1: CELLULAR PHYSIOLOGY

Transmembrane solute transport

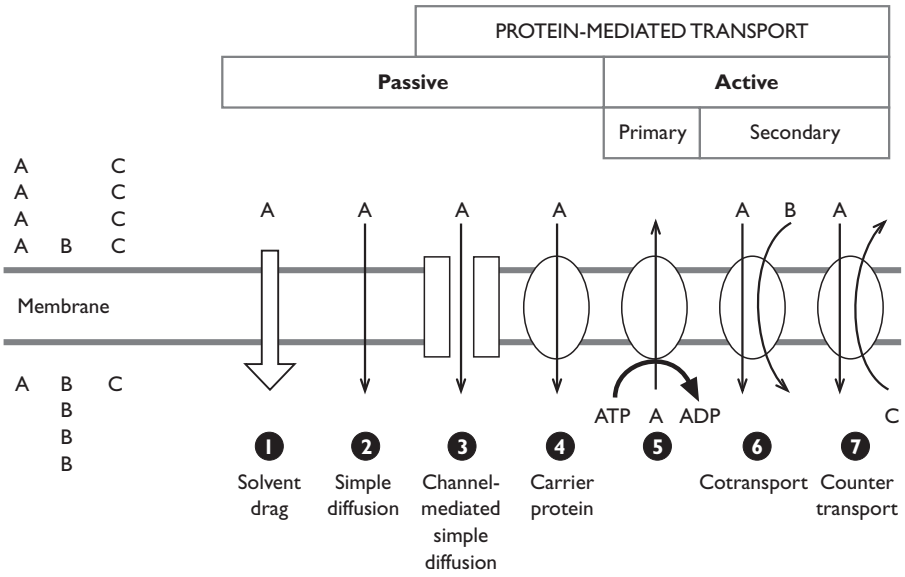


Fig. 1
A, B and C are different molecules.

Ion channels

Ion channels are protein tunnels spanning the cell membrane. Channel opening results in a current of the order of a few picoamps generated by the flow of highly specific ions.

Potassium channels

(a) Outward or delayed rectifier K^+ channel (Kv)
Activated by membrane depolarization
Produces an outward K^+ current
Responsible for the repolarization of the cardiac action potential

(b) ATP-sensitive K^+ channel (K^+-ATP)
Accelerates repolarization
Shortens the cardiac action potential

Prostacyclin, vasoactive intestinal peptide (VIP), nitric oxide (NO) and adenosine act in part via K^+-ATP opening
K^+-ATP channels open during ischaemia in response to a fall in intracellular ATP, acidosis, a rise in ADP and GDP, and the accumulation of extracellular adenosine
Antianginal (nicorandil) and vasodilator agents (diazoxide and minoxidil) act via myocyte K^+-ATP opening. Sulphonylureas such as glibenclamide are selective K^+-ATP blockers

(c) G-protein-activated K^+ channel (K-ACh)
Opened by vagally secreted acetylcholine (ACh)
Decreases spontaneous depolarization in the sinus node
Slows atrioventricular (AV) node conduction, underlying the vagal slowing of heart rate

(d) Inwardly rectifying K^+ channel
Opens at very negative potentials (less than −40 mV)
Shows a reduced K^+ conductance at positive membrane potentials (opposite to normal outward rectification seen in delayed rectifier channels)
K^+-ATP and K^+-ACh display some inward rectification

Calcium channels

(a) L-type Ca^{2+} channel (long lasting)
High voltage activated
Expressed in vascular and cardiac tissue
Generates a slow inward current

Blocked by dihydropyridines (nifedipine, amlodipine)

(b) T-type Ca^{2+} channel (transient)
Low voltage activated
Rapidly inactivated
High expression in the sinus node—possible role in pacemaking

Blocked by verapamil, diltiazem

(c) N-, P-, Q- and R-type Ca^{2+} channels
Found in neuronal cells

Ion channel disorders

Disorder		Channel	Clinical notes
Bartter's syndrome	AR	Bumetanide-sensitive $Na^+K^+Cl^-$ cotransporter (NKCC2)	*Hypokalaemia, alkalosis, renal salt wasting, hypotension, hyperreninaemia, hyperaldosteronism*
Liddle's syndrome (hereditary hypertension)	AR	ENaC (epithelial Na channel)	
Hyperkalaemic periodic paralysis	AD	Skeletal muscle Na channel	
Hypokalaemic periodic paralysis	AD	L-type Ca^{2+} channel	
Becker's generalized myotonia	AR	Skeletal muscle Cl channel	
Long QT syndrome	AD	Type 1, KVLQT1 (cardiac K^+ channel) Type 2, HERG (cardiac K^+ channel) Type 3, SCN5A (cardiac Na^+ channel)	*Characterized by prolonged and abnormal ventricular repolarization and risk of life-threatening arrhythmias (particularly torsades de pointes)*

AD, autosomal dominant; AR, autosomal recessive.

Cystic fibrosis (CF)

- The CF transmembrane conductance regulator (*CFTR*) gene is defective in CF.
- CFTR is a cAMP-regulated Cl channel found in the apical membrane of epithelial cells.
- CFTR also downregulates Na absorption via the amiloride-sensitive ENaC.
- Reduced Cl transport is thought to reduce Cl and water secretion into the airway lumen.

Ion ATPases

Na^+/K^+-ATPase

The chemical energy of ATP hydrolysis is used to extrude three Na^+ ions for every two K^+ ions entering the cell and every ATP molecule hydrolysed.

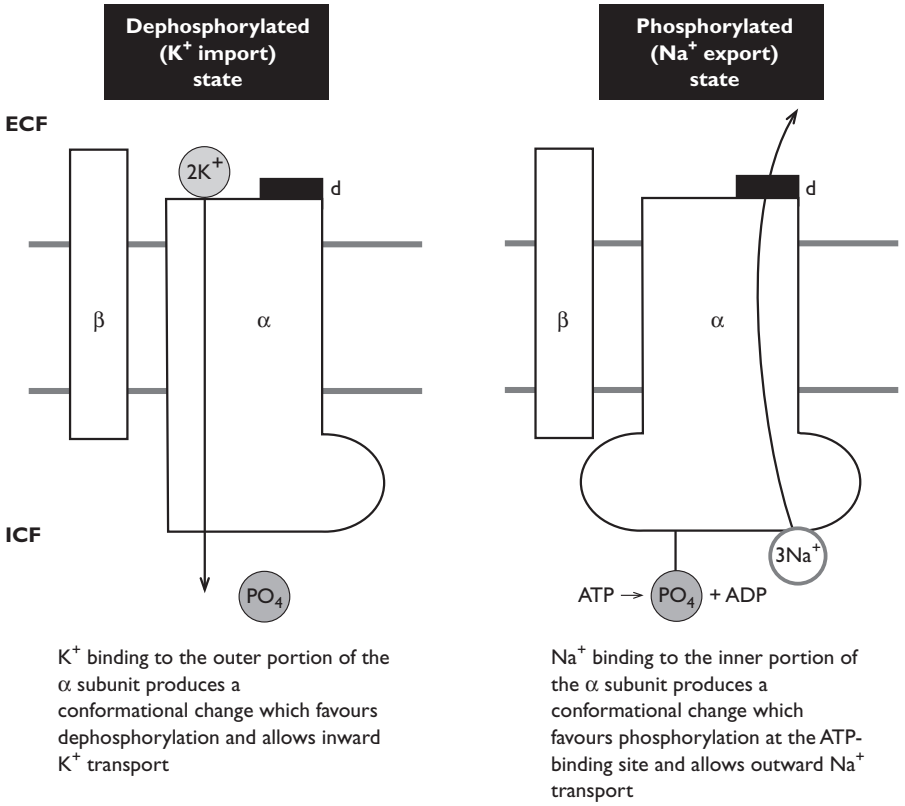


Fig. 2 Na^+/K^+-ATPase function
d, digoxin-binding site; ECF, extracellular fluid; ICF, intracellular fluid.

There is a net export of one third of a positive charge per Na^+ ion transported. Intracellular Na^+ is the substrate of the pump and a rise in intracellular Na^+ concentration favours Na^+/K^+ exchange.

Na^+/K^+-ATPase maintains intracellular and extracellular Na^+ and K^+ concentrations and is thus responsible for maintaining the resting mem-

brane potential. The active transport of Na^+ is also coupled to the transport of other substances (secondary active transport, counter transport and cotransport).

Magnesium is a cofactor of Na^+/K^+-ATPase and thus helps to maintain intracellular K^+.

Digoxin is an Na^+/K^+-ATPase inhibitor and thus produces a rise in intracellular Na^+ as well as a fall in intracellular K^+.

Other ATPases

Gastric H^+/K^+-ATPase

- Responsible for hydrogen ion secretion.
- *Antigen recognized by parietal cell autoantibodies in pernicious anaemia.*

Ca^{2+}/Mg^{2+}-ATPase

- Actively pumps Ca^{2+} into the sarcoplasmic reticulum during muscular relaxation (see 'Excitation–contraction coupling', p. 176).

H^+-ATPase

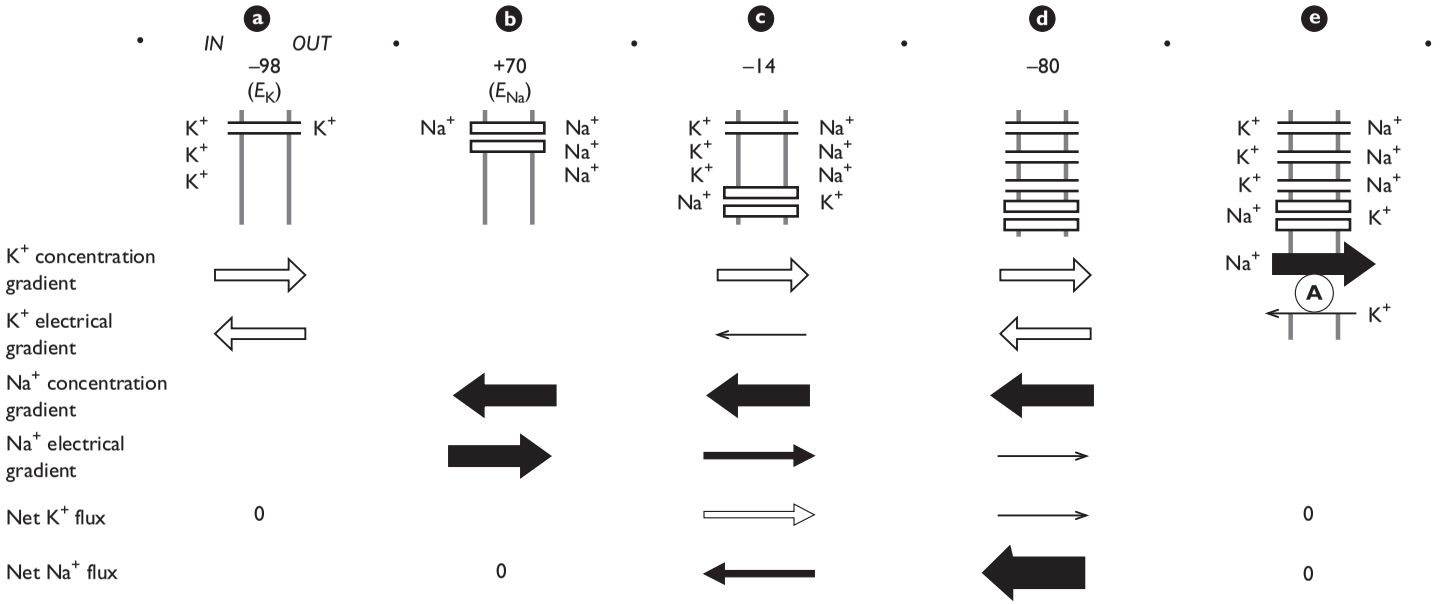
- Responsible for acid secretion in the distal convoluted tubule and collecting duct of the kidney.
- *A deficiency of this active proton pump (as in Sjögren's syndrome) results in distal (type 1) renal tubular acidosis* (see 'Renal', p. 97).

Resting membrane potential (E_m)

The Nernst potential (E_{rev}) for an ion is the point at which chemical and electrical driving forces across the cell membrane (occurring in opposite directions) are in equilibrium. At this potential, there is no net flow of that specific ion.

Ion	Extracellular concentration (mmol L^{-1})	Intracellular concentration (mmol L^{-1})	Nernst potential (mV)
Na^+	142	10	+70 (E_{Na})
K^+	4	155	−98 (E_K)
Ca^{2+}	2.5	0.0001	+150 (E_{Ca})
Cl^-	101	5–30	+30 to −65 (E_{Cl})

Under physiological conditions, Na^+, Ca^{2+} and Cl^- flow into cells to depolarize the cell towards E_{Na}, E_{Ca} and E_{Cl} respectively. Similarly, K^+ flows out of the cell to repolarize the cell towards E_K. E_m depends on the distribution of Na^+, Ca^{2+}, Cl^- and K^+ as well as membrane permeability to these ions.



At E_K (–98 mV), there is no net flow of K^+ ions through an open K^+ channel. The tendency to move outwards down a concentration gradient is opposed by an inward electrical force

At E_{Na} (+70 mV), there is no net flow through an open Na^+ channel

A cell with one open Na^+ and one open K^+ channel will have an E_m of –14 mV (halfway between E_{Na} and E_K). There is now a net K^+ efflux and a net Na^+ influx

As the number of open K^+ channels increases in comparison to the number of open Na^+ channels, E_m approaches E_K. Normal E_m in most cells is –80 mV because membrane conductance of K^+ exceeds that of Na^+

Net N^+a influx exceeds net K^+ efflux. There is a tendency for the cell interior to become depolarized. Intracellular and extracellular ion concentrations are restored by the action of Na^+/K^+-ATPase (A)

Fig. 3

Action potential

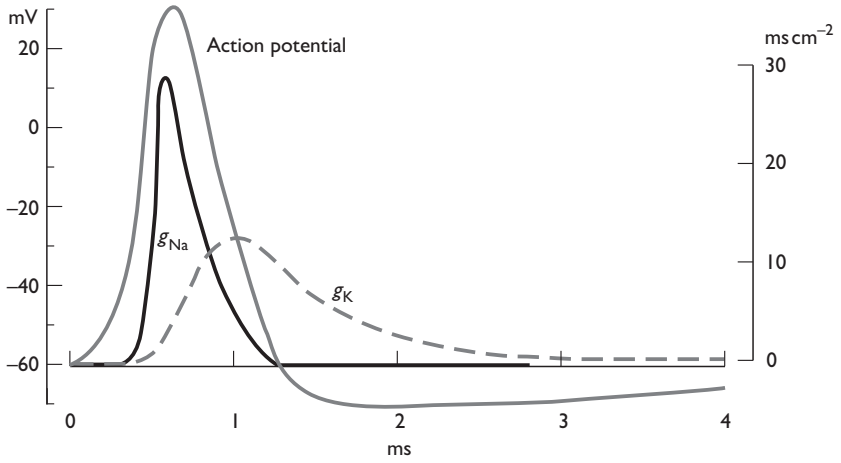


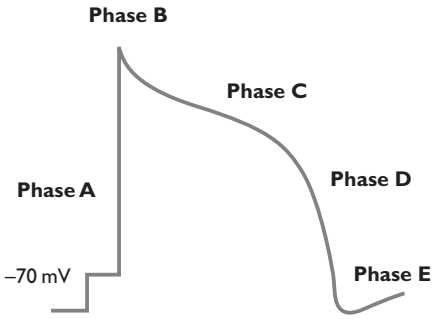
Fig. 4 Axonal action potential
(From Schmidt, R.F. & Thews, G. (eds) (1983) *Human Physiology*. Springer-Verlag, Berlin.)

The action potential is an all or nothing event triggered by the arrival of a depolarizing stimulus when Na^+ influx (g_{Na}) exceeds K^+ efflux (g_K).

Depolarization	When a critical threshold (–55 mV) is reached, all voltage-gated Na^+ channels open, causing E_m to approach E_{Na} (+55 mV) rapidly
Repolarization	A delayed voltage-dependent Na^+ channel inactivation and K^+ channel activation causes E_m to fall, exceeding the resting potential briefly (hyperpolarization) before returning to the starting point

The action potential is followed by an absolute and then relative refractory period.

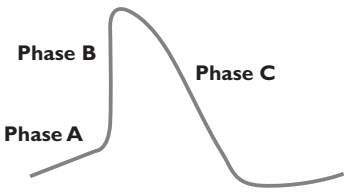
Non-nodal (Purkinje cell)



Resting membrane potential (E_m): –90 mV
Threshold potential: –70 to –60 mV

A Upstroke due to fast Na^+ influx causes depolarization to approximately +15 mV
B E_m repolarization to approximately 0 mV as Na^+ influx stops
C Plateau phase due to voltage-sensitive Ca^{2+} influx and K^+ efflux
D Repolarization due to outward K^+ current (via delayed rectifier K^+ channels)
E Slow upward drift of E_m

Nodal (SA node, AV node)



Resting membrane potential (E_m): –60 mV
Na^+ channels absent

A Prepotential due to residual Ca^{2+} influx
B Depolarization due to Ca^{2+} influx (via T-type Ca^{2+} channels)
C Repolarization due to outward K^+ current

Fig. 5 Cardiac action potential
SA, sinoatrial; AV, atrioventricular.

Second messenger pathways

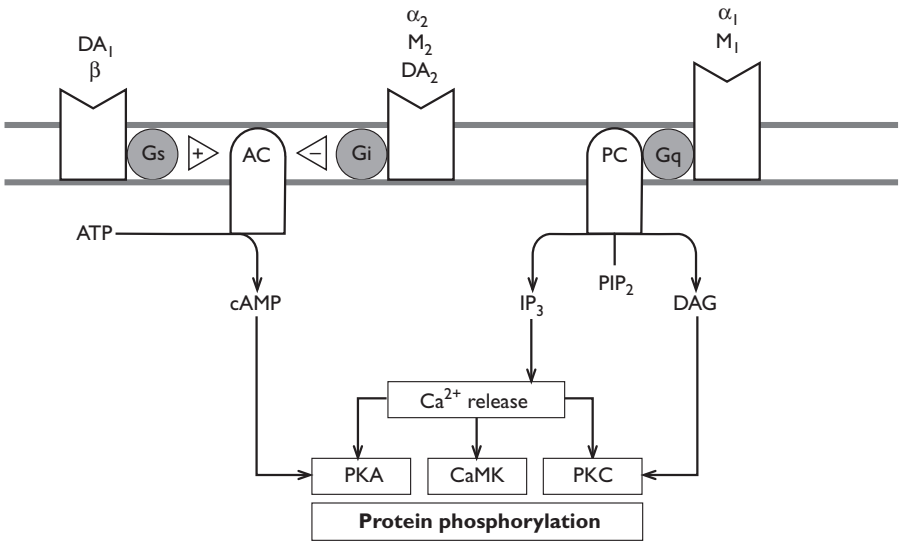


Fig. 6
AC, adenyl cyclase; Ca^{2+}; CaMK, calmodulin-dependent kinase; DAG, 1,2-diacylglycerol; Gs, Gi, Gq, G proteins; IP_3, inositol 1,4,5-triphosphate; PC, phospholipase C; PIP_2, phosphatidylinositol 4,5-biphosphate; PKA, protein kinase A; PKC, protein kinase C. Receptors: DA, dopamine; M, muscarinic.

cAMP pathway	IP_3 pathway
Activated β_1 and α_2 adrenergic receptors, for example, act via Gs or Gi proteins to stimulate or inhibit AC respectively	Activated α_1 adrenergic receptors, for example, act via G proteins to stimulate PC
AC induces cAMP synthesis	PC cleaves phosphoinositide to give IP_3 and DAG
cAMP stimulates target gene expression (tyrosine hydroxylase, somatostatin) via: **1** PKA induction	IP_3 mobilizes Ca^{2+} from intracellular stores
2 phosphorylation of transcription factors (cAMP-responsive element (CRE)-binding protein, CREB)	Ca^{2+} and DAG activate calmodulin kinases and PKC
	These in turn phosphorylate a number of important proteins (epidermal growth factor receptor (EGFR), glycogen synthase)

Notes:
Ca may modulate CREB activity via calmodulin kinases but also induces target gene expression via the cAMP pathway.
Other second messengers include cGMP (atrial natriuretic peptide (ANP), NO, phototransduction).

Use of second messenger pathways by various agonists

Agonist	cAMP raised	cAMP reduced	IP_3/DAG
ACh		M_2	M_1
Epinephrine	β_1	α_2	α_1
Dopamine	DA_1	DA_2	
ADH	VP_2		VP_1
Histamine	H_2		H_1
Adenosine	A_2	A_1	
Other	TSH	Somatostatin	Gastrin
	LH	AII	CCK
	FSH	5HT	GABA

ADH, antidiuretic hormone; CCK, cholecystokinin; FSH, follicle-stimulating hormone; GABA, γ-aminobutyric acid; 5HT, 5-hydroxytryptamine; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; VP, vasopressin.

G proteins

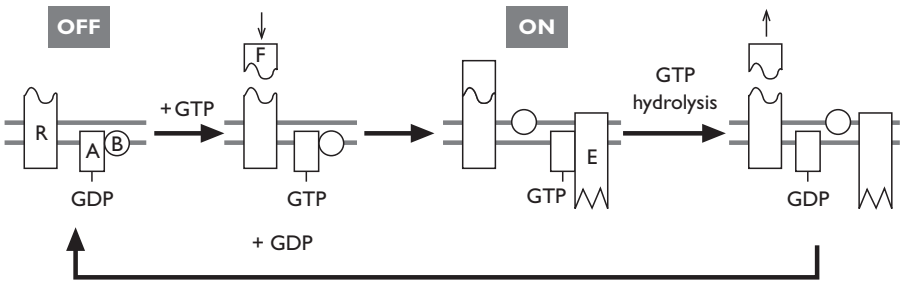


Fig. 7 G-protein function
E, effector molecule; F, first messenger; R, receptor. G protein: A, α subunit; B, β and γ subunits.

G proteins consist of three subunits (A, B, C).

1 In the resting state, GDP is bound to the A subunit which is a GTPase.

2 On hormone binding, GDP is displaced by GTP which activates the G protein.

3 The A subunit and BC complex dissociate to interact with effectors.

4 GTP is then rapidly hydrolysed to GDP.

G-protein abnormalities are implicated in human disease:
1 continued Gs activation is a pathophysiological mechanism in acromegaly, McCune–Albright syndrome and *Vibrio cholerae* infection;
2 the oncogene *ras* encodes p21 which is a G protein;
3 Gs activity is reduced by 50% in pseudohypoparathyroidism.