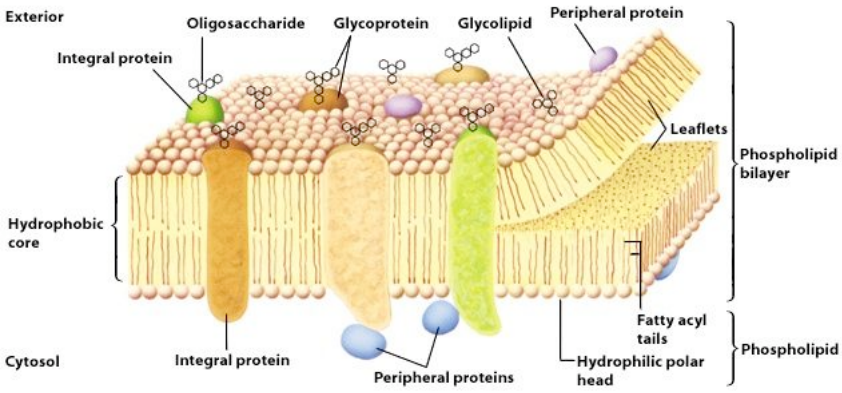
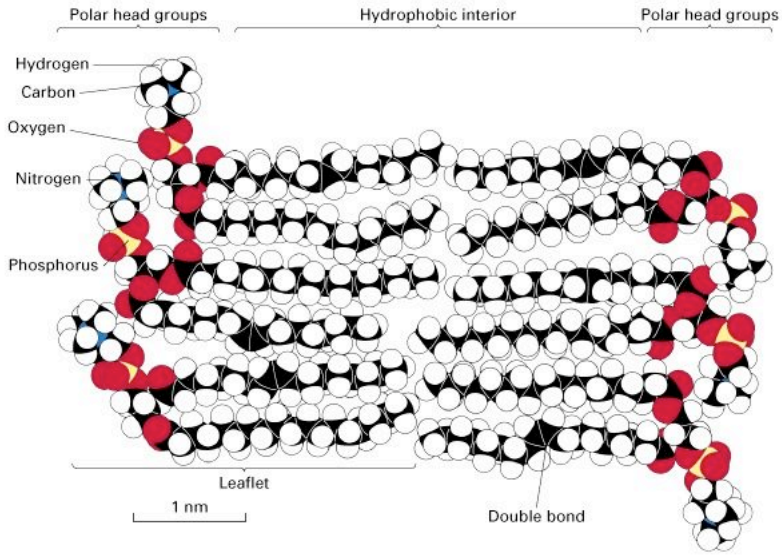
Many important drugs affect cell surface transport proteins

DRUG	TARGET PROTEIN	DISEASE
Omeprazole (Losec)	gastric H^+/K^+ ATPase	ulcers, gastric reflex
oral rehydration therapy	intestinal Na^+ glucose symport	diarrhea caused by cholera and other intestinal pathogens
ouabain and digoxin	cardiac muscle cell Na^+/K^+ ATPase	congestive heart failure
cocaine	norepinephrine, serotonin, and dopamine Na^+ - coupled transporters	
fluoxetine (Prozac) and imipramine	Na^+ - coupled serotonin transporter	depression
tricyclic antidepressant desipramine	Na^+ - coupled norepinephrine transporter	depression
glibenclamide; glimepiride; other sulfonylureas	inhibit ATP- inhibited K^+ channels in beta islet cells; depolarize membrane and enhance insulin secretion	Type II diabetes
furosemide, bumetanide	renal Na^+ resorption; $Na^+/K^+/Cl^-_2$ cotransporter	hypertension
verapamil	inhibits endothelial and cardiac Ca^{2+} channels	cardiac arrhythmia; essential hypertension

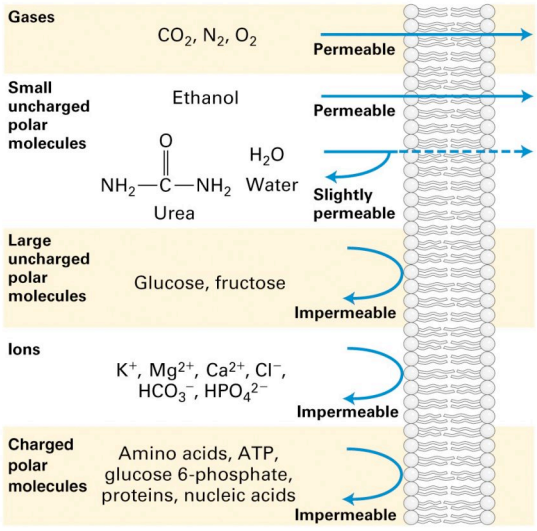
All biological membranes are bilayers of phospholipid.
The proteins in each type of membrane give it its unique properties.



A phospholipid bilayer in cross- section



Pure phospholipid bilayer membranes are impermeable to all proteins and to most small molecules



A variety of plasma membrane proteins allow specific ions and small molecules to enter and leave the cell.

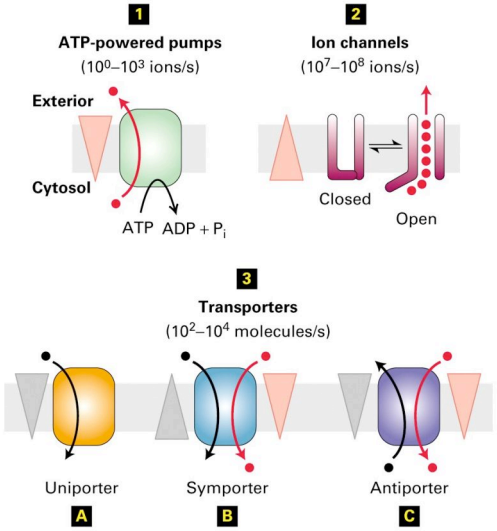
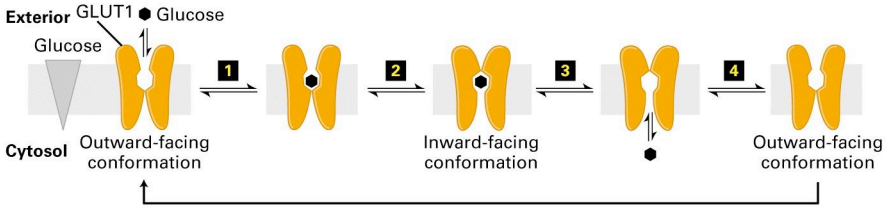


TABLE 7-1 Mechanisms for Transporting Ions and Small Molecules Across Cell Membranes

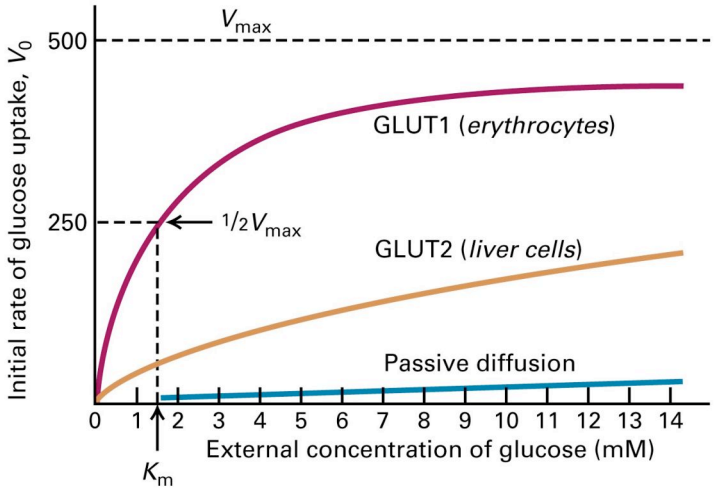
	Transport Mechanism			
Property	**Passive Diffusion**	**Facilitated Diffusion**	**Active Transport**	**Cotransport***
Requires specific protein	–	+	+	+
Solute transported against its gradient	–	–	+	+
Coupled to ATP hydrolysis	–	–	+	–
Driven by movement of a cotransported ion down its gradient	–	–	–	+
Examples of molecules transported	O_2, CO_2, steroid hormones, many drugs	Glucose and amino acids (uniporters); ions and water (channels)	Ions, small hydrophilic molecules, lipids (ATP-powered pumps)	Glucose and amino acids (symporters); various ions and sucrose (antiporters)

*Also called *secondary active transport*.

Glucose transport (Uniport) protein: Catalyzed "downhill" movement of glucose into or out of a cell.



Kinetic analysis of the glucose transport protein Glut1 in human erythrocytes and Glut2 in hepatocytes



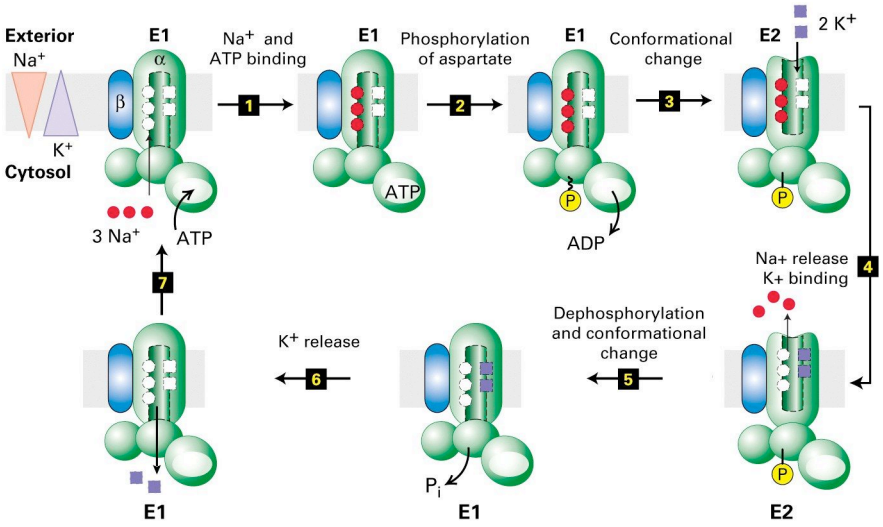
Typical ion concentrations in vertebrates and invertebrates

Concentration of free Ca^{2+} in the cytosol is < 10^{-4} that of the extracellular fluid

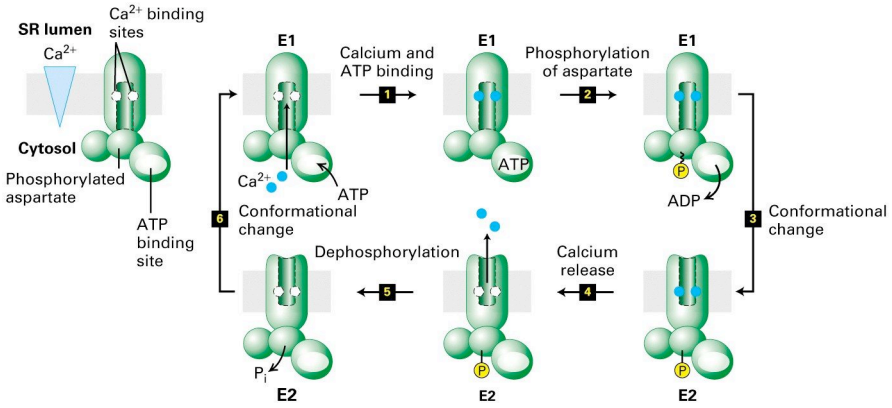
Ion	Cell (mM)	Blood (mM)
SQUID AXON*		
K^+	400	20
Na^+	50	440
Cl^-	40–150	560
Ca^{2+}	0.0003	10
$X^{-\dagger}$	300–400	5–10
MAMMALIAN CELL		
K^+	139	4
Na^+	12	145
Cl^-	4	116
HCO_3^-	12	29
X^-	138	9
Mg^{2+}	0.8	1.5
Ca^{2+}	<0.0002	1.8

**The large nerve axon of the squid, an invertebrate cell, has been widely used in studies of the mechanism of conduction of electric impulses.*
$^{\dagger}X^-$ represents proteins, which have a net negative charge at the neutral pH of blood and cells.

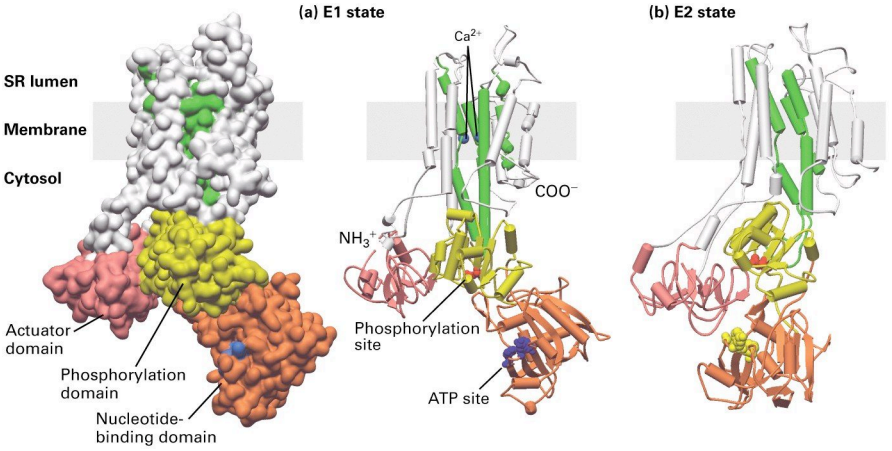
Conformational changes during operation of the ATP- powered Na^+/ K^+ pump



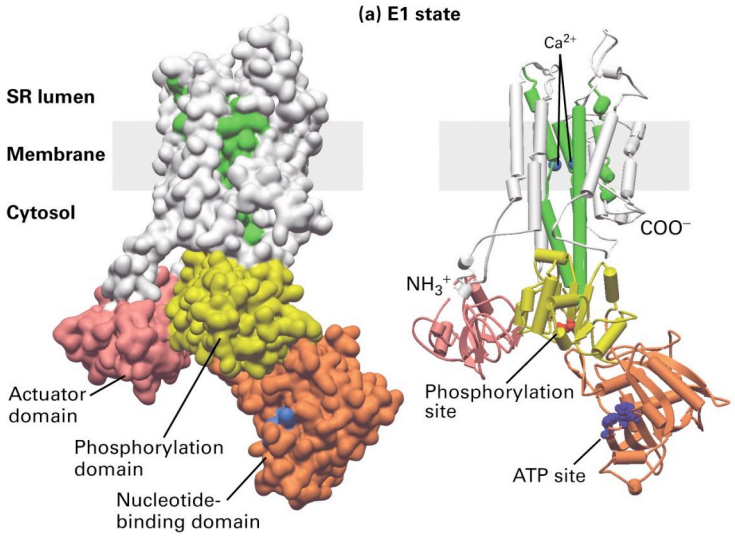
The plasma membrane Ca $^{2+}$ pump, similar in structure and function to the ATP- powered Na^+/ K^+ pump



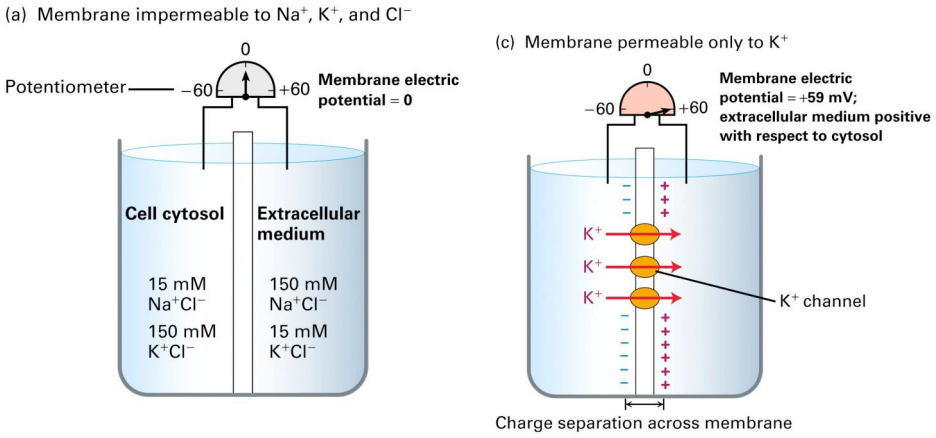
Three- dimensional structure of the sarcoplasmic reticulum Ca^{2+} pump at molecular resolution



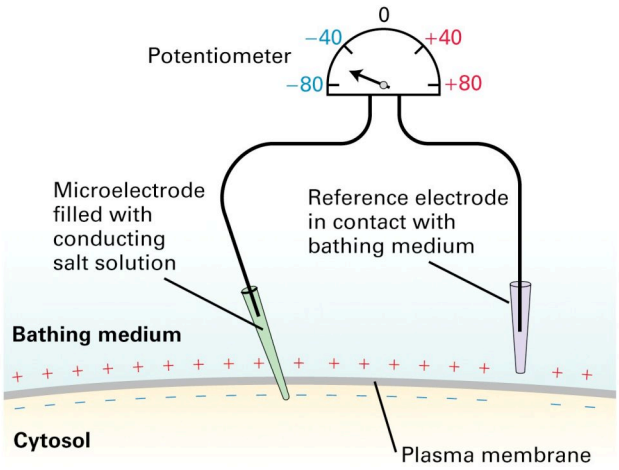
Three- dimensional structure of the sarcoplasmic reticulum Ca^{2+} pump at molecular resolution



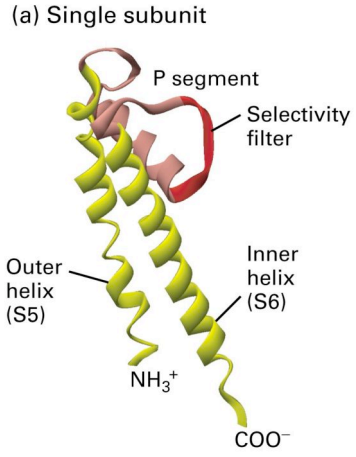
Selective permeability to K^+ ions, but not Na^+ or Cl^- ions, establishes the electric potential, always cytosolic face -, across the plasma membrane



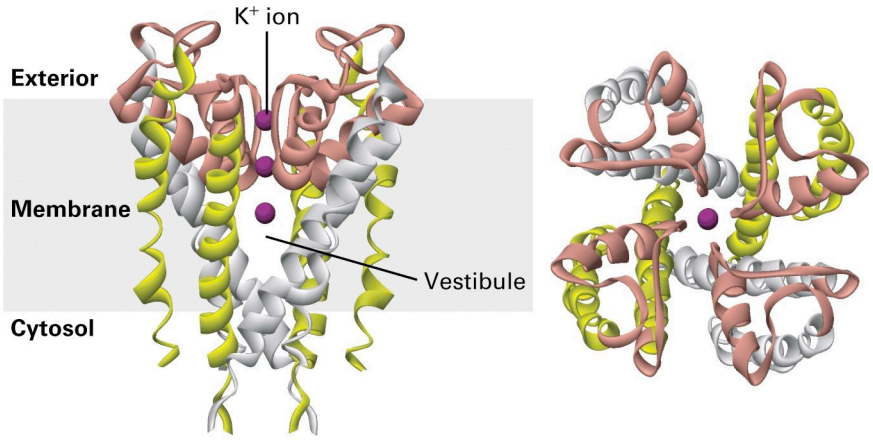
As measured by a microelectrode inserted across the plasma membrane, the resting potential of nerve cells, like most body cells, is about - 70 mV, inside (cytosolic) face negative



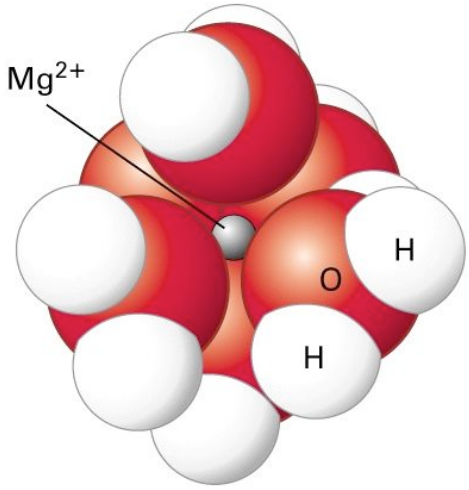
Structure of the pore segment found in the subunits of all K^+, Na^+, and Ca^{2+} channel proteins



Molecular structure of a bacterial K^+ channel protein

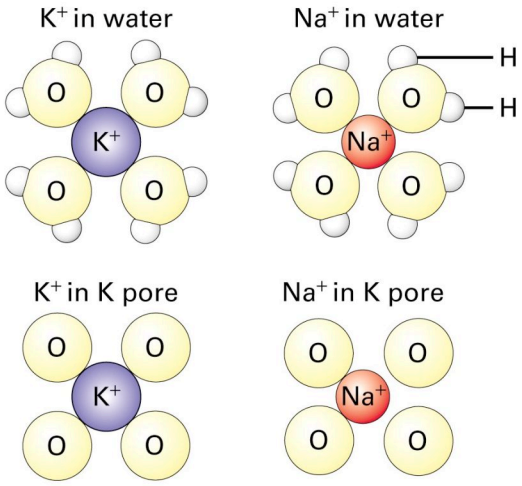


In aqueous solution all ions are surrounded by a shell of water molecules



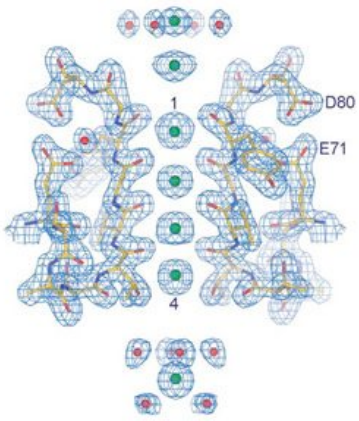
Molecular basis of selectivity of a bacterial K^+ channel protein for K^+ over Na^+.

(a) K^+ and Na^+ ions in the pore of a K^+ channel (top view)

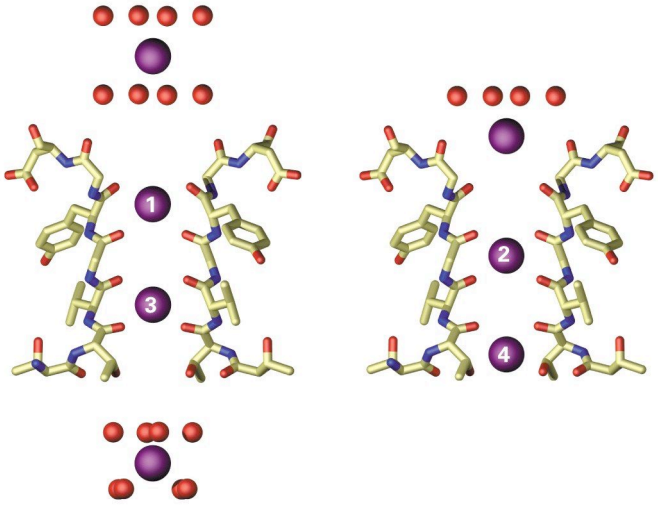


High resolution (0.2 nm) view of K^+ ions moving through a K^+ channel

K+ ions (green spheres) are shown along the ion pathway, and water molecules (red spheres) are in the vicinity.

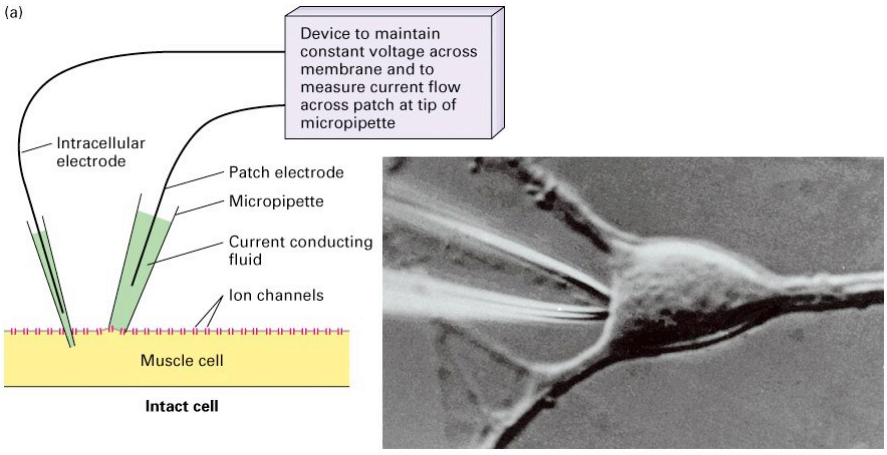


(c) Ion movement through selectivity filter

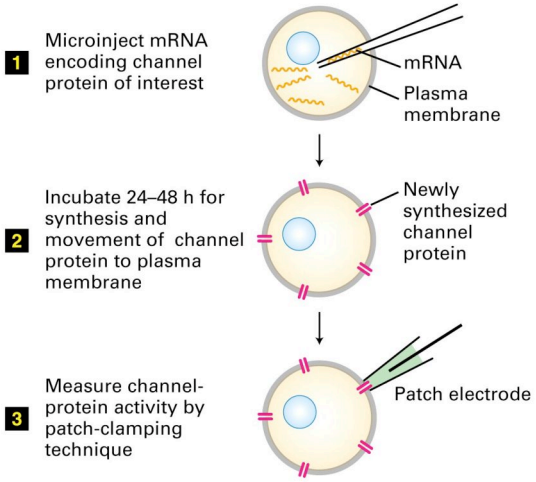


State 1 State 2

The patch- clamp technique for measuring ion movements through single ion channels

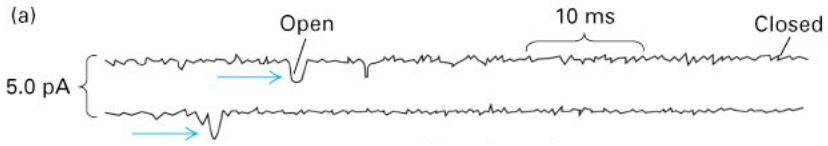


Frog oocyte expressior assay* for study of properties of ion channel proteins



*** A follicular frog oocyte is first treated with collagenase to remove the surrounding follicle cells, leaving a denuded oocyte, which is microinjected with mRNA encoding the channel protein under study.**

Ion movements, measured by flux of electric current, through individual Na^+ channels using patch clamping of cultured muscle cells

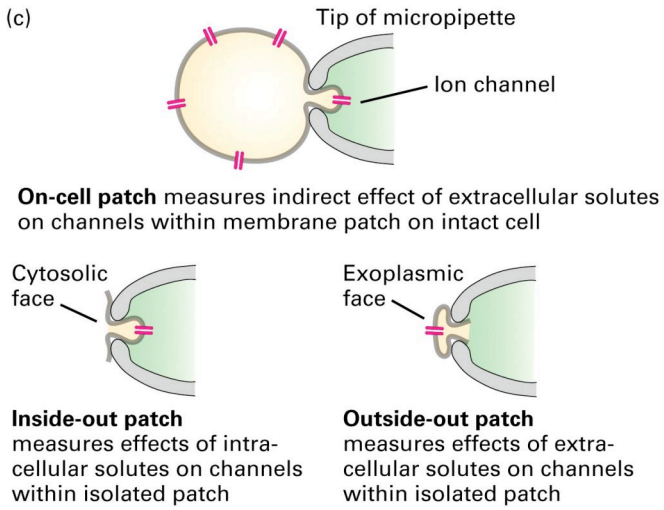


Opening of a Na^+ channel leads to inward movement of Na^+ ions across the membrane.

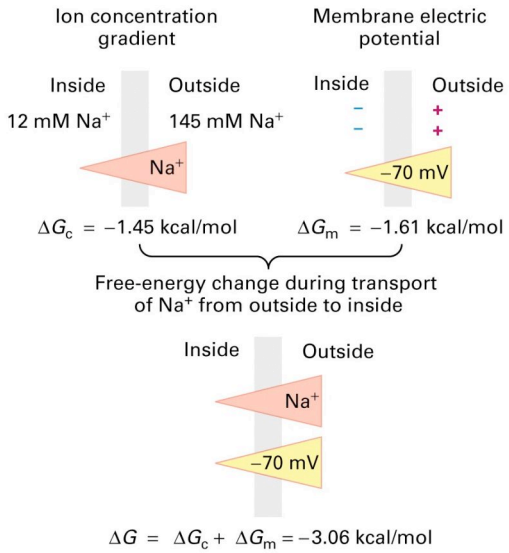
The average current through an open channel is 1.6 pA, or 1.6 x 10^{-12} amperes. Since 1 ampere = 1 coulomb (C) of charge per second, this current is equivalent to the movement of about 9900 Na^+ ions per channel per millisecond:

(1.6 x 10^{-12} C/s)(10^{-3} s/ms)(6 x 10^{23} molecules/mol) ÷ 96,500 C/mol = 9990 molecules/sec

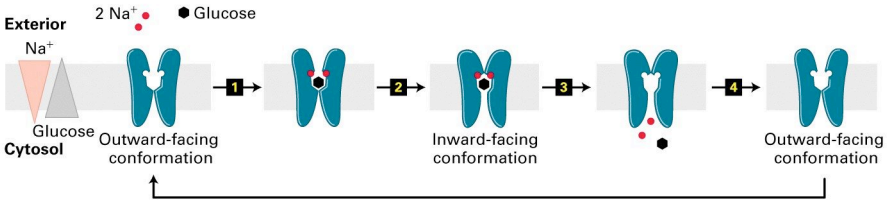
Patch- clamp techniques for measuring ion movements through single ion channels



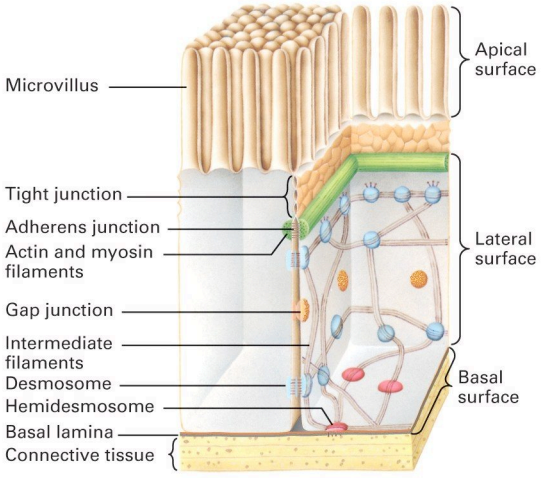
Two forces combine to power the entry of Na^+ into the cell across the plasma membrane

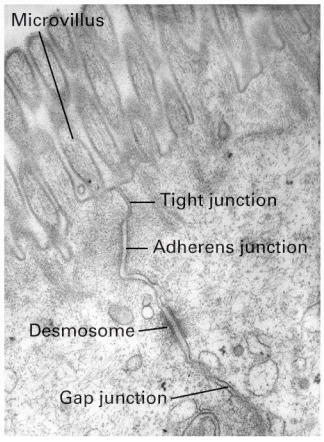


The Na^+ glucose symport protein: Coupled downhill movement of Na^+ and uphill movement of glucose

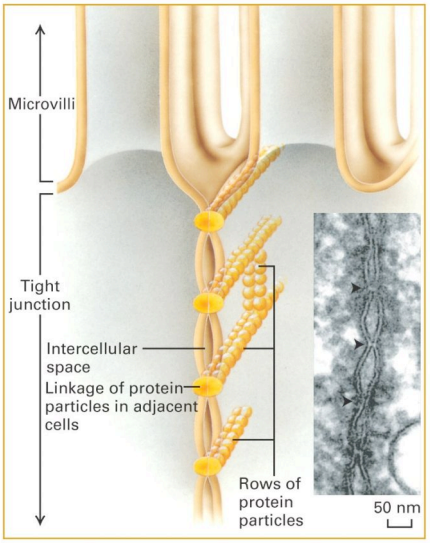


Structure of the intestinal epithelial cell



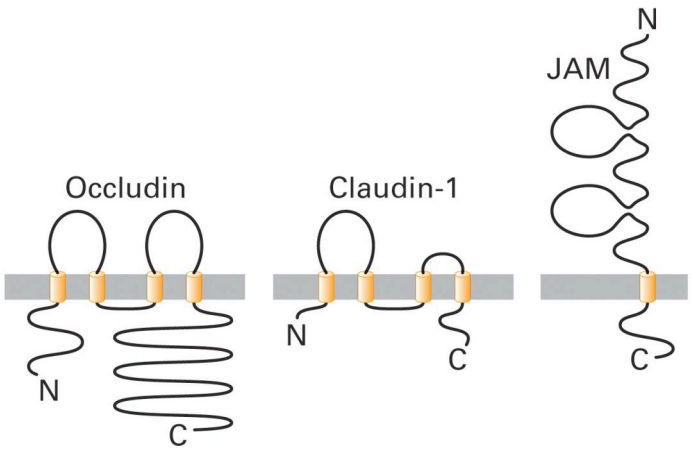


Model of a tight junction between two epithelial cells

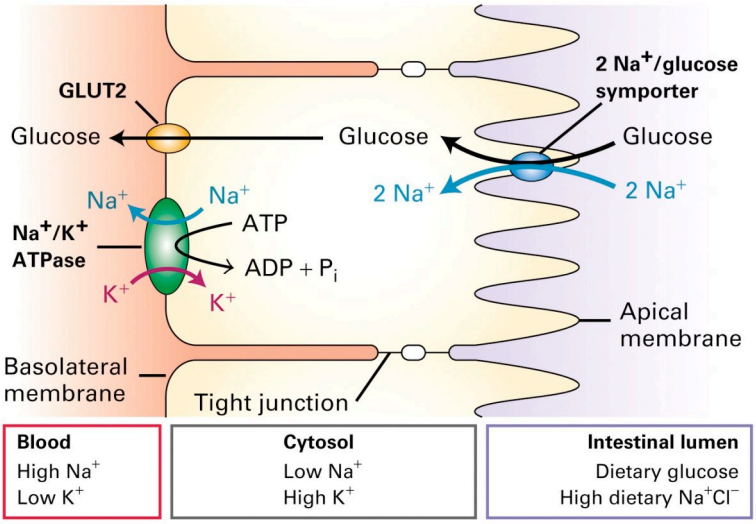


Freeze fracture image of a tight junction in the plasma membrane of one of two adjacent epithelial cells

Structure of major tight junction proteins

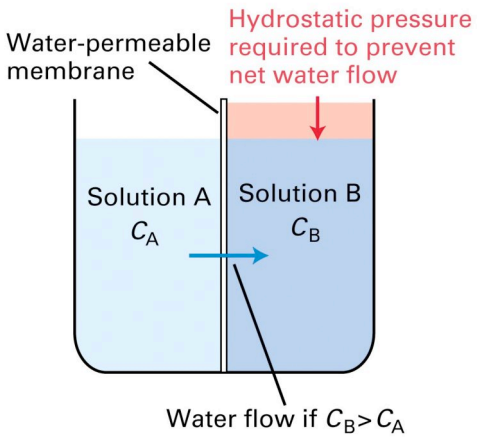


Transport of glucose from the intestinal lumen into the blood



Osmotic pressure -

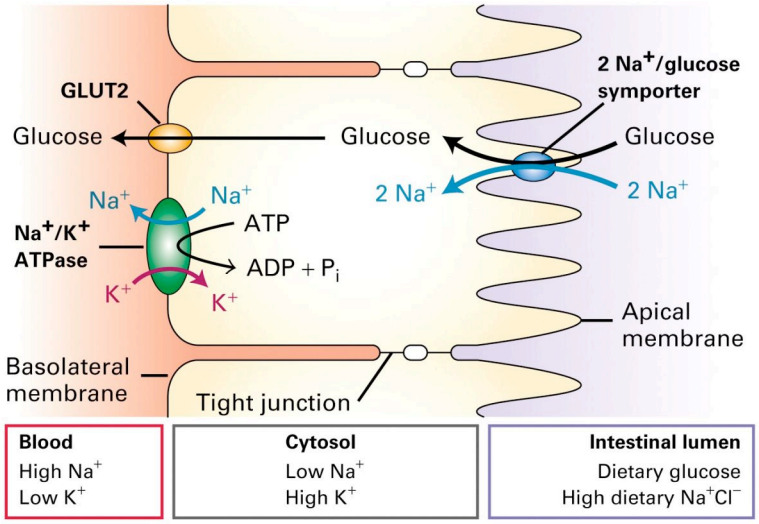
Water tends to move from low solute concentration
(high water concentration)
to high solute concentration
(low water concentration)



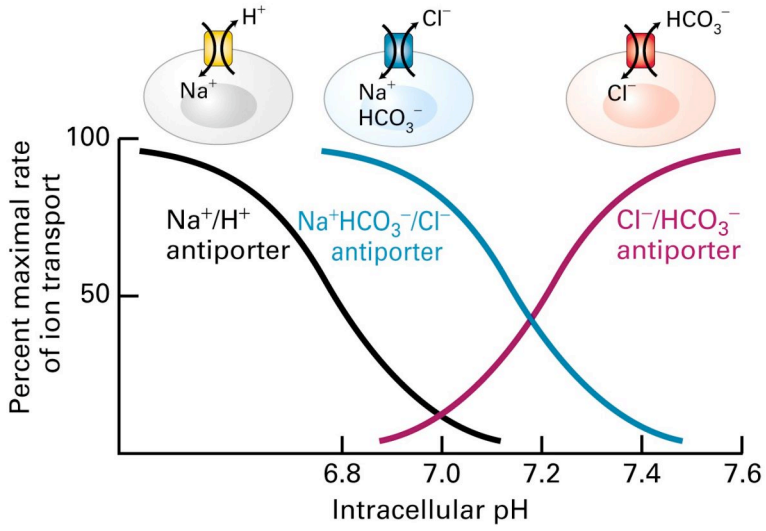
Oral rehydration therapy

- **Requires both NaCl and glucose; neither alone works**
- **The Na^+/ glucose symport must transport Na^+ together with glucose**
- **Transport of glucose and NaCl across the intestinal epithelium causes osmotic flow of water from the intestinal lumen into the blood, leading to rehydration**

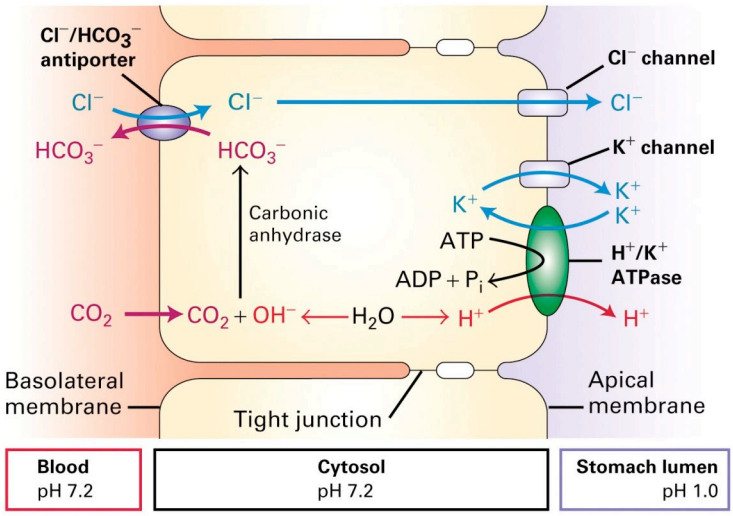
Transport of glucose from the intestinal lumen into the blood



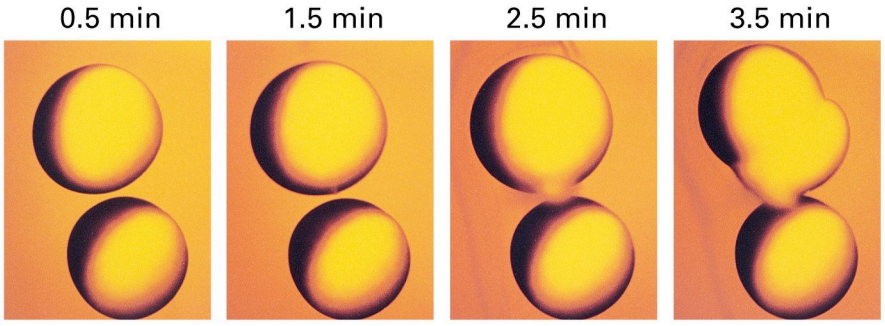
Anion antiporters maintain cytosolic pH



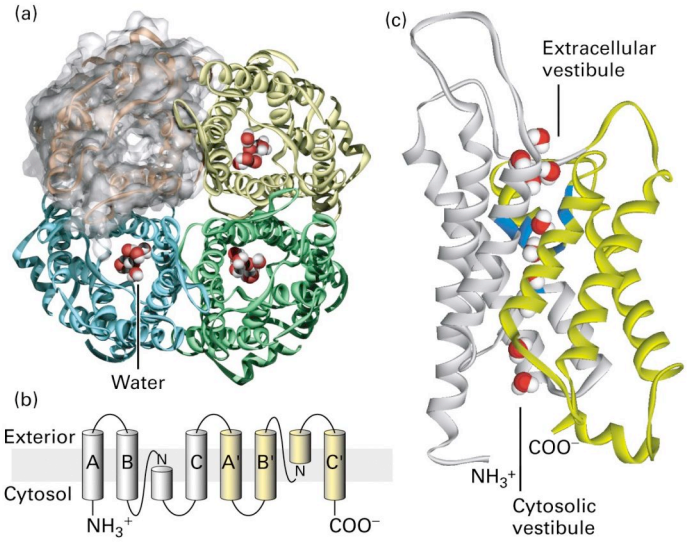
Acidification of the stomach lumen



Expression of aquaporin by frog oocytes increases their permeability to water



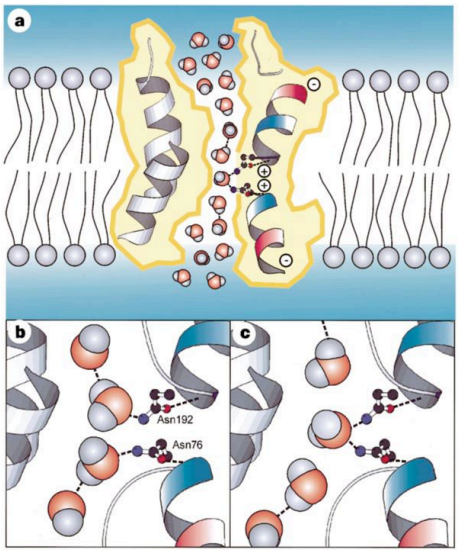
Molecular structure of the water channel protein aquaporin



Schematic representations explaining the mechanism for blocking proton permeation of Aquaporin.

a, Diagram illustrating how partial charges from the helix dipoles restrict the orientation of the water molecules passing through the constriction of the pore.

b and c Diagram illustrating hydrogen bonding of a water molecule with Asn 76 and/or Asn 192, which extend their amido groups into the constriction of the pore.



Nature **407**, 599 - 605 (2000);
K. MURATA, K. MITSUOKA, T. HIRAI, T. WALZ, P. AGRE, J. HEYMANN, A. ENGEL, and Y. FUJIYOSHI **Structural determinants of water permeation through aquaporin-1**