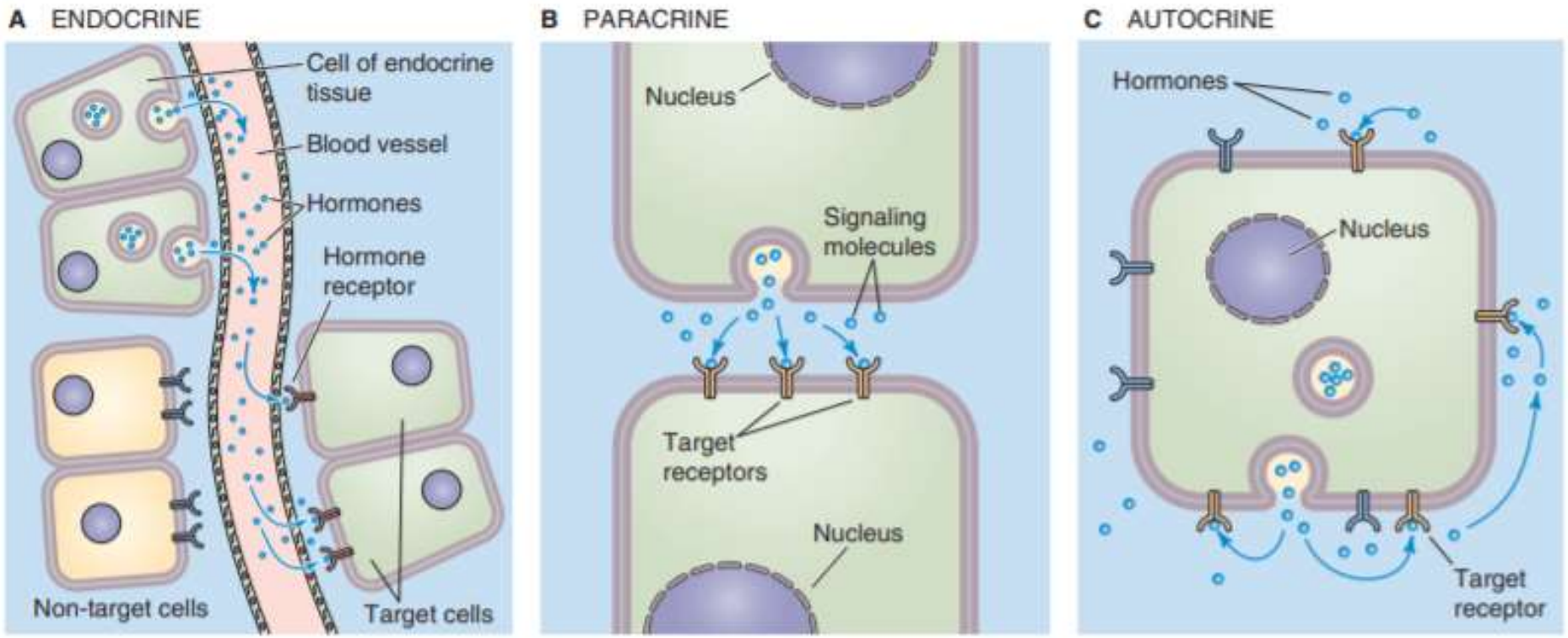


Figure 3-1 Modes of cell communication.

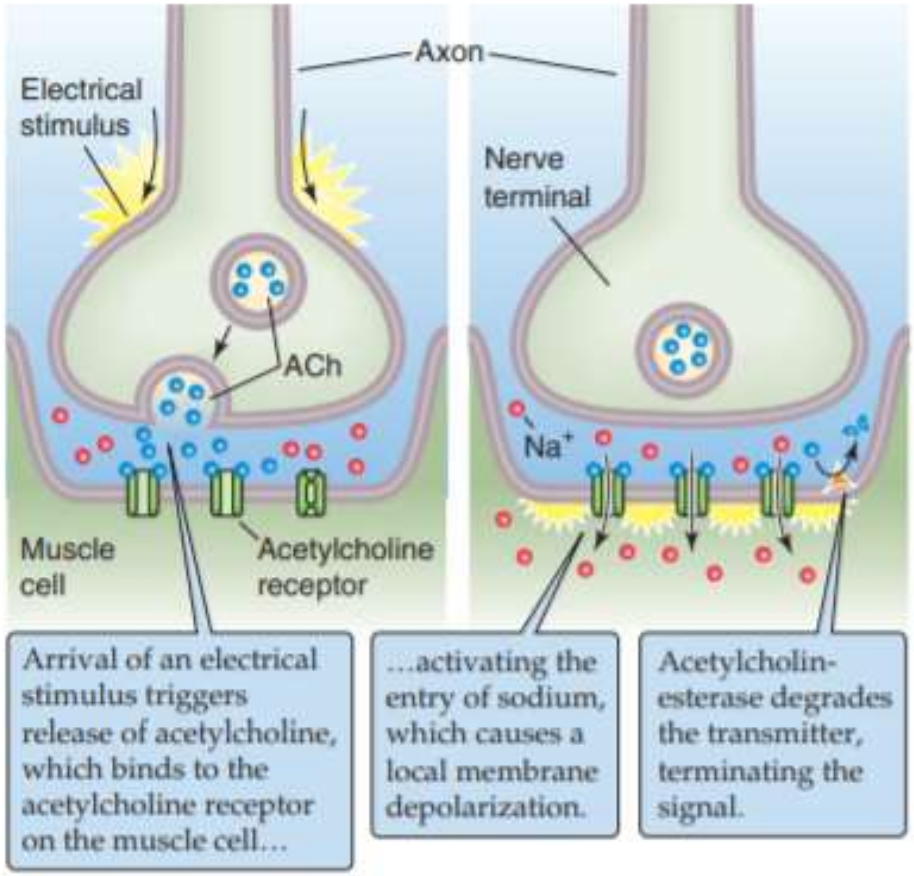


Figure 3-2 Example of paracrine signaling. The release of ACh at the neuromuscular junction is a form of paracrine signaling because the nerve terminal releases a chemical (i.e., ACh) that acts on a neighboring cell (i.e., the muscle).

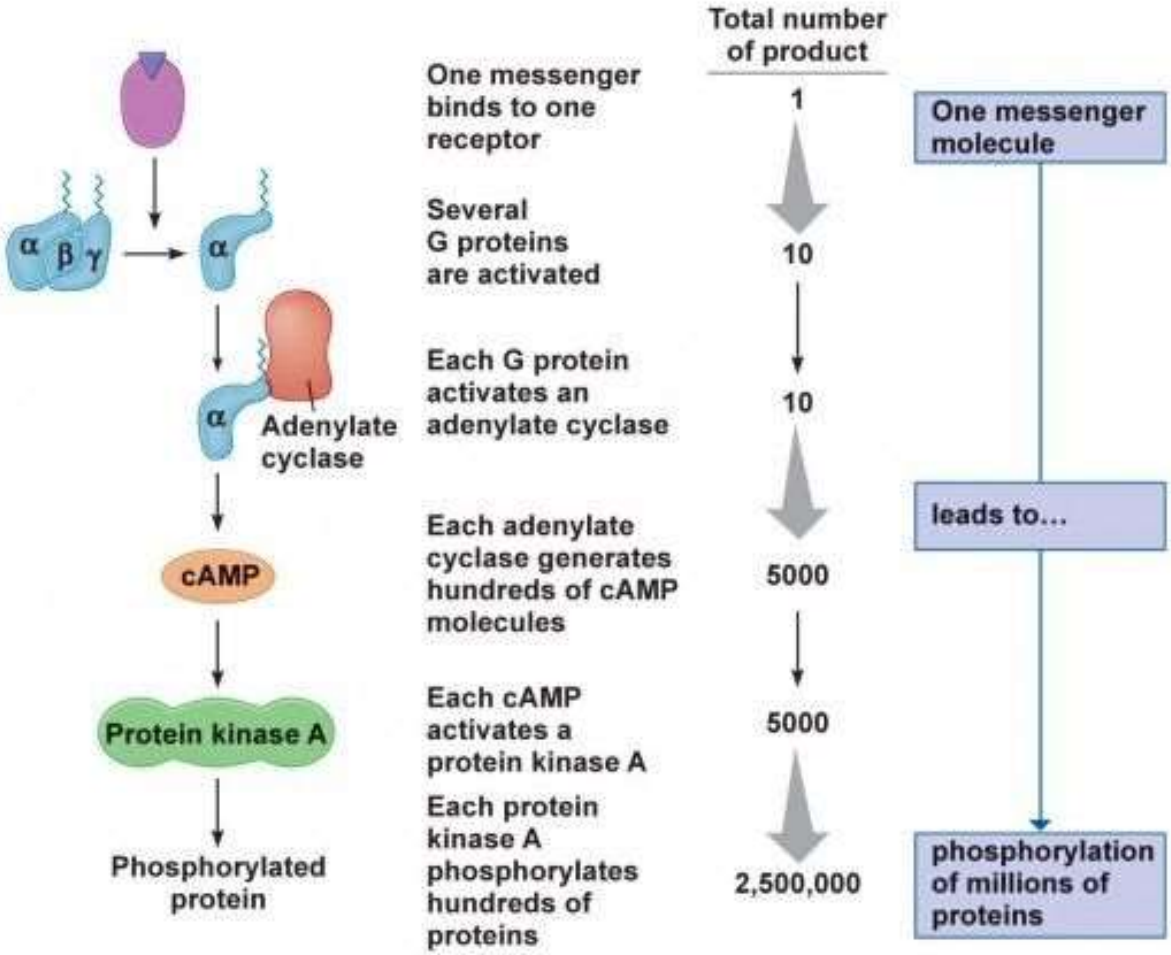
Signaling events initiated by plasma membrane receptors can generally be divided into six steps

- Recognition
- Transduction
- Transmission
- Modulation of the effector (phosphatases/kinases)
- Response
- Termination

Cells can also communicate by direct interactions

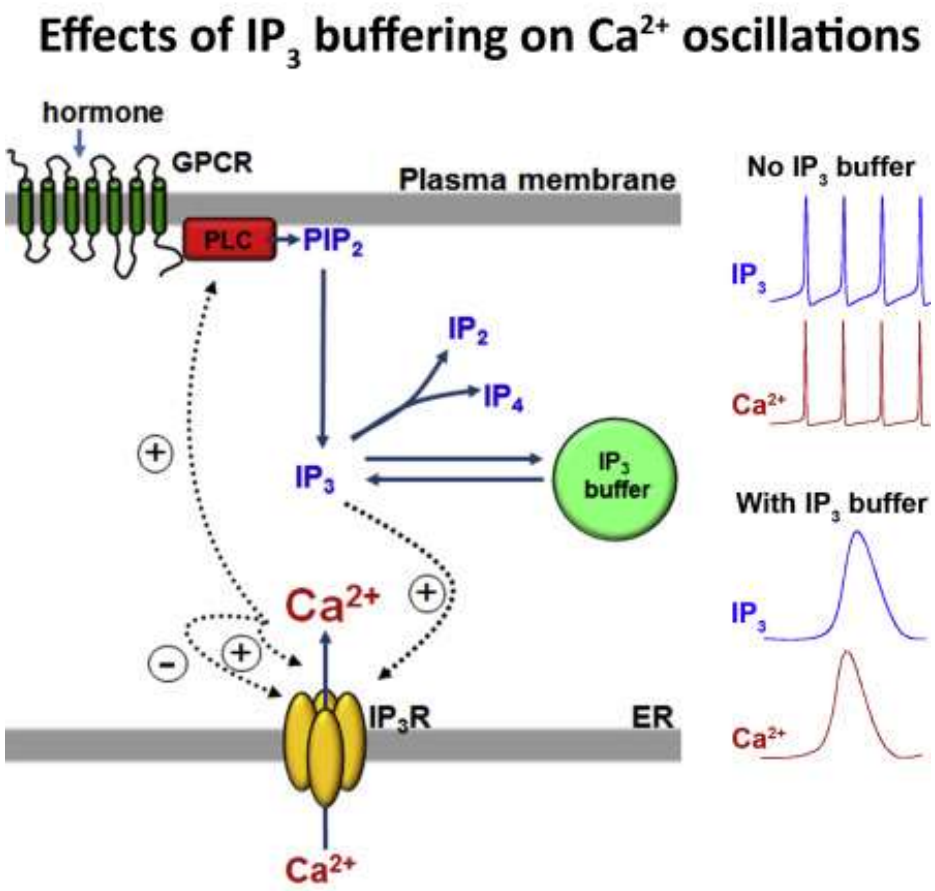
- Gap junctions
- Adhering and Tight Junctions
- Membrane-Associated Ligands

Second-messenger systems amplify signals and integrate responses among cell types



Receptors that are ion channels

- Ligand-gated ion channels transduce a chemical signal into an electrical signal
- Ionotropic receptors
  - ACh, serotonin, γ-aminobutyric acid (GABA), and glycine
  - IP3 receptor
  - ryanodine receptor



G protein–coupled receptors (GPCRs)

- G proteins are heterotrimers that exist in many combinations of different α, β, and γ subunits

Table 3-2 Families of G Proteins

Family/Subunit	% Identity	Toxin	Distribution	Receptor	Effector/Role
α_s $\alpha_{s(s)}$ $\alpha_{s(l)}$	100	CTX	Ubiquitous	β-adrenergic, TSH, glucagon	↑ Adenylyl cyclase ↑ Ca^{2+} channel ↑ Na^+ channel
α_{olf}	88	CTX	Olfactory epithelium	Odorant	↑ Adenylyl cyclase Open K^+ channel
G_i α_1 α_2 α_3	100 88	PTX PTX PTX	–Ubiquitous Ubiquitous –Ubiquitous	M_2, α_2-adrenergic, others	↑ IP_3, DAG, Ca^{2+}, and AA release ↓ Adenylyl cyclase
α_{O1A} α_{O1B}	73 73	PTX PTX	Brain, others Brain, others	Met-enkephalin, α_2-adrenergic, others	
α_{t1} α_{t2}	68 68	PTX, CTX PTX, CTX	Retinal rods Retinal cones	Rhodopsin Cone opsin	↑ cGMP-phosphodiesterase
α_g α_z	67 60	PTX, CTX (?)	Taste buds Brain, adrenal, platelet	Taste (?) M_2 (?), others (?)	? ↓ Adenylyl cyclase
G_q α_q α_{11} α_{14} α_{15} α_{16}	 100 88 79 57 58		 –Ubiquitous –Ubiquitous Lung, kidney, liver B cell, myeloid T cell, myeloid	 M_1, α_1-adrenergic, others Several receptors	 ↑ PLCβ1, β2, β3 ↑ PLCβ1, β2, β3
G_{12} α_{12} α_{13}	 100 67		 Ubiquitous Ubiquitous		

CTX, cholera toxin; M_1 and M_2, muscarinic cholinergic receptors; PTX, pertussis toxin; TSH, thyrotropin (thyroid-stimulating hormone).

G protein–coupled receptors (GPCRs)

- G protein activation follows a cycle
- Activated a subunits couple to a variety of downstream effectors, including enzymes, ion channels, and membrane trafficking machinery
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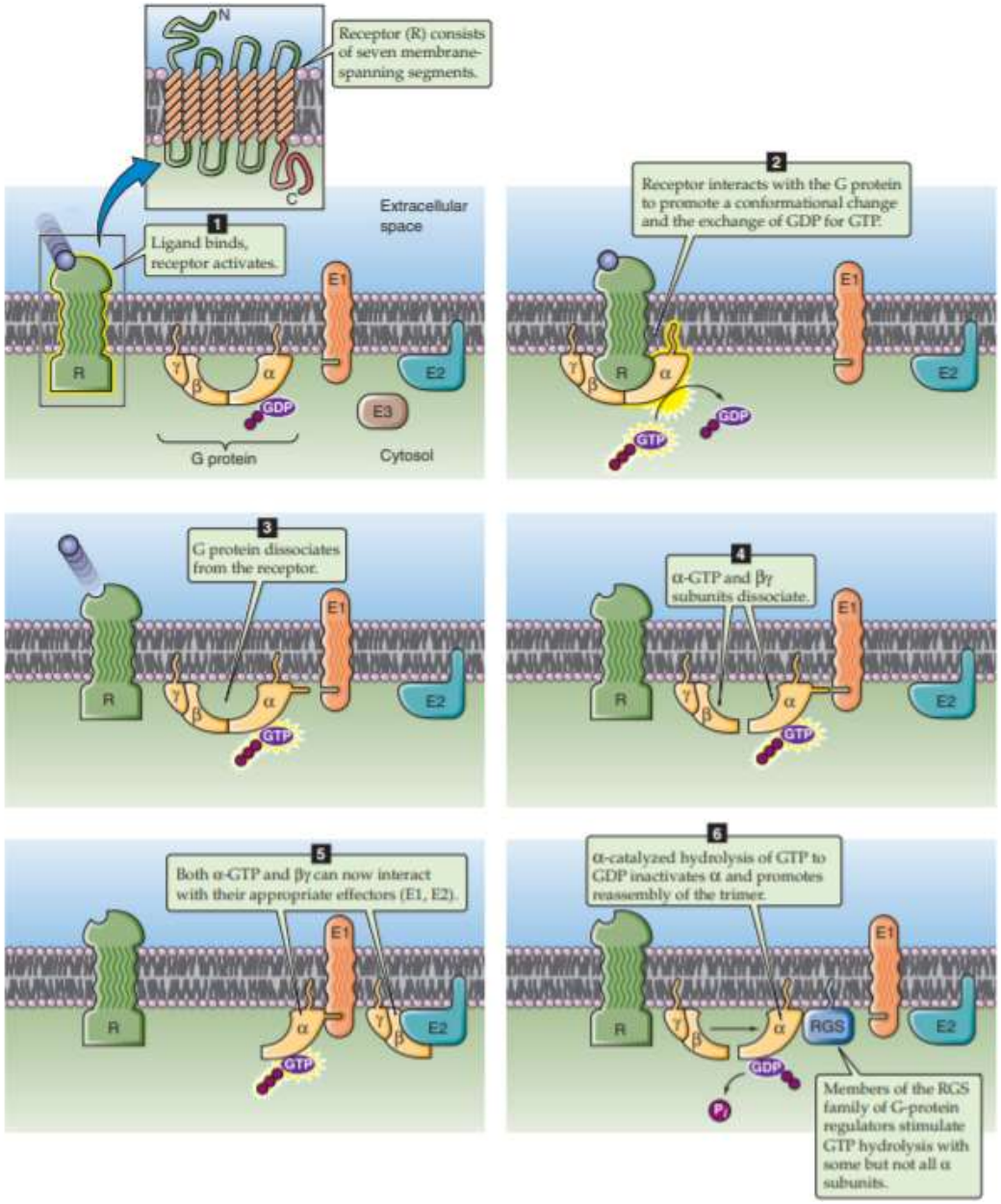


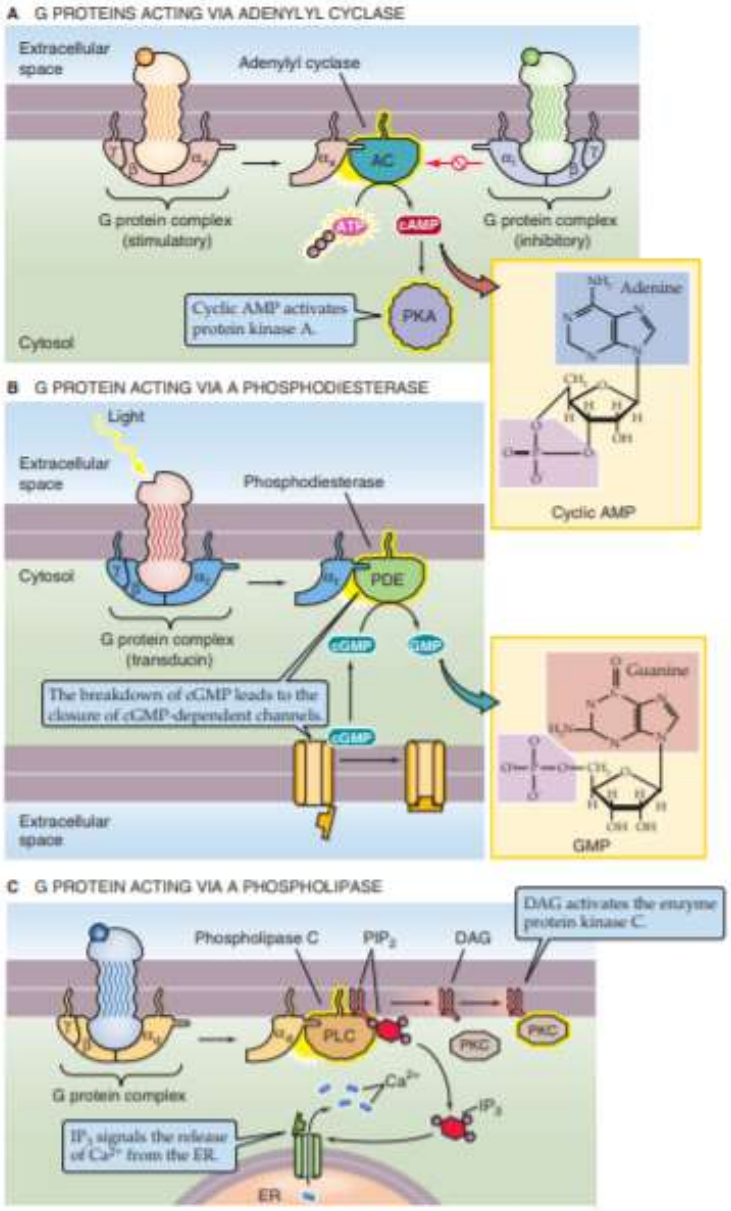


Figure 3-5 Downstream effects of activated G protein α subunits. **A,** When a ligand binds to a receptor coupled to α_s, adenylyl cyclase (AC) is activated, whereas when a ligand binds to a receptor coupled to α_i, the enzyme is inhibited. The activated enzyme converts ATP to cAMP, which then can activate protein kinase A (PKA). **B,** In phototransduction, a photon interacts with the receptor and activates the G protein transducin. The α_t activates phosphodiesterase (PDE), which in turn hydrolyzes cGMP and lowers the intracellular concentrations of cGMP and therefore closes the cGMP-activated channels. **C,** In this example, the ligand binds to a receptor that is coupled to α_q, which activates phospholipase C (PLC). This enzyme converts PIP_2 to IP_3 and diacylglycerol (DAG). The IP_3 leads to the release of Ca^{2+} from intracellular stores, whereas the diacylglycerol activates protein kinase C (PKC). ER, endoplasmic reticulum.

IP3 and DAG

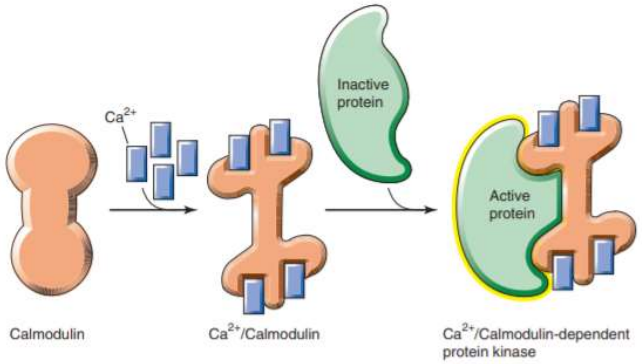
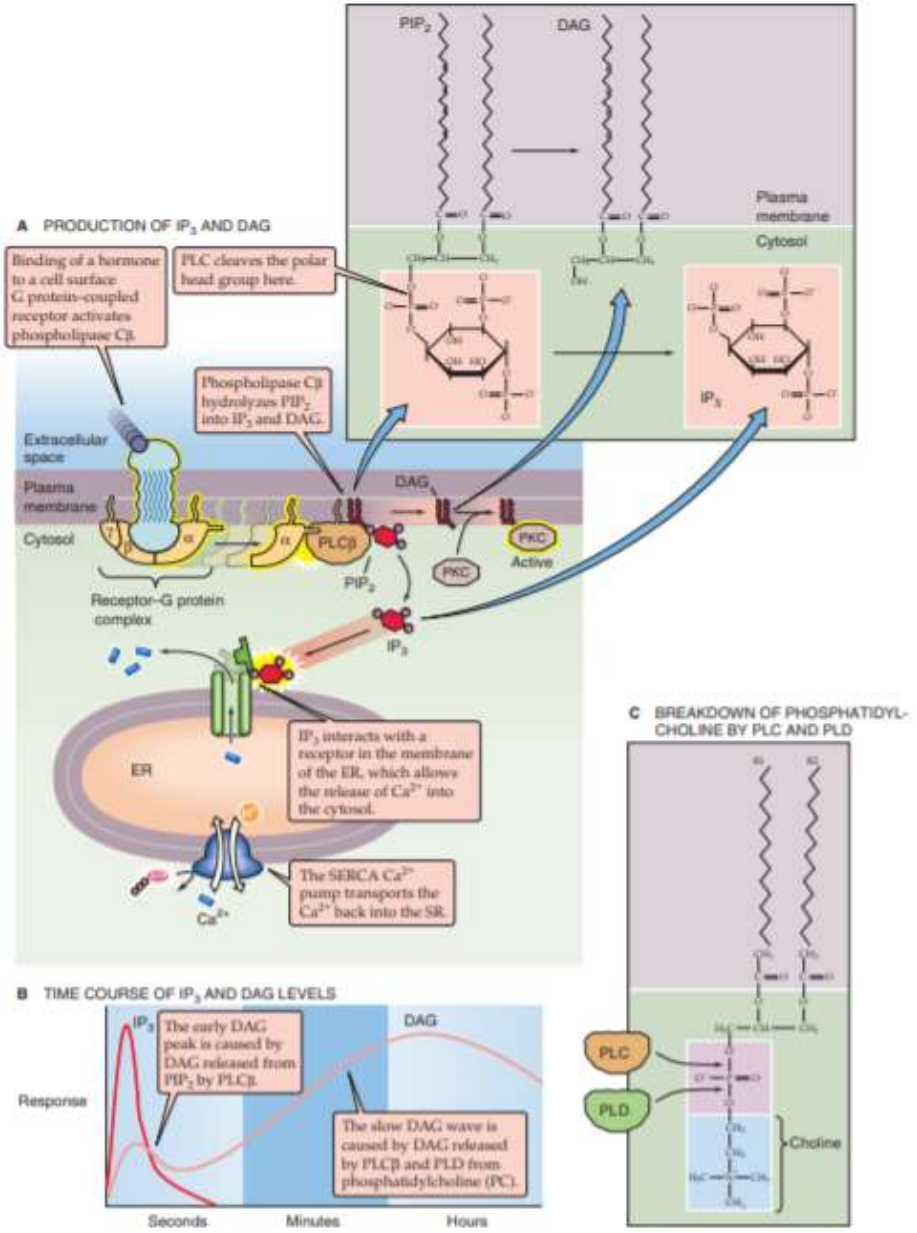


Figure 3-9 Calmodulin. After four intracellular Ca^{2+} ions bind to calmodulin, the Ca^{2+}-CaM complex can bind to and activate another protein. In this example, the activated protein is a Ca^{2+}-CaM–dependent kinase.



Calcium signalling

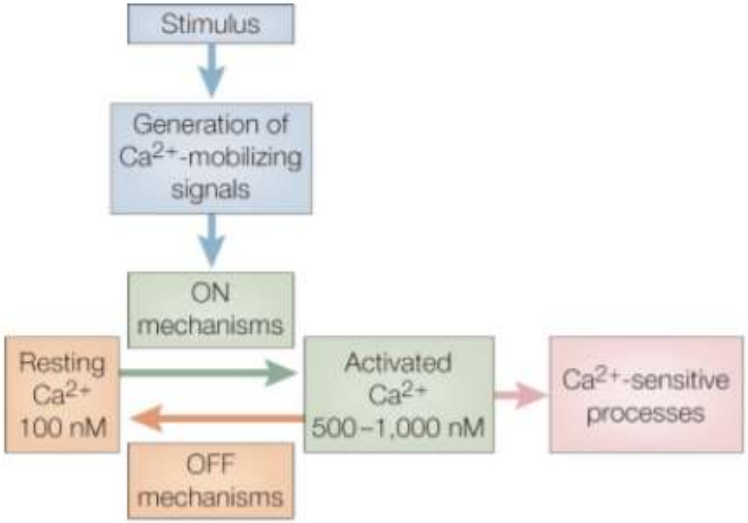
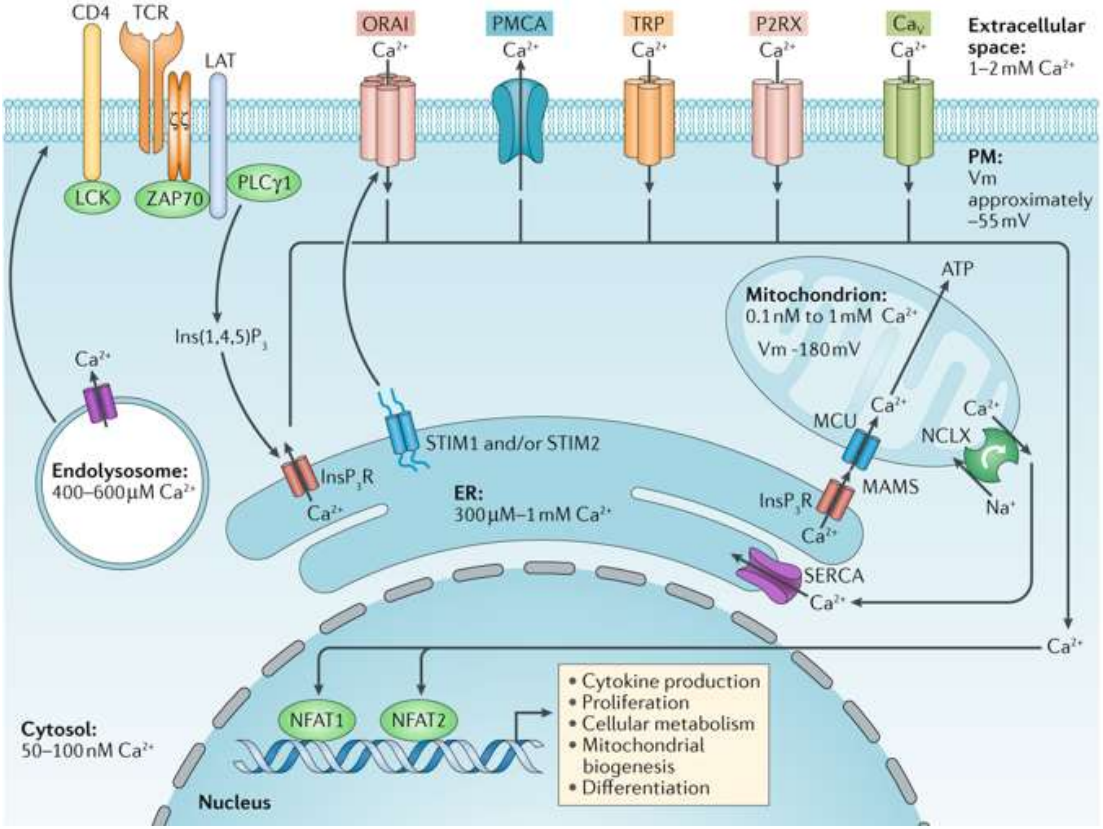


Figure 1 | **The four units of the Ca^{2+} signalling network.** Stimuli act by generating Ca^{2+}-mobilizing signals that act on various ON mechanisms to trigger an increase in the intracellular concentration of Ca^{2+}. The increased level of Ca^{2+} stimulates various Ca^{2+}-sensitive processes to trigger many different cellular pathways. The response is terminated by OFF mechanisms that restore Ca^{2+} to its resting level. Details of these four functional units, with the same colour coding, are revealed in FIG. 2.



Calcium signalling

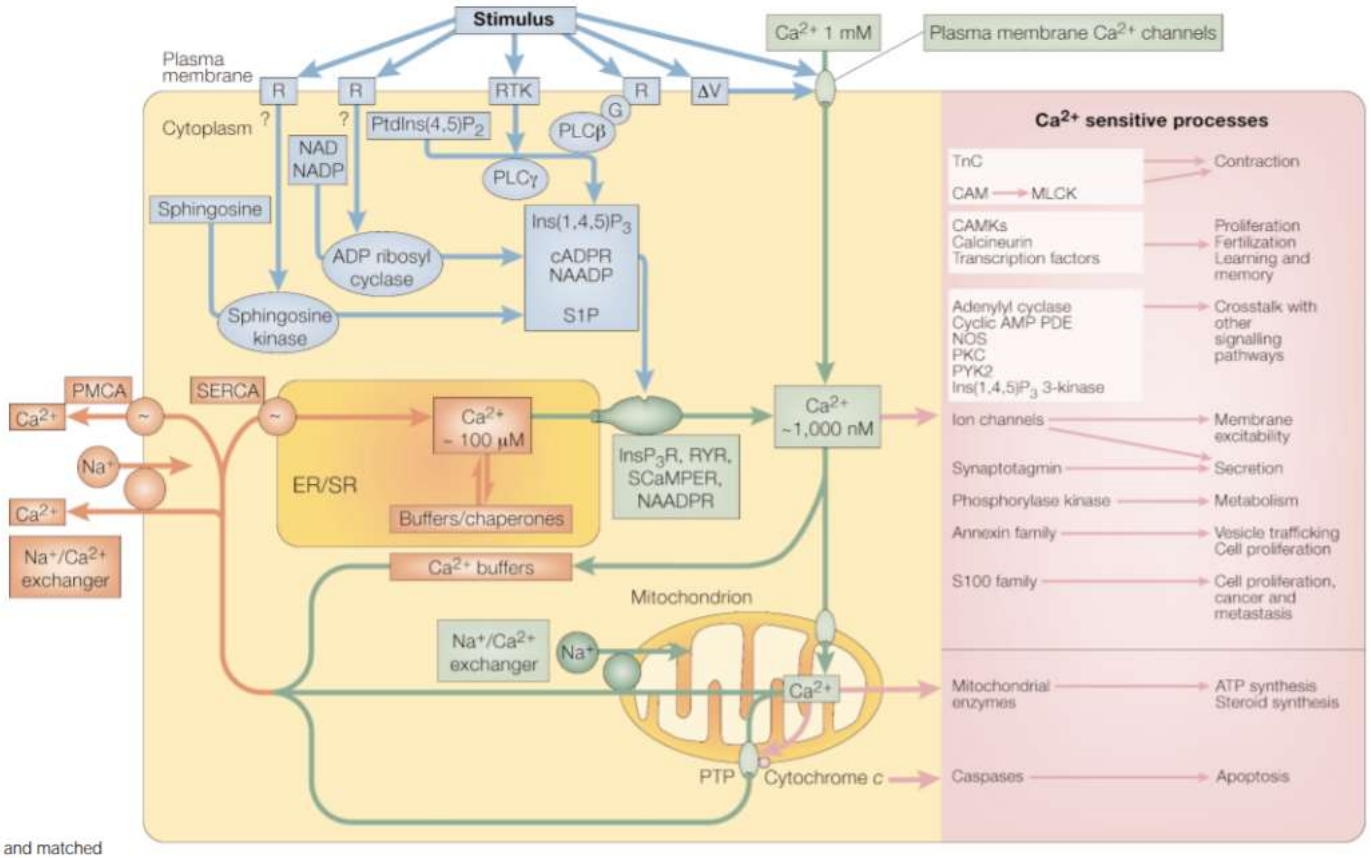


Figure 2 | **Elements of the Ca^{2+} signalling toolkit.** Cells have an extensive signalling toolkit that can be mixed and matched to create Ca^{2+} signals of widely different properties. Ca^{2+}-mobilizing signals (blue) are generated by stimuli acting through a variety of cell-surface receptors (R), including G-protein (G)-linked receptors and receptor tyrosine kinases (RTK). The signals generated include: inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$), generated by the hydrolysis of phosphatidylinositol-4,5-bisphosphate ($PtdIns(4,5)P_2$) by a family of phospholipase C enzymes (PLCβ, PLCγ); cyclic ADP ribose (cADPR) and nicotinic acid dinucleotide phosphate (NAADP), both generated from nicotinamide-adenine dinucleotide (NAD) and its phosphorylated derivative NADP by ADP ribosyl cyclase; and sphingosine 1-phosphate (S1P), generated from sphingosine by a sphingosine kinase. ON mechanisms (green) include plasma membrane Ca^{2+} channels, which respond to transmitters or to membrane depolarization (ΔV), and intracellular Ca^{2+} channels — the $Ins(1,4,5)P_3$ receptor ($InsP_3R$), ryanodine receptor (RYR), NAADP receptor and sphingolipid Ca^{2+} release-mediating protein of the ER (SCaMPER). The Ca^{2+} released into the cytoplasm by these ON mechanisms activates different Ca^{2+} sensors (purple), which augment a wide range of Ca^{2+}-sensitive processes (purple), depending on cell type and context. OFF mechanisms (red) pump Ca^{2+} out of the cytoplasm: the Na^+/Ca^{2+} exchanger and the plasma membrane Ca^{2+} ATPase (PMCA) pumps Ca^{2+} out of the cell and the sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA) pumps it back into the ER/SR. (TnC, troponin C; CAM, calmodulin; MLCK, myosin light chain kinase; CAMK, Ca^{2+}/calmodulin-dependent protein kinase; cyclic AMP PDE, cyclic AMP phosphodiesterase; NOS, nitric oxide synthase; PKC, protein kinase C; PYK2, proline-rich kinase 2; PTP, permeability transition pore.)

Calcium signalling

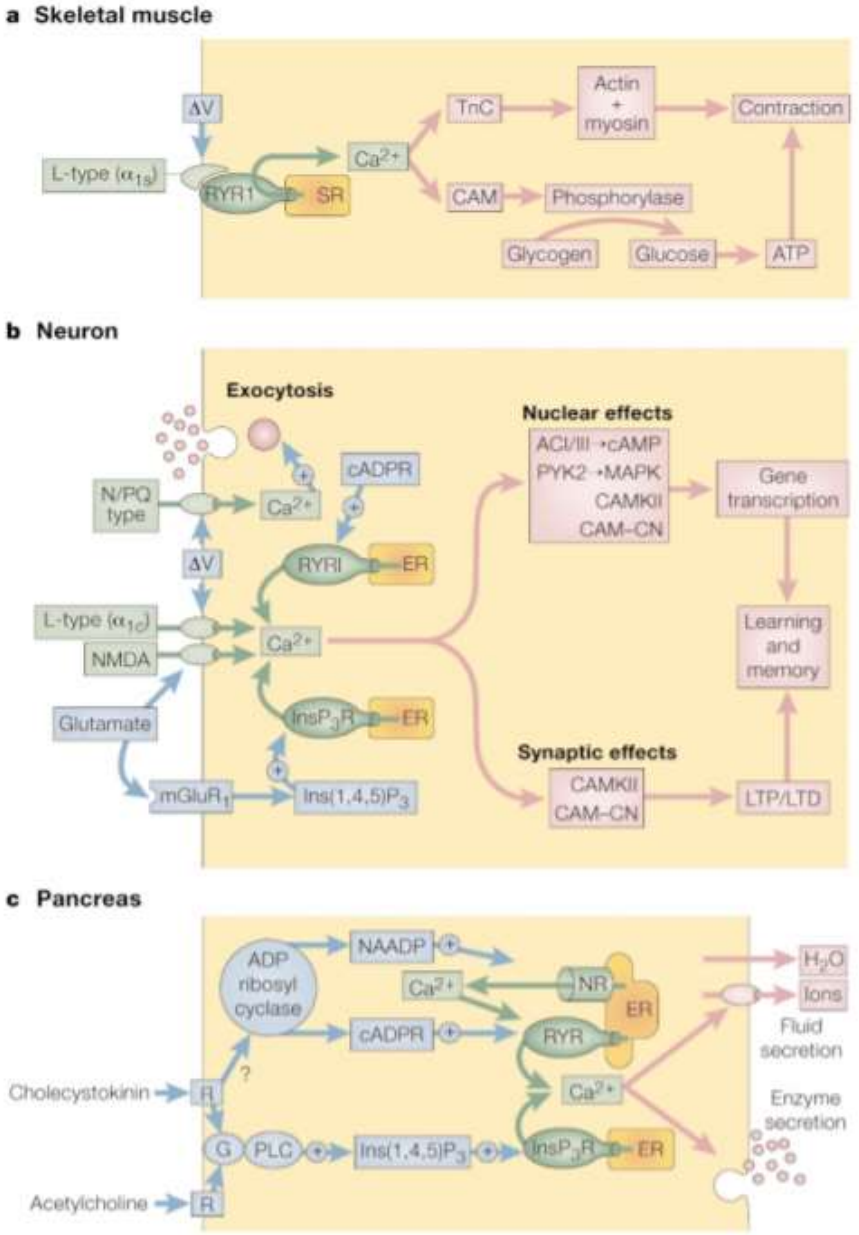
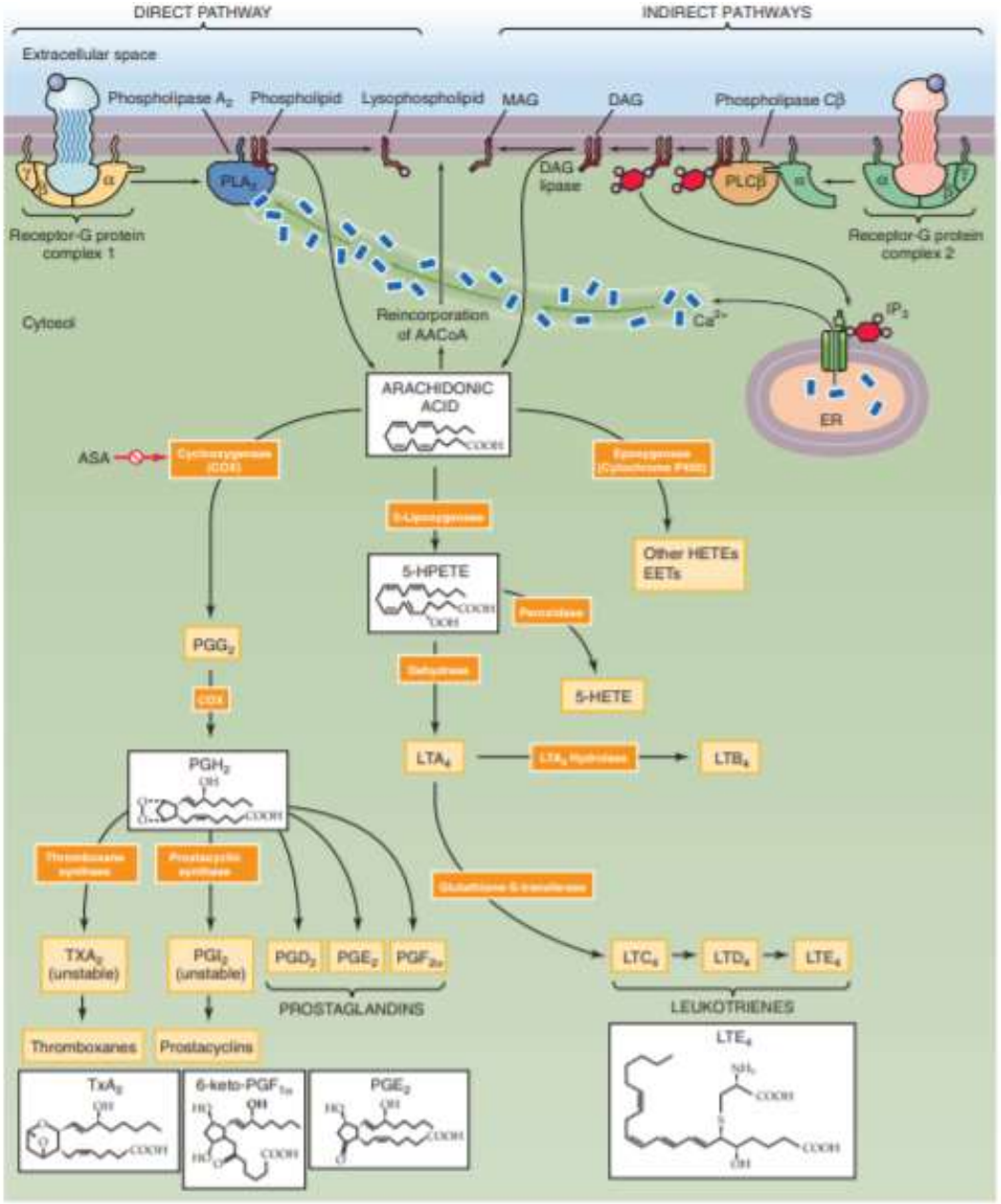


Figure 4 | **Application of the Ca^{2+} signalling toolkit to regulate different cellular processes. a** | In skeletal muscle, an L-type Ca^{2+} channel (α_{1S}) senses membrane depolarization (ΔV) and undergoes a conformational change that is transmitted to the ryanodine receptor 1 (RYR1) **(FIG. 3b)**. Ca^{2+} released from the sarcoplasmic reticulum (SR) interacts with two sensors, troponin C (TnC), which triggers contraction, and calmodulin (CAM), which activates glycogen metabolism to synthesize ATP. **b** | Neurons have several Ca^{2+}-sensitive processes located in different regions. Membrane depolarization (ΔV) is sensed by N- or P/Q-type channels at the synaptic endings to produce a localized pulse of Ca^{2+} that triggers exocytosis. In the cell body and dendrites, L-type channels sense the same depolarization and induce the entry of Ca^{2+} which has a number of targets: adenylyl cyclase I or III (AC I/III) leading to cyclic AMP production, proline-rich tyrosine kinase (PYK2), mitogen-activated protein kinase (MAPK), Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII) and calmodulin–calcineurin (CAM–CN). Some of these targets induce gene transcription. The neurotransmitter glutamate can also generate Ca^{2+} signals either by activating receptor-operated channels such as NMDA (*N*-methyl-D-aspartate) receptors, or by stimulating the metabotropic glutamate receptor $mGluR_1$ to produce inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$) to mobilize internal Ca^{2+} from the endoplasmic reticulum (ER). These glutamate-induced Ca^{2+} signals are localized to synaptic endings, where they contribute to processes such as long-term potentiation (LTP) and long-term depression (LTD), which have been implicated in learning and memory. **c** | The exocrine pancreas uses two signalling systems regulated by separate receptors. Acetylcholine uses $Ins(1,4,5)P_3$ to release internal Ca^{2+}. As well as stimulating $Ins(1,4,5)P_3$ formation, cholycystokinin also acts through both cyclic ADP ribose (cADPR) and nicotinic acid dinucleotide phosphate (NAADP). The latter seems to act by releasing a small amount of trigger Ca^{2+} through the NAADP receptor (NR) that then acts together with cADPR to release further Ca^{2+} through RYRs.

Metabolites of arachnidonic acid

AA signaling pathways. In the direct pathway, an agonist binds to a receptor that activates PLA2, which releases AA from a membrane phospholipid (see Fig. 3-10). In one of three indirect pathways, an agonist binds to a different receptor that activates PLC and thereby leads to the formation of DAG and IP3, as in Figure 3-8; DAG lipase then releases the AA from DAG. In a second indirect pathway, the IP3 releases Ca2+ from internal stores, which leads to the activation of PLA2 (see the direct pathway). In a third indirect pathway (not shown), mitogen-activated protein kinase stimulates PLA2. Regardless of its source, the AA may follow any of three pathways to form a wide array of eicosanoids. The cyclooxygenase pathway produces thromboxanes, prostacyclins, and prostaglandins. The 5-lipoxygenase pathway produces 5-HETE and the leukotrienes. The epoxygenase pathway leads to the production of other HETEs and EETs. ASA, acetylsalicylic acid; EET, cis-epoxyeicosatrienoic acid; ER, endoplasmic reticulum; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; MAG, monoacylglycerol.



Receptors that are catalytic

- Receptor guanylyl cyclases
- Receptor serine/threonine kinases
- Receptor tyrosine kinases
- Tyrosine kinase–associated receptors
- Receptor tyrosine phosphatases

Receptors that are catalytic

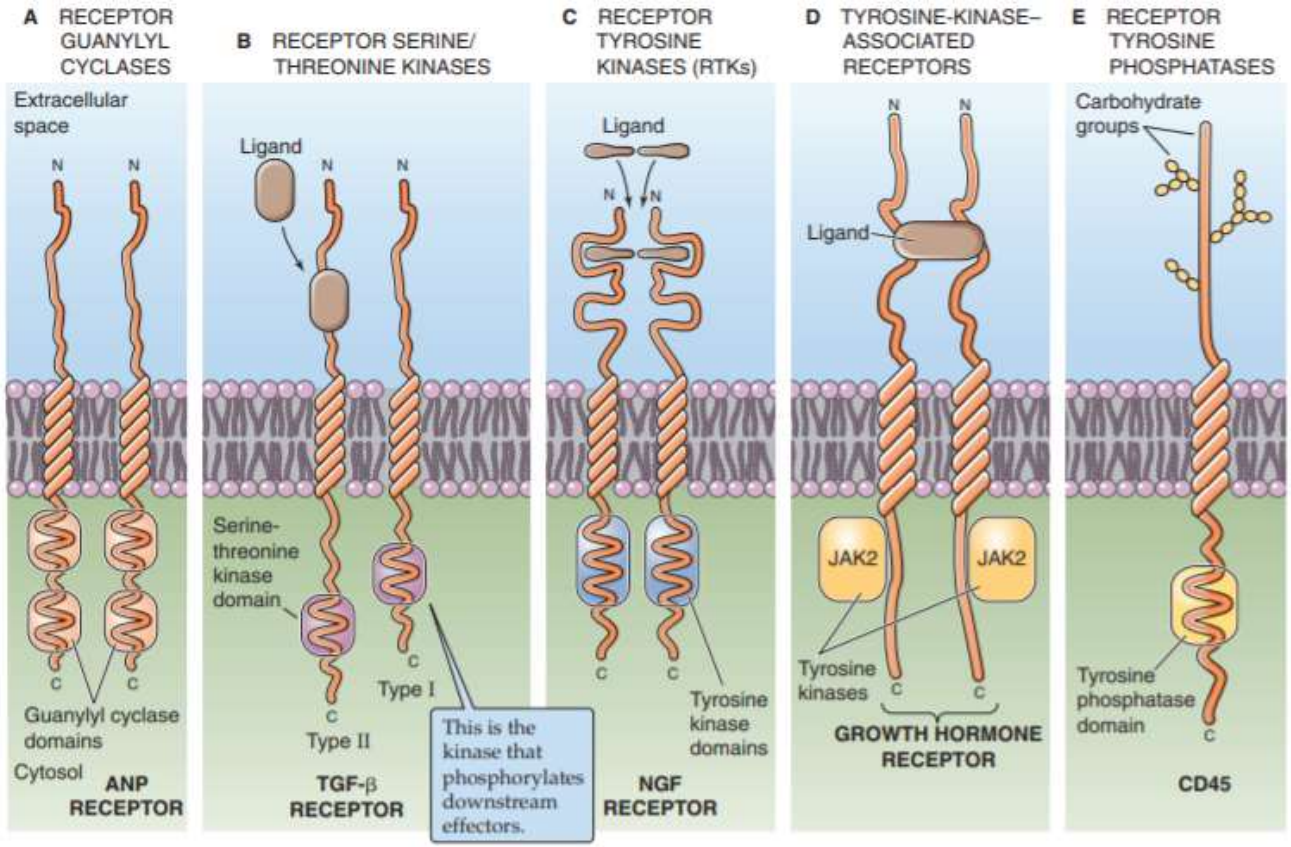


Figure 3-12 Catalytic receptors. **A,** Receptor guanylyl cyclases have an extracellular ligand-binding domain. **B,** Receptor serine/threonine kinases have two subunits. The ligand binds only to the type II subunit. **C,** Receptor tyrosine kinases (RTKs) similar to the NGF receptor dimerize on binding a ligand. **D,** Tyrosine kinase–associated receptors have *no* intrinsic enzyme activity but associate noncovalently with soluble, non-receptor tyrosine kinases. **E,** Receptor tyrosine phosphatases have intrinsic tyrosine phosphatase activity. ANP, atrial natriuretic peptide; JAK, Janus kinase (originally "just another kinase"); NGF, nerve growth factor; TGF-β, transforming growth factor β.

Receptors that are catalytic

- The receptor guanylyl cyclase transduces the activity of atrial natriuretic peptide, whereas a soluble guanylyl cyclase transduces the activity of nitric oxide
- Receptor tyrosine kinases produce phosphotyrosine motifs recognized by SH domains of downstream effectors
- Tyrosine kinase–associated receptors activate loosely associated tyrosine kinases such as Src and JAK
- Receptor tyrosine phosphatases are required for lymphocyte activation

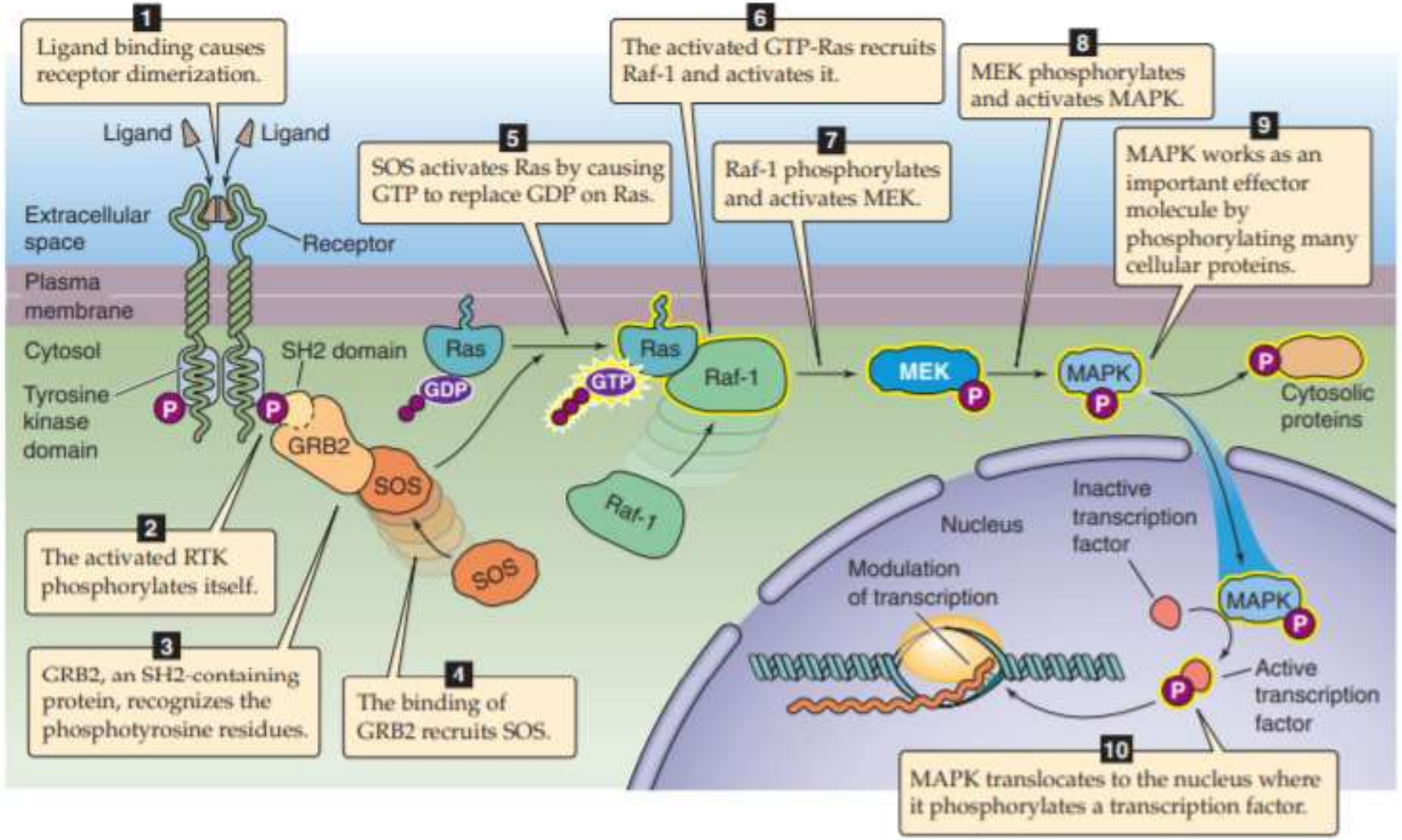


Figure 3-13 Regulation of transcription by the Ras pathway. A ligand, such as a growth factor, binds to a specific RTK, leading to an increase in gene transcription in a 10-step process.

Nuclear receptors

- Steroid and thyroid hormones enter the cell and bind to members of the nuclear receptor superfamily in the cytoplasm or nucleus

Receptor	Full Name	Dimeric Arrangement
GR	Glucocorticoid receptor	GR/GR
MR	Mineralocorticoid receptor	MR/MR
PR	Progesterone receptor	PR/PR
ER	Estrogen receptor	ER/ER
AR	Androgen receptor	AR/AR
VDR	Vitamin D receptor	VDR/RXR
TR	Thyroid hormone receptor	TR/RXR
RAR	Retinoic acid receptor	RAR/RXR
SXR	Steroid and xenobiotic receptor	SXR/RXR
CAR	Constitutive androstane receptor	CAR/RXR

Nuclear receptors

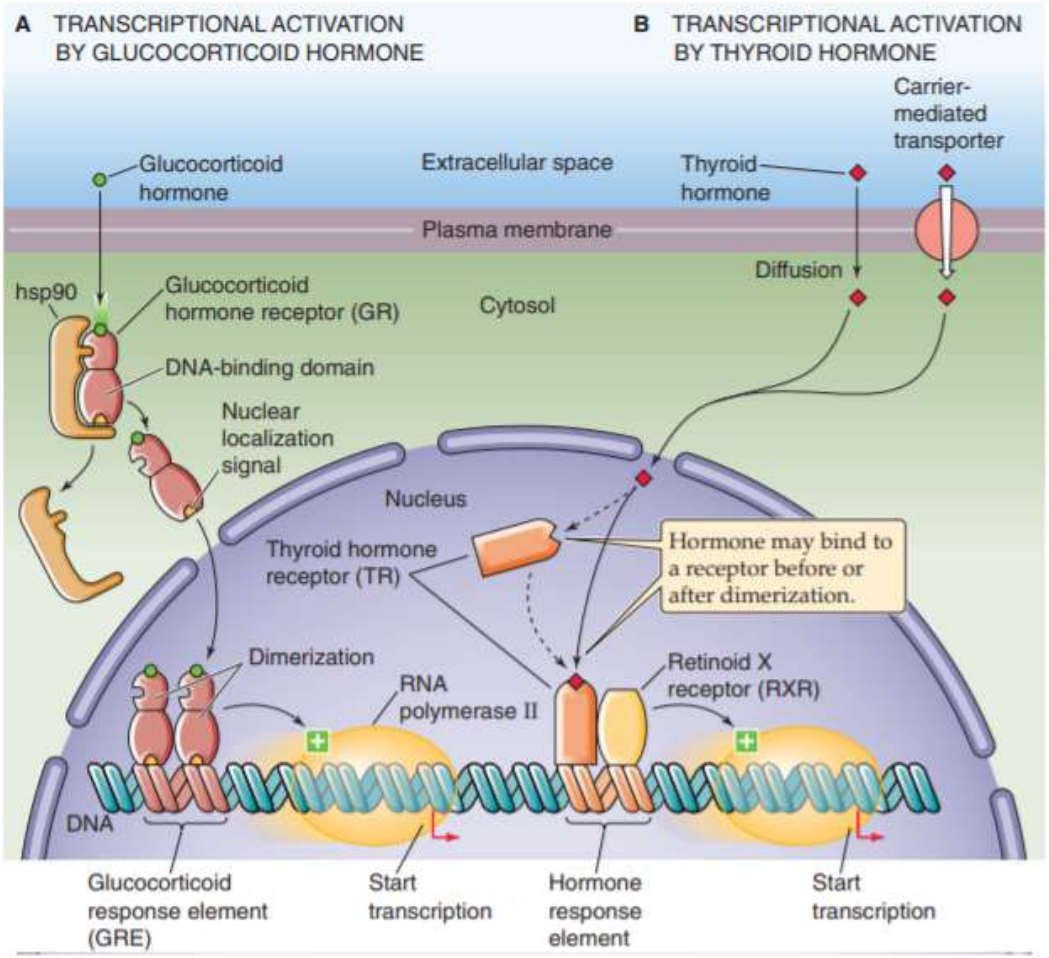


Figure 4-16 Transcriptional activation by glucocorticoid and thyroid hormones. **A,** The binding of a glucocorticoid hormone to a cytoplasmic receptor causes the receptor to dissociate from the chaperone hsp90 (90-kDa heat shock protein). The free hormone-receptor complex can then translocate to the nucleus, where dimerization leads to transactivation. **B,** The binding of thyroid hormone to a receptor in the nucleus leads to transactivation. The active transcription factor is a heterodimer of the thyroid hormone receptor and the retinoid X receptor.

Transport of solutes and water

- Total body water is the sum of the intracellular and extracellular fluid volumes

	Men	Typical Volume (liters)	Women	Typical Volume (liters)
Total body water (TBW)	60% of body weight	42	50% of body weight	35
Intracellular fluid (ICF)	60% of TBW	25	60% of TBW	21
Extracellular fluid (ECF)	40% of TBW	17	40% of TBW	14
Interstitial fluid	75% of ECF	13	75% of ECF	10
Plasma volume (PV)	20% of ECF	3	20% of ECF	3
Blood volume (BV)	PV/(1 – Hct)	5.5	PV/(1 – Hct)	5
Transcellular fluid	5% of ECF	1	5% of ECF	1

Total body water

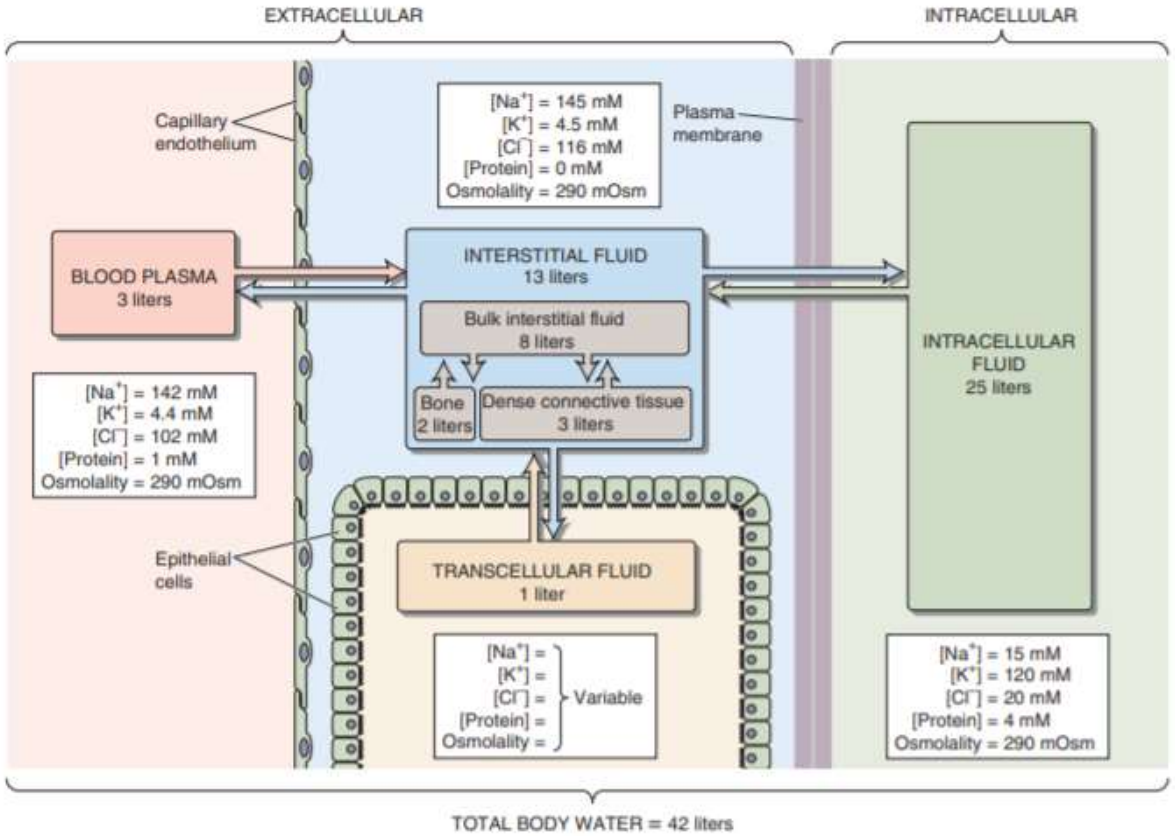


Figure 5-1 The fluid compartments of a prototypic adult human weighing 70 kg. Total body water is divided into four major compartments: intracellular fluid *(green)*, interstitial fluid *(blue)*, blood plasma *(red)*, and transcellular water such as synovial fluid *(tan)*. Color codes for each of these compartments are maintained throughout this book.

Total body water

Intracellular fluid is rich in K+, whereas the extracellular fluid is rich in Na+ and Cl

Table 5-2 Approximate Solute Composition of Key Fluid Compartments

Solute	Plasma	Protein-Free Plasma	Interstitium	Cell
Na^+ (mM)	142	153	145	15
K^+ (mM)	4.4	4.7	4.5	120
Ca^{2+} (mM)	1.2 (ionized) 2.4 (total)*	1.3 (ionized)	1.2 (ionized)	0.0001 (ionized)
Mg^{2+} (mM)	0.6 (ionized) 0.9 (total)*	0.6 (ionized)	0.55 (ionized)	1 (ionized) 18 (total)
Cl^- (mM)	102	110	116	20
HCO_3^- (mM)	22†	24	25	16
$H_2PO_4^-$ and HPO_4^{2-} (mM)	0.7 (ionized) 1.4 (total)‡	0.75 (ionized)	0.8 (ionized)	0.7 (free)
Proteins	7 g/dL 1 mmol/L 14 mEq/L	—	1 g/dL	30 g/dL
Glucose (mM)	5.5	5.9	5.9	Very low
pH	7.4	7.4	7.4	~7.2
Osmolality (mosmole/kg H_2O)	291	290	290	290

*Total includes amounts ionized, complexed to small solutes, and protein bound.
†Arterial value. The value in mixed-venous blood would be ~24 mM.
‡As discussed in Chapter 52, levels of total plasma inorganic phosphate are not tightly regulated and vary between 0.8 and 1.5 mM.

All body fluids have approximately the same osmolality, and each fluid has equal numbers of positive and negative charges

- Osmolality
- Bulk elektronegativity
  - the number of positive charges in the overall solution must be the same as the number of negative charges

$$\text{Anion gap}_{\text{plasma}} = [Na^+]_{\text{plasma}} - ([Cl^-]_{\text{plasma}} + [HCO_3^-]_{\text{plasma}})$$

Solute transport across cell membranes

- In passive, noncoupled transport across a permeable membrane, a solute moves down its electrochemical gradient
- At equilibrium, the chemical and electrical potential energy differences across the membrane are equal but opposite
- In simple diffusion, the fl ux of an uncharged substance through membrane lipid is directly proportional to its concentration difference

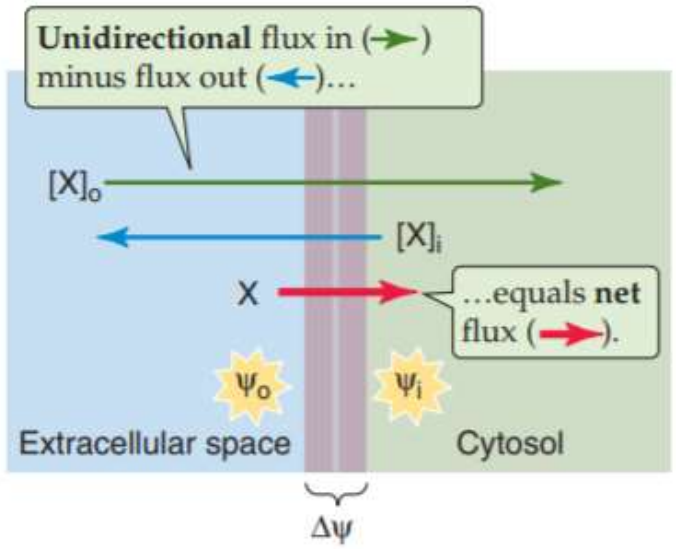


Figure 5-2 Uncoupled transport of a solute across a cell membrane. The net passive movement of a solute (X) depends on both the difference in concentration between the inside of the cell ($[X]_i$) and the outside of the cell ($[X]_o$) and the difference in voltage between the inside of the cell (Ψ_i) and the outside of the cell (Ψ_o).

Solute transport across cell membranes

Table 5-3 Net Electrochemical Driving Forces Acting on Ions in a Typical Cell*

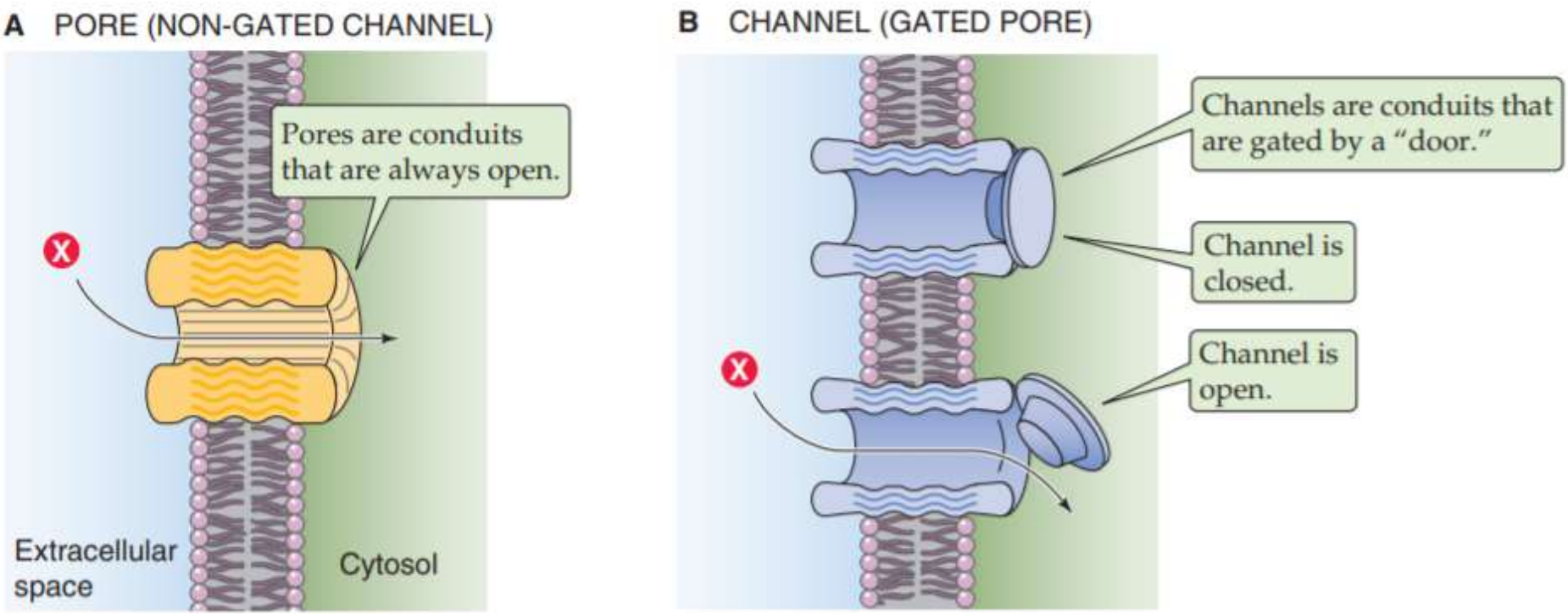
Extracellular Concentration $[X]_o$	Intracellular Concentration $[X]_i$	Membrane Voltage V_m	Equilibrium Potential (mV) $E_x = -(RT/zF) \ln ([X]_i/[X]_o)$	Electrochemical Driving Force $(V_m - E_x)$
Na^+ 145 mM	15 mM	–60 mV	+61 mV	–121 mV
K^+ 4.5 mM	120 mM	–60 mV	–88 mV	+28 mV
Ca^{2+} 1.2 mM	10^{-7} M	–60 mV	+125 mV	–185 mV
Cl^- 116 mM	20 mM	–60 mV	–47 mV	–13 mV
HCO_3^- 25 mM	16 mM	–60 mV	–12 mV	–48 mV
H^+ 40 nM pH 7.4	63 nM 7.2	–60 mV	–12 mV	–48 mV

*Calculated at 37°C using -RT/zF = -26.71 mV.

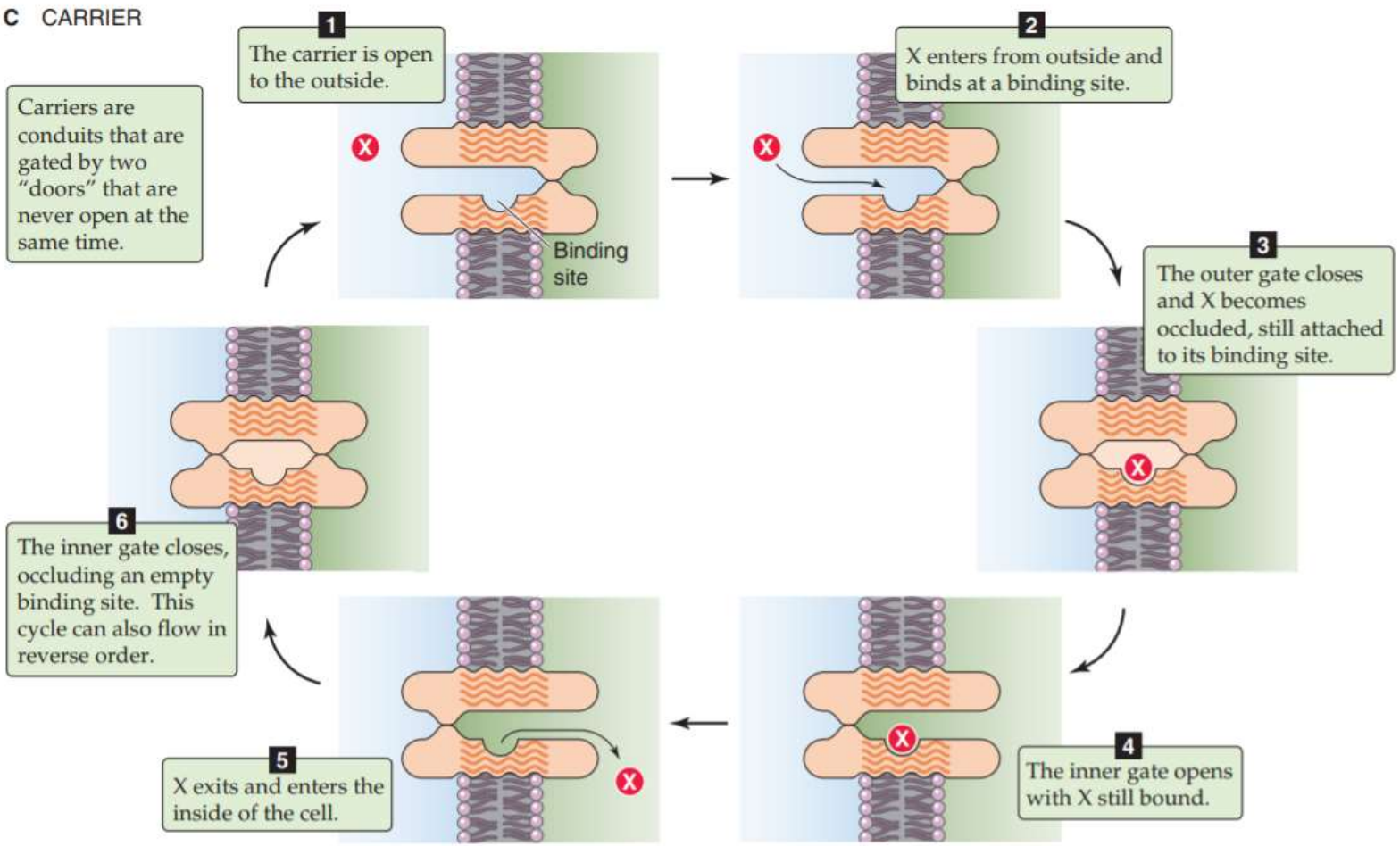
Solute transport across cell membranes

- Some substances cross the membrane passively through intrinsic membrane proteins that can form
  - pores
  - channels
  - carriers
- Water-fi lled pores can allow molecules, some as large as 45 kDa, to cross membranes passively
- Gated channels, which alternately open and close, allow ions to cross the membrane passively

Solute transport across cell membranes



Solute transport across cell membranes



Solute transport across cell membranes

- **Na+ channels** - because the electrochemical driving force for Na+ (Vm − ENa) is always strongly negative (Table 5-3), a large, inwardly directed net driving force or gradient favors the passive movement of Na+ into virtually every cell of the body

- **K+ channels** - the electrochemical driving force for K+ (Vm − EK) is usually fairly close to zero or somewhat positive (Table 5-3), so K+ is either at equilibrium or tends to move out of the cell

- **Ca2+ channels** - the electrochemical driving force for Ca2+ (Vm − ECa) is always strongly negative (Table 5-3), so Ca2+ tends to move into the cell

- **Anion channels - m**ost cells contain one or more types of anion-selective channels through which the passive, noncoupled transport of Cl− —and, to a lesser extent, HCO3 − —can take place. The electrochemical driving force for Cl− (Vm − ECl) in most cells is modestly negative (Table 5-3), so Cl− tends to move out of these cells

Solute transport across cell membranes

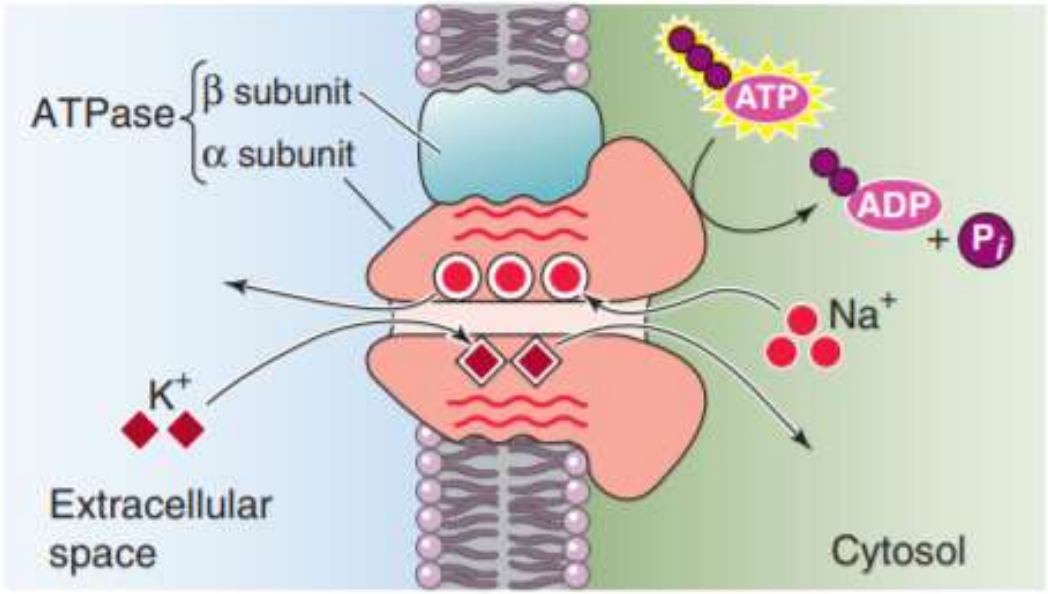
Table 5-5 Comparison of Properties of Pores, Channels, and Carriers

	Pores	Channels	Carriers
Example	Water channel (AQP1)	Shaker K^+ channel	Glucose transporter (GLUT1)
Conduit through membrane	Always open	Intermittently open	Never open
Unitary event	None (continuously open)	Opening	Cycle of conformational changes
Particles translocated per "event"	—	6×10^{4}*	1-5
Particles translocated per second	up to 2×10^{9}	10^{6} to 10^{8} when open	200-50,000

*Assuming a 100-pS channel, a driving force of 100 mV, and an opening time of 1 ms.

Solute transport across cell membranes

- The Na-K pump, the most important primary active transporter in animal cells, uses the energy of ATP to extrude Na+ and to take up K+



Solute transport across cell membranes

Besides the Na-K pump, other P-type ATPases include the H-K and Ca2+ pumps

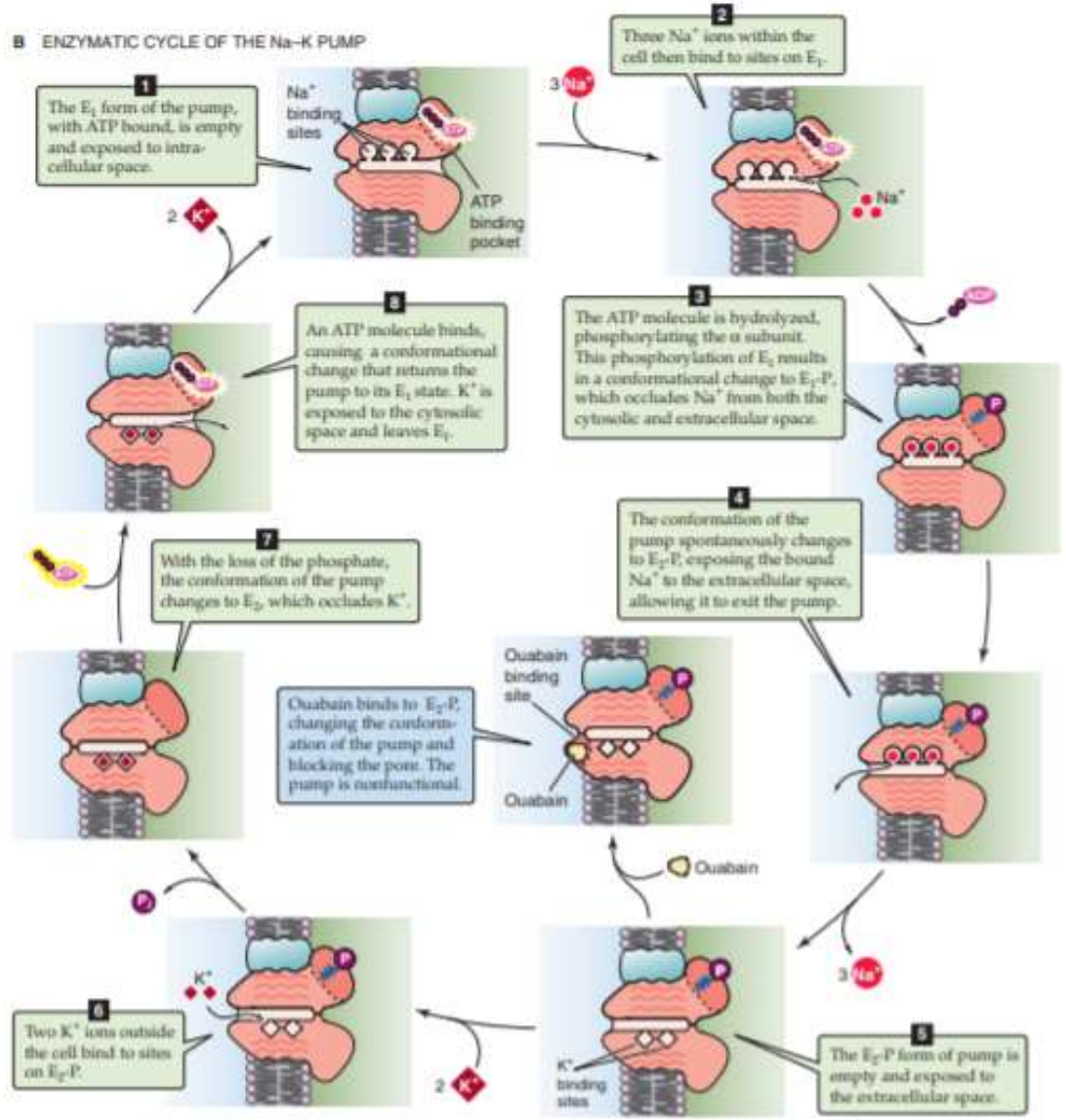


Figure 5-8 Model of the sodium pump. **A,** Schematic representation of the α and β subunits of the pump. **B,** The protein cycles through at least eight identifiable stages as it moves 3 Na^+ ions out of the cell and 2 K^+ ions into the cell.

ATP-binding cassette (ABC) transporters can act as pumps, channels, or regulators

Table 5-6 ABC Transporters

Subfamily*	Alternative Subfamily Name	Examples
ABCA (12)	ABC1	ABCA1 (cholesterol transporter)
ABCB (11)	MDR (multidrug resistance)	ABCB1 (MDR1 or P-glycoprotein 1) ABCB4 (MDR2/3) ABCB11 (bile salt export pump, BSEP)
ABCC (13)	MRP/CFTR	ABCC2 (multidrug resistance–associated protein 2, MRP2) ABCC7 (cystic fibrosis transmembrane regulator, CFTR) ABCC8 (sulfonylurea receptor, SUR1) ABCC9 (SUR2)
ABCD (4)	ALD	ABCD1 (ALD, mediates uptake of fatty acids by peroxisomes)
ABCE (1)	OABP	ABCE1 (RNASELI, blocks RNase L)
ABCF (3)	GCN20	ABCF1 (lacks transmembrane domains)
ABCG (5)	White	ABCG2 (transports sulfated steroids) ABCG5/ABCG8 (heterodimer of "half" ABCs that transport cholesterol)

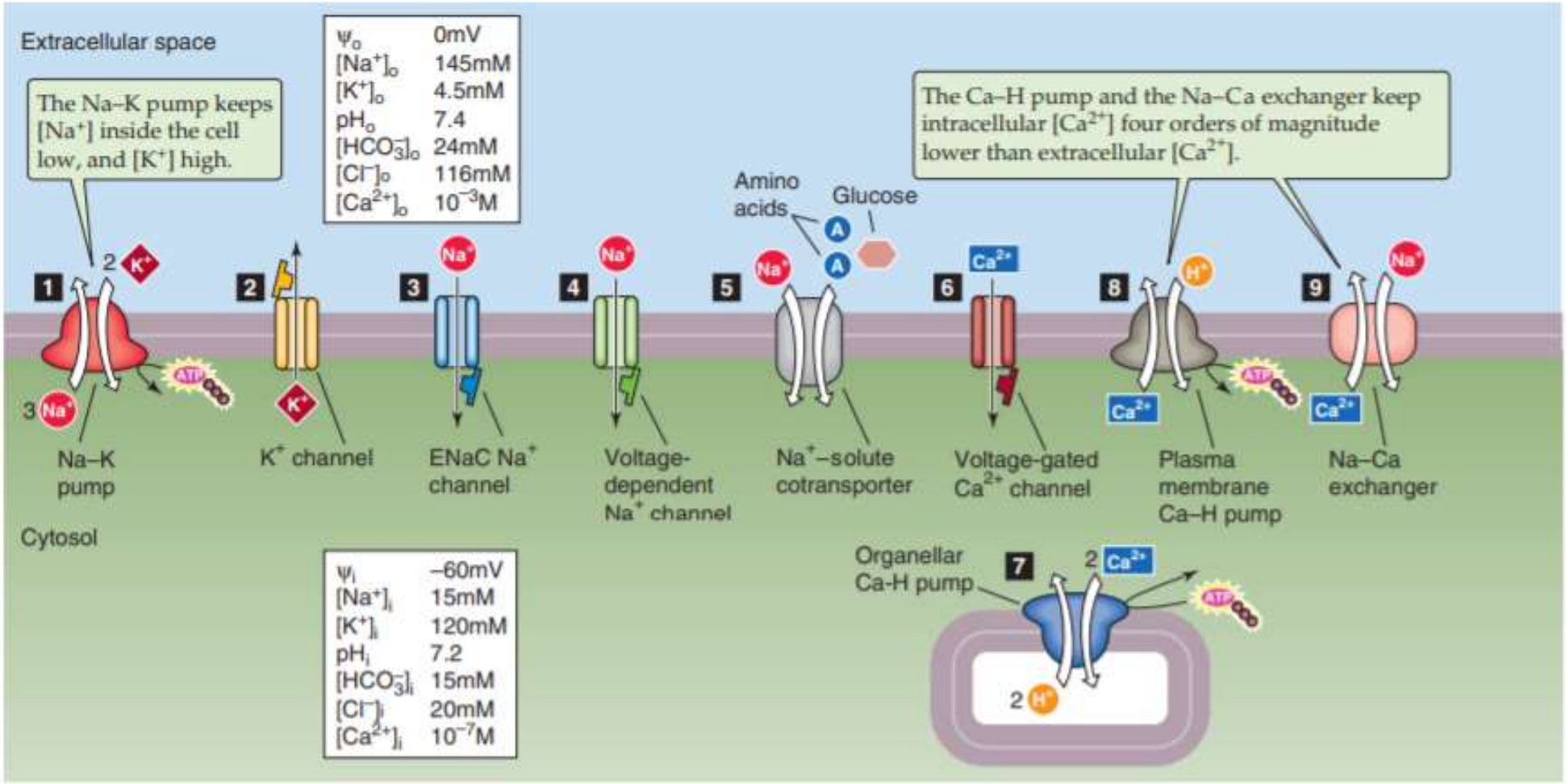
*Number of genes in parentheses.

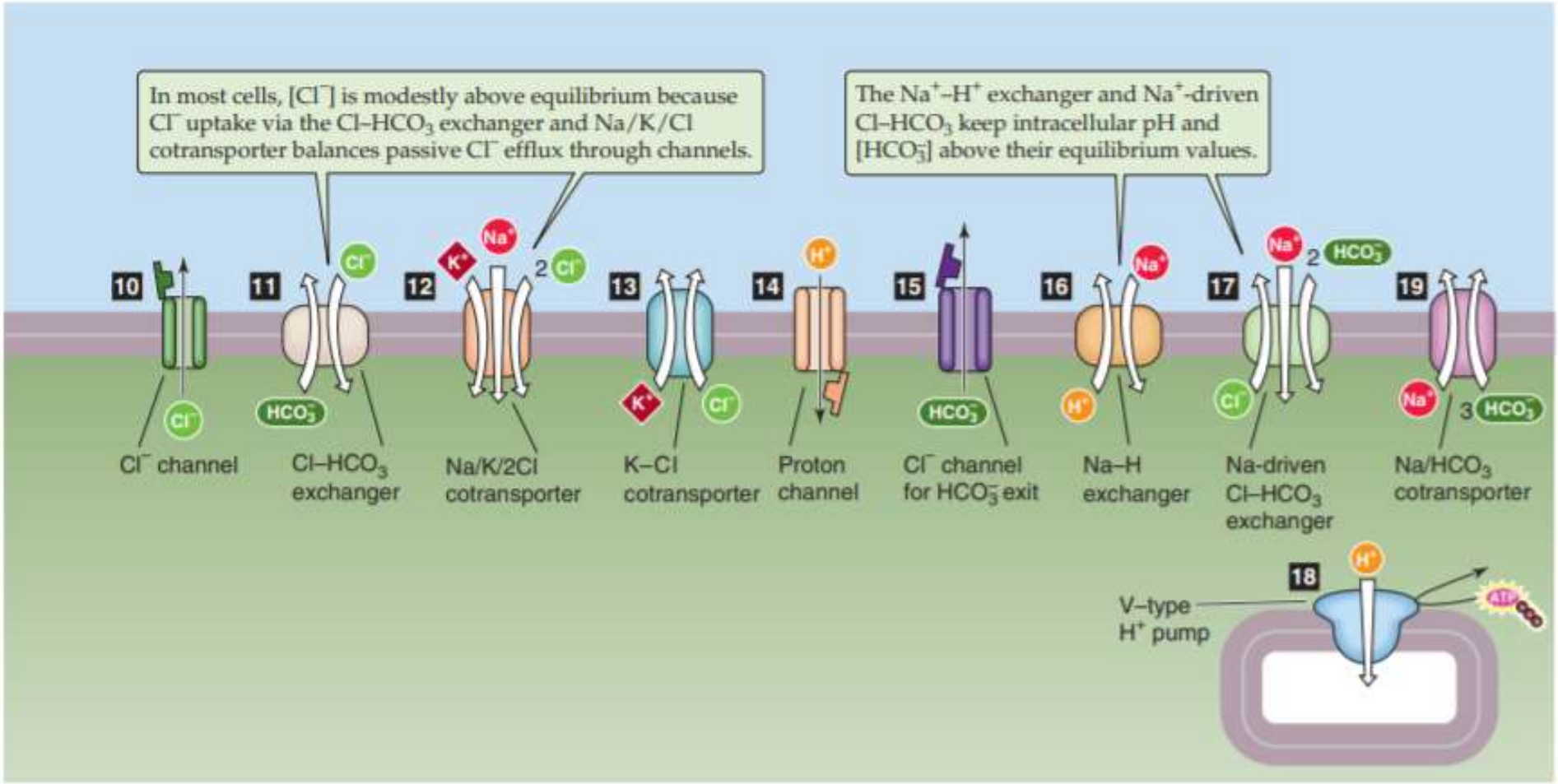
Cotransporters, one class of secondary active transporters, are generally driven by the energy of the inwardly directed Na+ gradient

- Na+ /glucose cotransporter (SGLT)
- Na+-Driven Cotransporters for Organic Solutes
- Na/HCO3 Cotransporters
- Na+-Driven Cotransporters for Other Inorganic Anions
- Na/K/Cl Cotransporter
- Na/Cl Cotransporter
- K/Cl Cotransporter
- H+-Driven Cotransporters

Exchangers, another class of secondary active transporters, exchange ions for one another

- Na-Ca Exchanger
- Na-H Exchanger
- Na+-Driven Cl-HCO3 Exchanger
- Cl-HCO3 Exchanger
- Other Anion Exchangers


Extracellular space
The Na–K pump keeps [Na+] inside the cell low, and [K+] high.
ψo 0mV
[Na+]o 145mM
[K+]o 4.5mM
pHo 7.4
[HCO3−]o 24mM
[Cl−]o 116mM
[Ca2+]o 10−3M
The Ca–H pump and the Na–Ca exchanger keep intracellular [Ca2+] four orders of magnitude lower than extracellular [Ca2+].
Amino acids
Glucose
1
2
3
4
5
6
7
8
9
Na–K pump
K+ channel
ENaC Na+ channel
Voltage-dependent Na+ channel
Na+–solute cotransporter
Voltage-gated Ca2+ channel
Plasma membrane Ca–H pump
Na–Ca exchanger
Organellar Ca-H pump
Cytosol
ψi −60mV
[Na+]i 15mM
[K+]i 120mM
pHi 7.2
[HCO3−]i 15mM
[Cl−]i 20mM
[Ca2+]i 10−7M


In most cells, [Cl⁻] is modestly above equilibrium because Cl⁻ uptake via the Cl–HCO3 exchanger and Na/K/Cl cotransporter balances passive Cl⁻ efflux through channels.
The Na⁺–H⁺ exchanger and Na⁺-driven Cl–HCO3 keep intracellular pH and [HCO3⁻] above their equilibrium values.
10
11
12
13
14
15
16
17
18
19
Cl⁻ channel
Cl–HCO3 exchanger
Na/K/2Cl cotransporter
K–Cl cotransporter
Proton channel
Cl⁻ channel for HCO3⁻ exit
Na–H exchanger
Na-driven Cl–HCO3 exchanger
Na/HCO3 cotransporter
V–type H⁺ pump
Cl⁻
HCO3⁻
Na⁺
K⁺
H⁺
2
3
ATP

Regulation of intracellular ion concentration

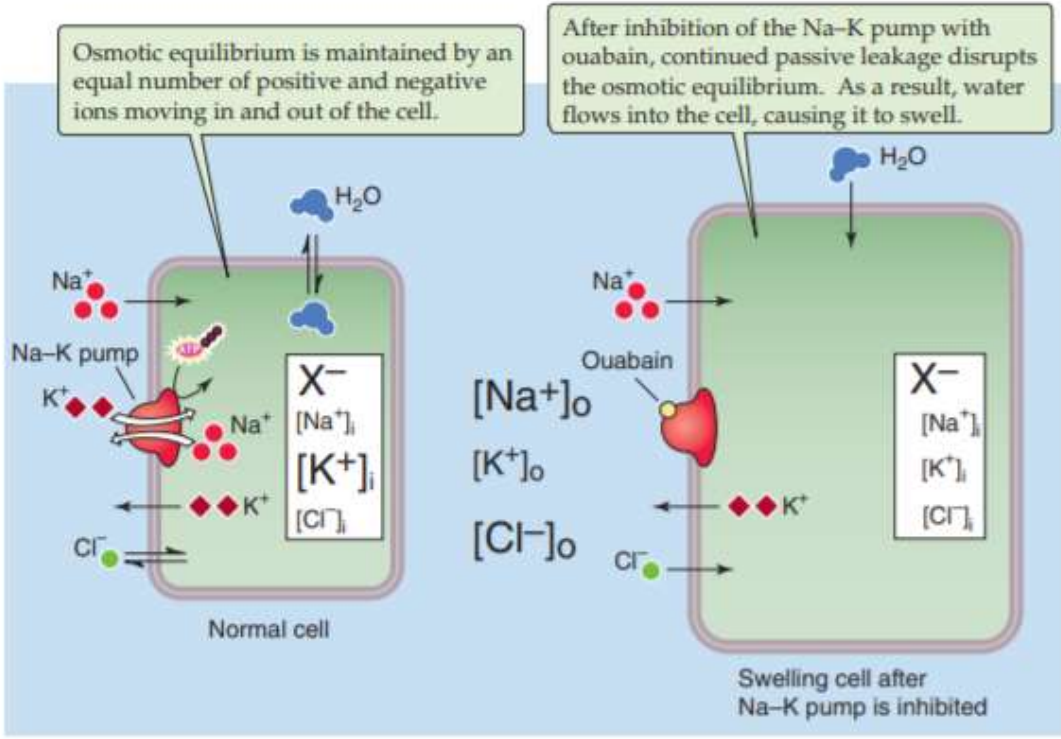
- The Na-K pump keeps [Na+] inside the cell low and [K+] high
- The Ca2+ pump and the Na-Ca exchanger keep intracellular [Ca2+] four orders of magnitude lower than extracellular [Ca2+]
- Ca2+ Pumps (SERCA) in Organelle Membranes
- Ca2+ Pump (PMCA) on the Plasma Membrane
- Na-Ca Exchanger (NCX) on the Plasma Membrane

Regulation of intracellular ion concentration

- In most cells, [Cl-] is modestly above equilibrium because Cl- uptake by the Cl-HCO3 exchanger and Na/K/Cl cotransporter balances passive Cl- efflux through channels
- The Na-H exchanger and Na+ -driven HCO3 - transporters keep the intracellular pH and [HCO3 -] above their equilibrium values

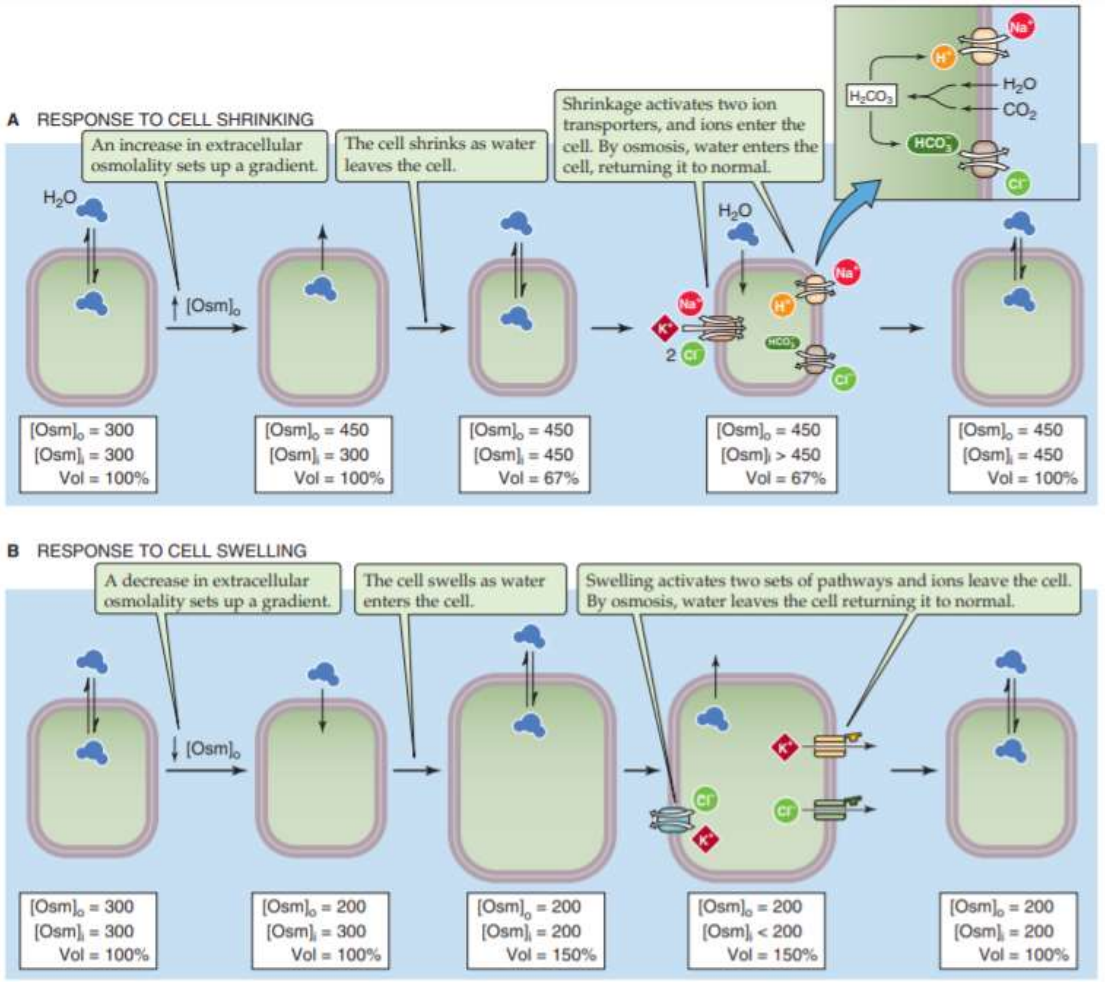
Water transport and cell volume

- Water transport is driven by osmotic and hydrostatic pressure differences across membranes
- The Na-K pump maintains cell volume by doing osmotic work that counteracts the passive Donnan forces



Water transport and cell volume

- Cell volume changes trigger rapid changes in ion channels or transporters, returning volume toward normal



The gradient in tonicity—or effective osmolality— determines the osmotic flow of water across a cell membrane

- Water Exchange Across Cell Membranes

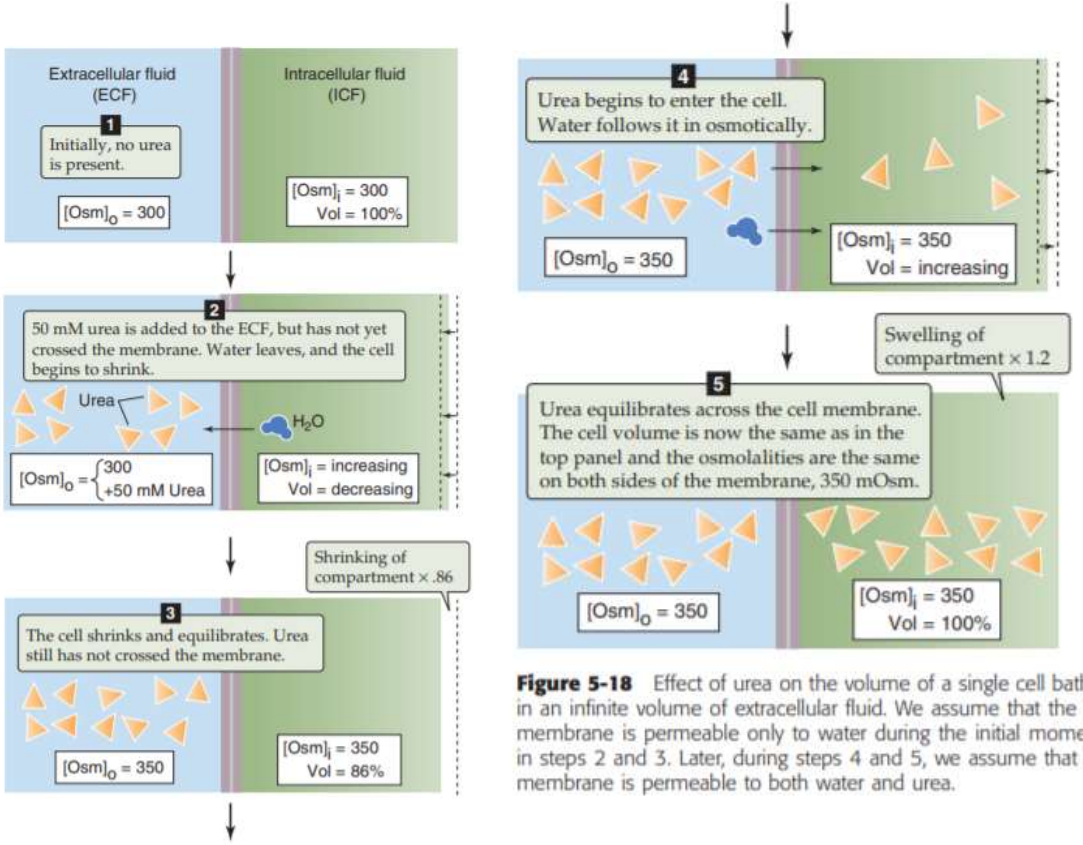


Figure 5-18 Effect of urea on the volume of a single cell bathed in an infinite volume of extracellular fluid. We assume that the cell membrane is permeable only to water during the initial moments in steps 2 and 3. Later, during steps 4 and 5, we assume that the membrane is permeable to both water and urea.

Water Exchange Across the Capillary Wall

- Adding isotonic saline, pure water, or pure NaCl to the ECF will increase ECF volume but will have divergent effects on ICF volume and ECF osmolality

- Infusion of Isotonic Saline
- Infusion of "Solute-Free" Water
- Ingestion of Pure NaCl Salt

- Whole-body Na+ content determines ECF volume, whereas whole-body water content determines osmolality

Transport of solutes and water across epithelia

- The epithelial cell generally has different electrochemical gradients across its apical and basolateral membranes

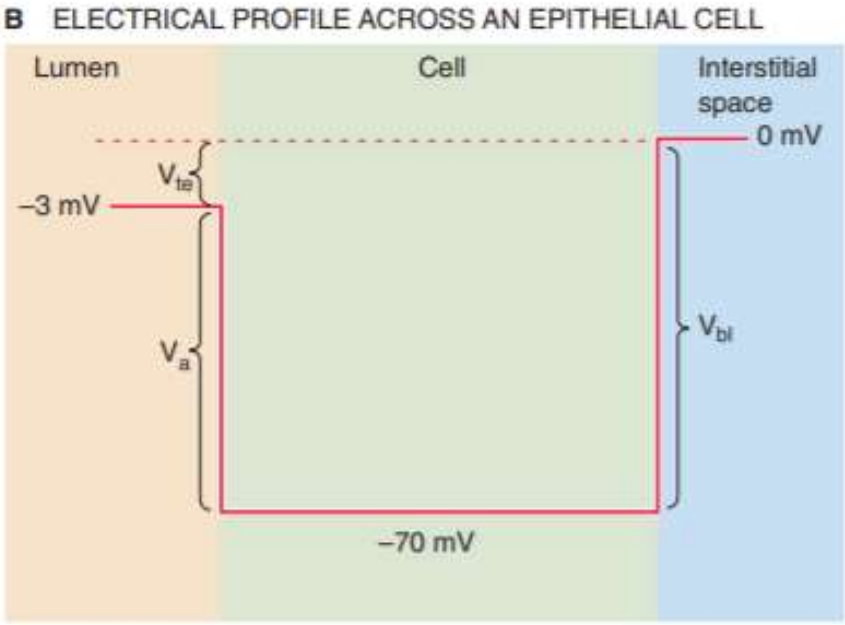
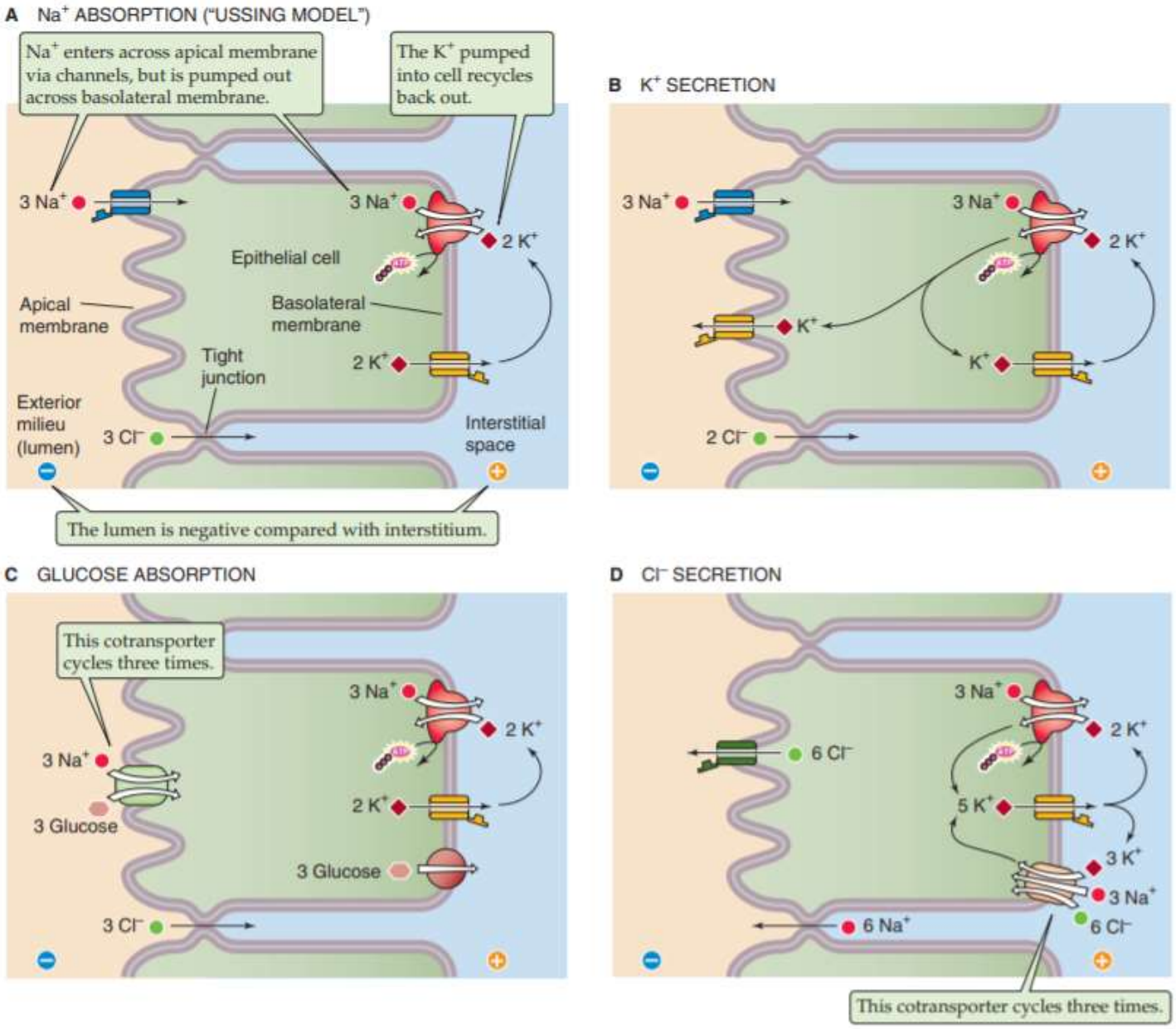


Figure 5-20 Measurement of voltages in an epithelium. **A,** The transepithelial voltage difference between electrodes placed in the lumen and interstitial space (or blood) is V_{te}. The basolateral voltage difference between electrodes placed in the cell and interstitial space is V_{bl}. The apical voltage difference between electrodes placed in the lumen and cell is V_a. **B,** Relative to the reference voltage of zero in the interstitial space, the voltage inside the cell in this example is −70 mV, and the voltage in the lumen is −3 mV. These values are typical of a cell in the renal proximal tubule or a small intestine.

Transport of solutes and water across epithelia

- Epithelial cells can absorb or secrete different solutes by inserting specific channels or transporters at either the apical or basolateral membrane

- Epithelia can regulate transport by controlling transport proteins, tight junctions, and the supply of the transported substances
  - Increased Synthesis (or Degradation) of Transport Proteins
  - Recruitment of Transport Proteins to the Cell Membrane
  - Post-translational Modifi cation of Preexisting Transport Proteins
  - Changes in the Paracellular Pathway
  - Luminal Supply of Transported Species


A Na+ ABSORPTION ("USSING MODEL")
Na+ enters across apical membrane via channels, but is pumped out across basolateral membrane.
The K+ pumped into cell recycles back out.
3 Na+
3 Na+
2 K+
Epithelial cell
Apical membrane
Basolateral membrane
Tight junction
2 K+
Exterior milieu (lumen)
3 Cl−
Interstitial space
The lumen is negative compared with interstitium.
B K+ SECRETION
3 Na+
3 Na+
2 K+
K+
K+
2 Cl−
C GLUCOSE ABSORPTION
This cotransporter cycles three times.
3 Na+
3 Na+
2 K+
3 Na+
2 K+
3 Glucose
3 Glucose
3 Cl−
D Cl− SECRETION
3 Na+
2 K+
6 Cl−
5 K+
3 K+
3 Na+
6 Na+
6 Cl−
This cotransporter cycles three times.

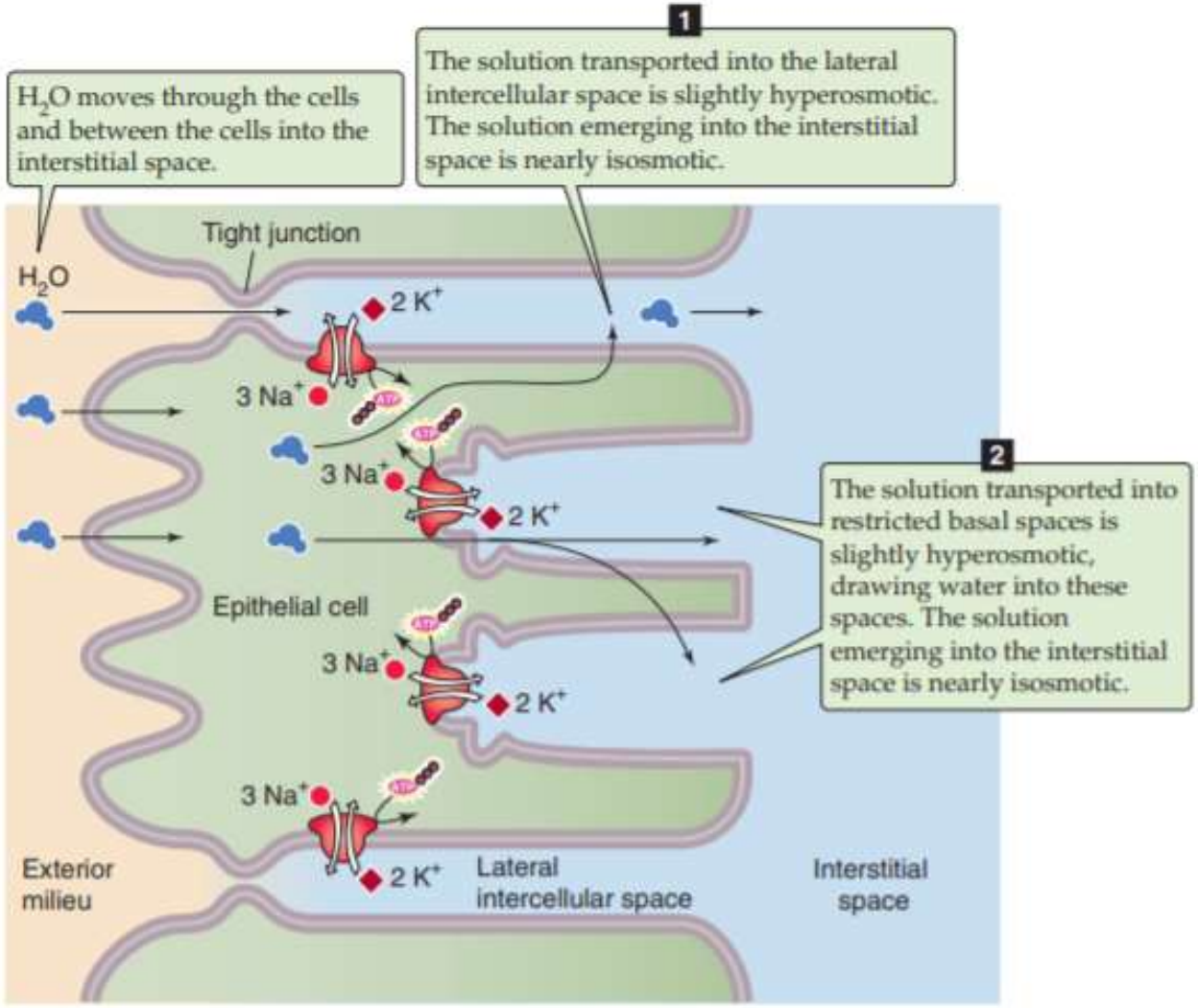


Figure 5-22 Model of isotonic water transport in a leaky epithelium. Na-K pumps present on the lateral and basal membrane pump Na^+ into two restricted spaces: the lateral intercellular space and restricted spaces formed by infoldings of the basal membrane. The locally high osmolality in the lateral intercellular space pulls water from the lumen and the cell. Similarly, the locally high osmolality in the restricted basal spaces pulls water from the cell. The solution that emerges from these two restricted spaces—and enters the interstitial space—is only slightly hypertonic (virtually isotonic) compared with the luminal solution.