

Drugs produce effects in the body mainly in the following ways: (i) by acting on *receptors*, (ii) by inhibiting *carriers* (molecules that transport one or more ions or molecules across the plasma membrane), (iii) by modulating or blocking *ion channels*, (iv) by inhibiting *enzymes*.

RECEPTORS AS TARGETS FOR DRUG ACTION

Receptors are protein molecules in or on cells whose function is to interact with the body's endogenous chemical messengers (hormones, neurotransmitters, the chemical mediators of the immune system, etc.) and thus initiate cellular responses. They enable the responses of the body's cells to be coordinated. Drugs used in medicine make use of these chemical 'sensors'—either stimulating them (drugs that do this are termed agonists) or preventing endogenous mediators or agonists from stimulating them (drugs that do this are termed antagonists).

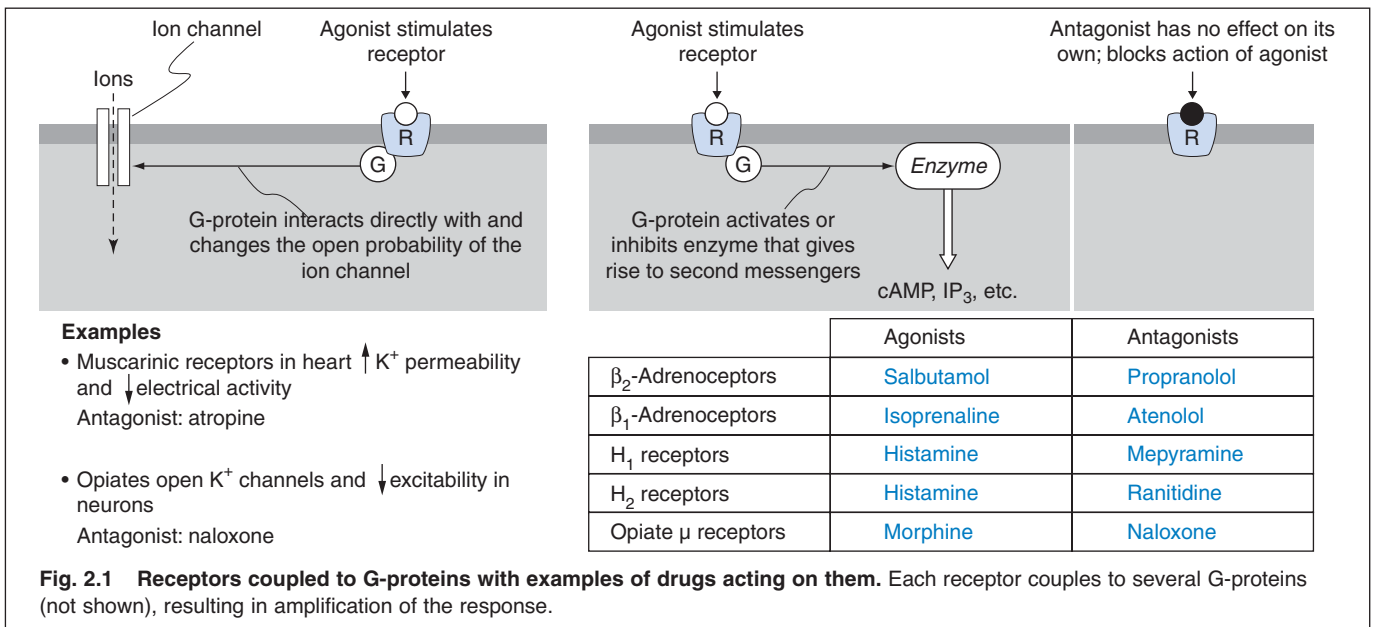
There are four types of receptor:

- receptors coupled to G-proteins (GPCR: guanine nucleotide-

- binding proteins); also termed metabotropic receptors
- receptors linked to ion channels; also termed ionotropic receptors or ligand-gated ion channels
- receptors that affect gene transcription
- receptors linked to enzymes (e.g. kinases, guanylate cyclase, etc); these mostly initiate a kinase cascade within the cell.

Receptors coupled to G proteins

GPCRs occur in the cell membrane and respond in seconds. They have a single polypeptide chain that has seven transmembrane helices. Signal transduction occurs by activation of particular G-proteins that modulate enzyme activity or ion channel function (Figs 2.1–2.3).

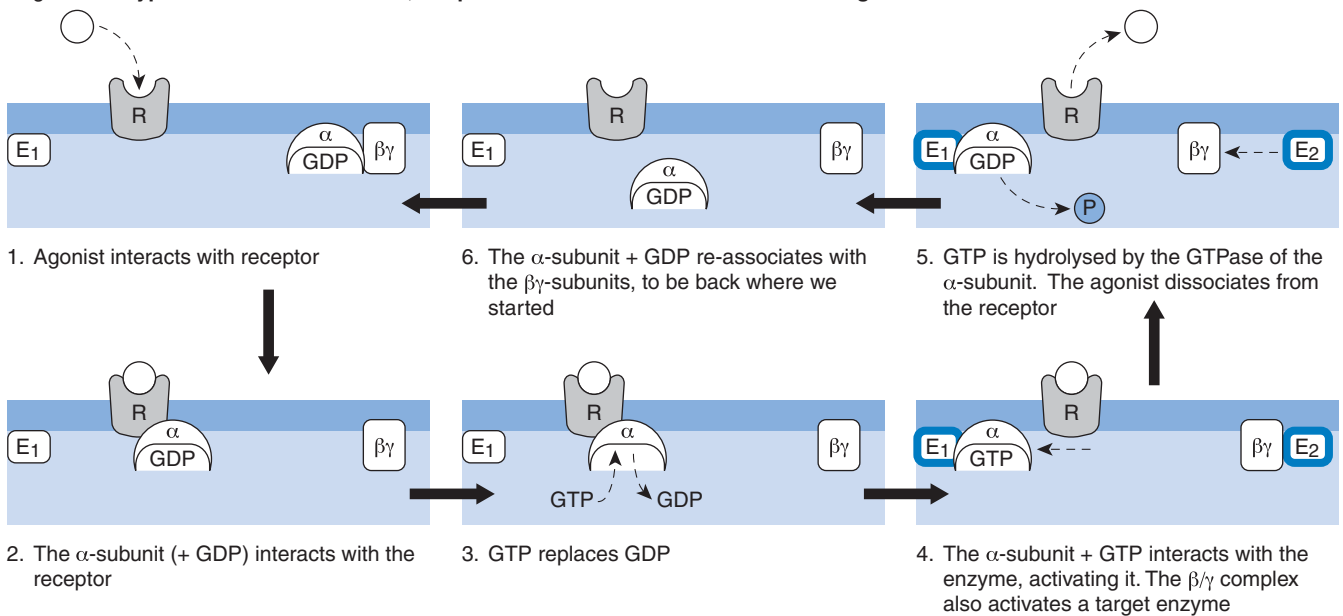


G-proteins	Targets activated	Example of receptor involved	Typical effect	Produced by agonists	Antagonist
G _q (+)	Phospholipase C → PIP ₂ , IP ₃ , DAG IP ₃ — Releases Ca ²⁺ from intracellular stores DAG — Activates protein kinase C	H ₁ -histamine	Smooth muscle contraction (↑IP ₃) A variety of effects due to protein phosphorylation	Histamine Ch. 15	Mepyramine
G _s (+)	Adenylate cyclase → ATP, cAMP cAMP — Activates protein kinase A	β ₂ -Adrenoceptor →	Smooth muscle relaxation (↑cAMP)	Adrenaline Ch. 11, salbutamol Ch. 24	Propranolol
G _i (-)	K ⁺ channels in cell membrane Increased opening of the channels resulting in hyperpolarisation	M ₂ -muscarinic →	Decreased force of contraction of the heart (↓cAMP) Cardiac slowing	Acetylcholine Ch. 10	Atropine

Fig. 2.2 Examples of G-protein-coupled actions. The pathways are shown for three different G-proteins. IP₃, inositol trisphosphate, PIP₂, phosphatidylinositol 4,5-bisphosphate.

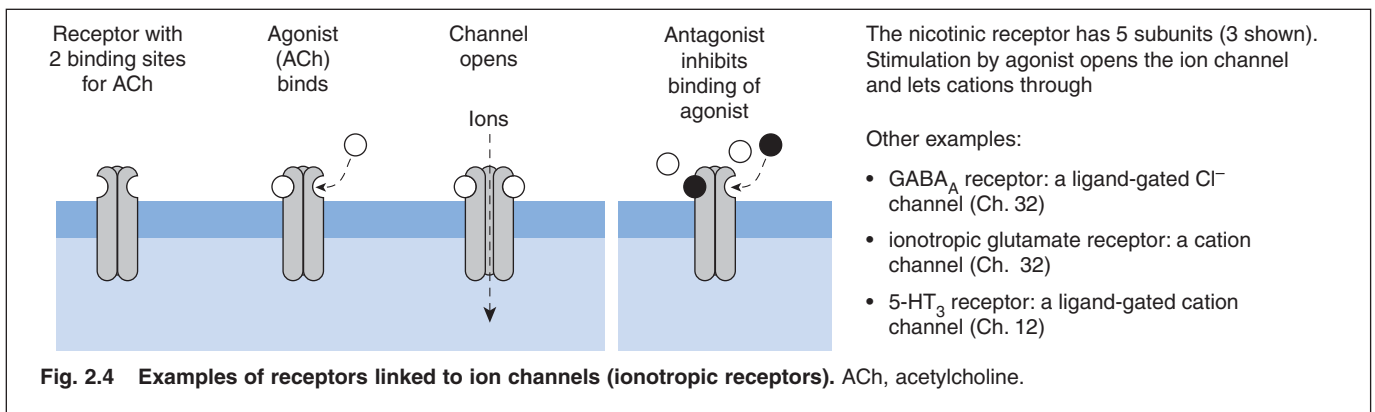
G-proteins are attached to the membrane and consist of 3 subunits α , β and γ , the last two being closely associated:

In the free G protein, GDP occupies the binding site on the α -subunit. The α subunit and the β/γ complex can each activate intracellular targets. **Subtypes of all 3 subunits exist; the particular subunit determines which targets are activated**



Receptors linked to ion channels (i.e. ionotropic receptors)

Receptors linked to ion channels are located in the cell membrane and respond in milliseconds. The channel forms part of the receptor. The nicotinic receptor for acetylcholine (see Ch. 10) is an example (Fig. 2.4).



Receptors linked to gene transcription

The receptors that regulate gene transcription are called nuclear receptors although some are located in the cytosol (e.g. glucocorticoid receptors) and migrate to the nucleus after binding a ligand (Fig. 2.5).

Receptors linked to enzymes

These receptors are transmembrane proteins with a large extracellular portion that contains the binding sites for ligands (e.g. growth factors, cytokines) and an intracellular portion that has integral enzyme activity—usually tyrosine kinase activity (Fig. 2.6). Activation initiates an intracellular pathway involving cytosolic and nuclear transducers and eventually gene transcription. Cytokine

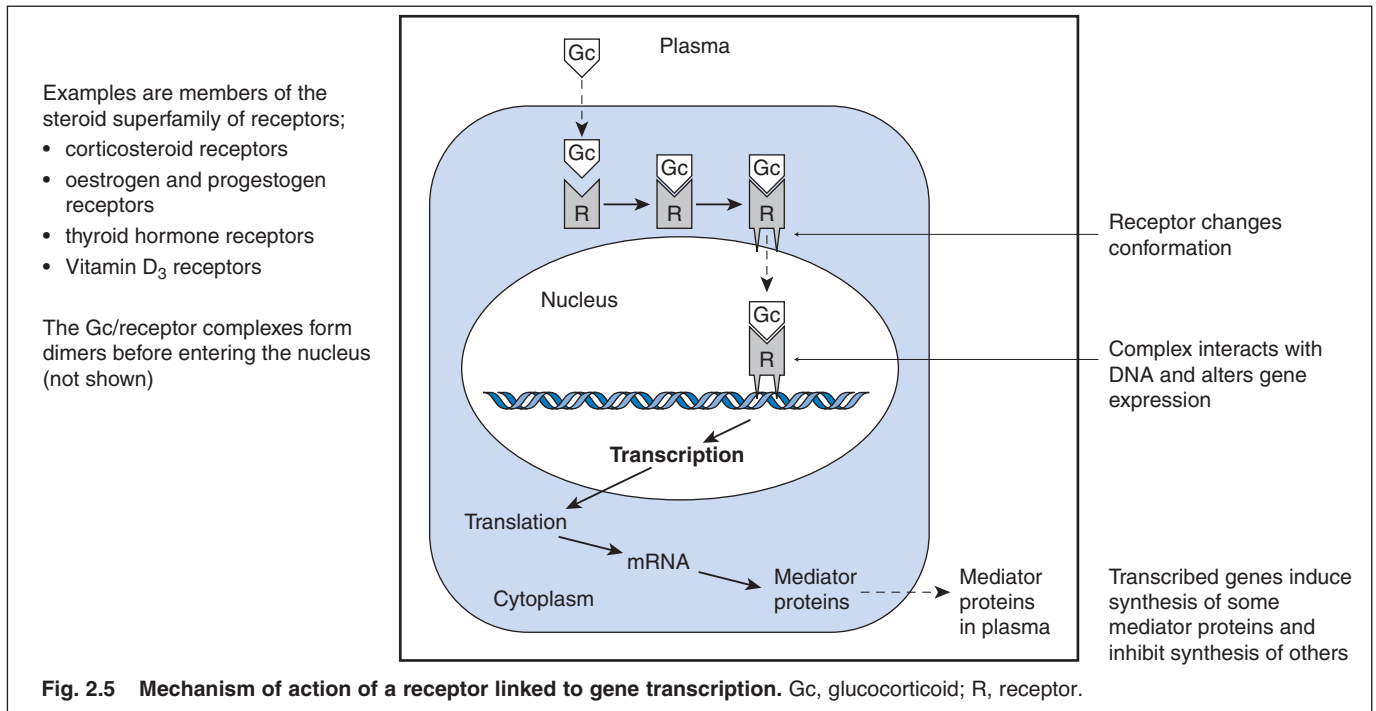
receptors activate Jak kinases, which, in turn, activate Stat transcription factors and these activate gene transcription (Fig. 2.6).

CARRIERS AS TARGETS FOR DRUG ACTION

The classification of membrane transport proteins varies between authorities, but in essence there are two main types:

- ATP-powered ion pumps
- transporters (Table 3.1)

Both are transmembrane proteins. In Rang et al. *Pharmacology*, these are termed 'carriers'.



ATP-powered ion pumps

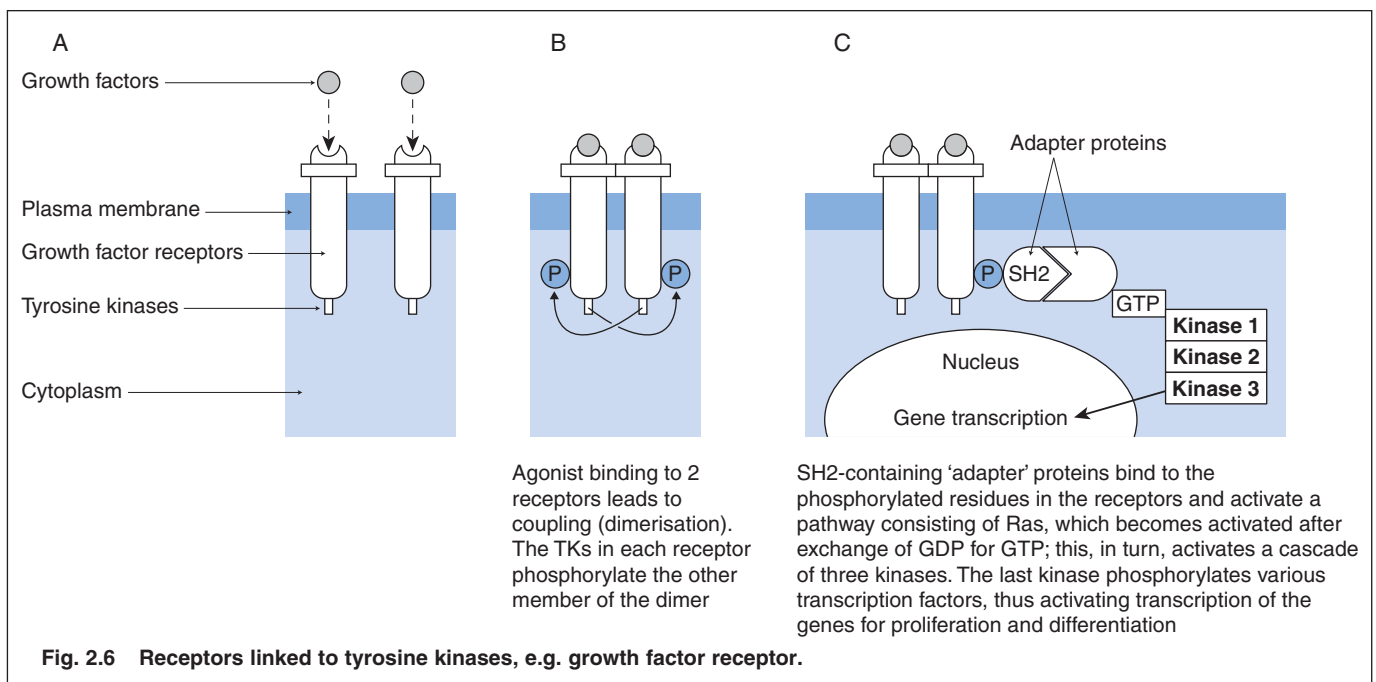
The three principal ion pumps are the sodium pump (the Na⁺/K⁺ ATPase), the calcium pump, and the Na⁺/H⁺ pump in the gastric parietal cell, which is the target for the proton pump inhibitor **omeprazole**. Here we will concentrate on the sodium pump. This is important in maintaining cellular osmotic balance and cell volume and in maintaining the membrane potential. In many cells (e.g. in the myocardium, the nephron) it is the primary mechanism for transporting Na⁺ out of the cell (Fig. 2.7).

The K⁺ concentration is 140 mmol/l inside cells and 5 mmol/l outside. For each molecule of ATP hydrolysed, the sodium pump pumps 3Na⁺ out of the cell and 2K⁺ in against their chemical gradients. (The pump in Fig. 2.7 has simplified stoichiometry.)

Transporters

The main transporters involved in drug action are symporters and antiporters (exchangers) (see Fig. 2.7).

Symporters These use the electrochemical gradient of one ion (usually Na⁺) to carry another ion (or molecule or several ions)



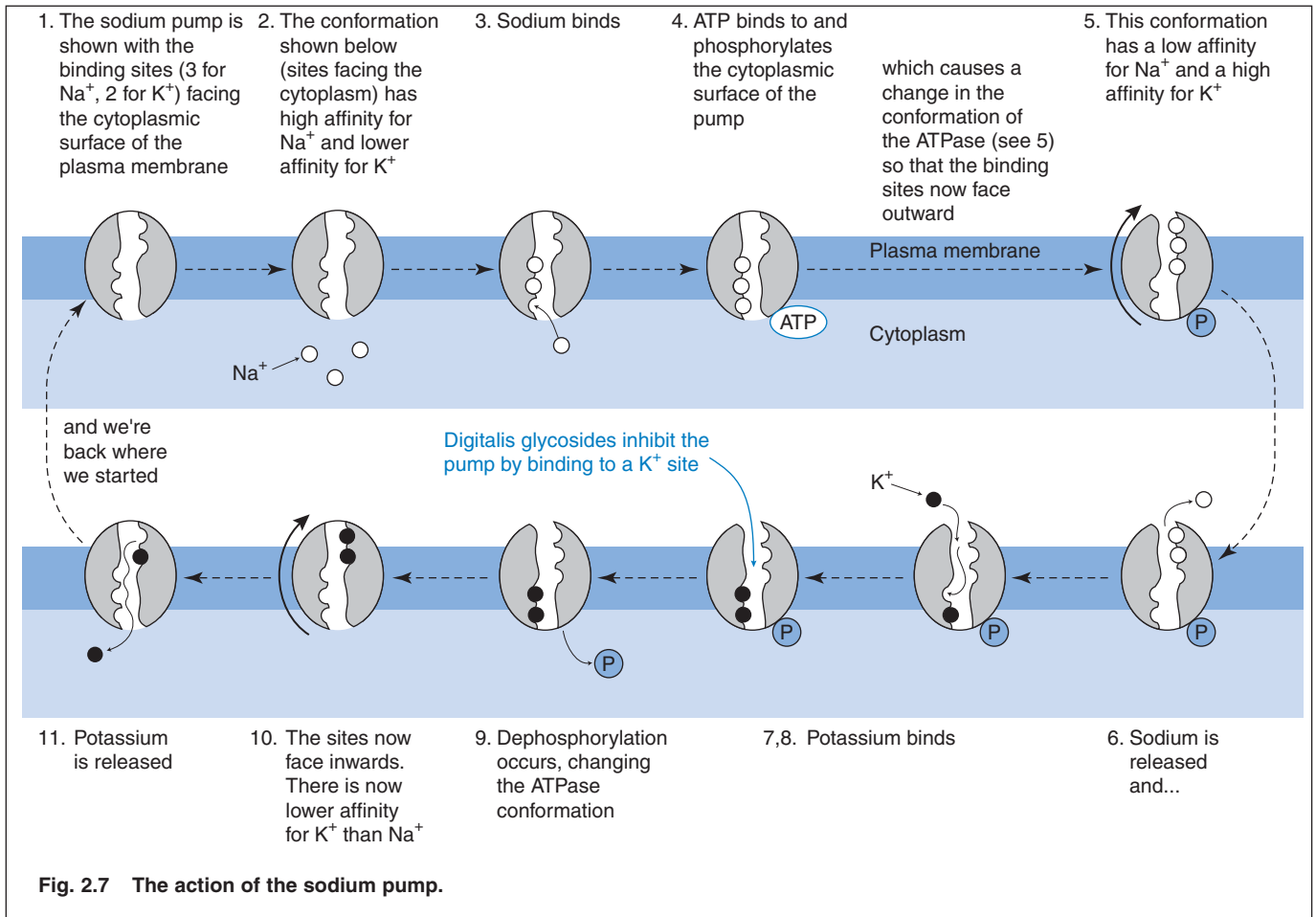


Fig. 2.7 The action of the sodium pump.

across a cell membrane. Drugs can modify this action by occupying a binding site (e.g. the action of furosemide (frusemide) on the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ symport in the nephron (Fig. 2.8). Similarly, thiazide diuretics bind to and inhibit the Na^+/Cl^- symporter in the distal tubule.

Antiporters These use the electrochemical gradient of one ion (usually Na^+) to drive another ion (or molecule) across the membrane in the opposite direction. An important example is the

Ca^{2+} exchanger, which exchanges 3Na^+ for 1Ca^{2+} (Fig. 2.8). Note that this calcium exchanger should be distinguished from the ATP-driven calcium pump and the ligand-gated and voltage-gated Ca^{2+} channels (see Fig. 4.1 in Rang et al.). The calcium exchanger is crucial in the maintenance of the Ca^{2+} concentration in blood vessel smooth muscle and cardiac muscle (see Ch. 20). Another example is the uptake carrier in the noradrenergic varicosity, which transports noradrenaline into the cell (see Ch. 11).

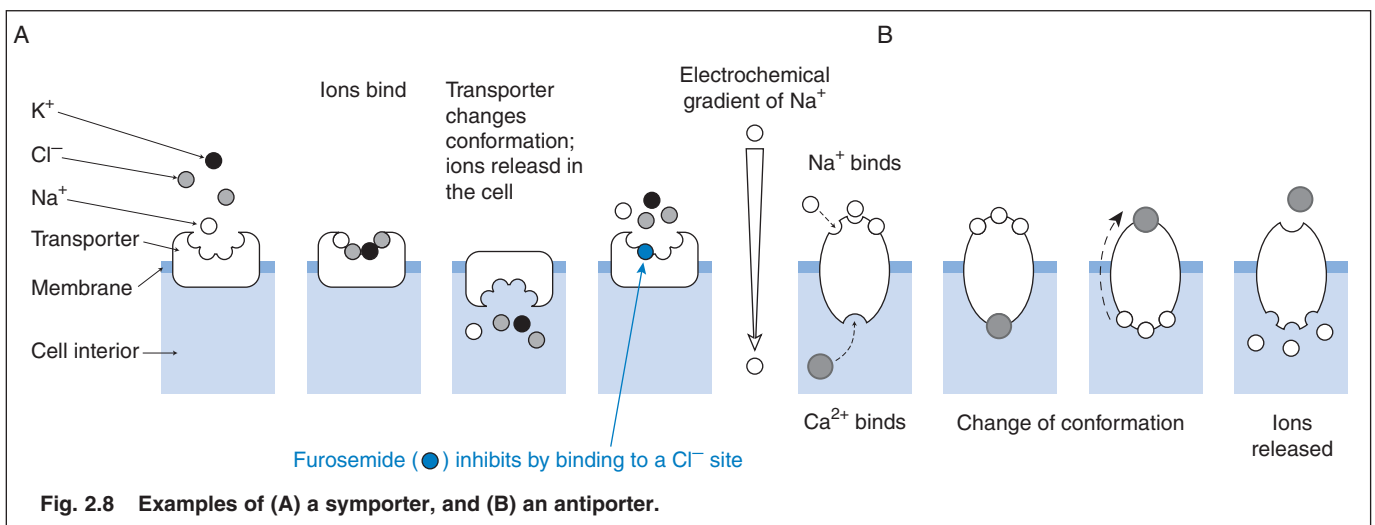
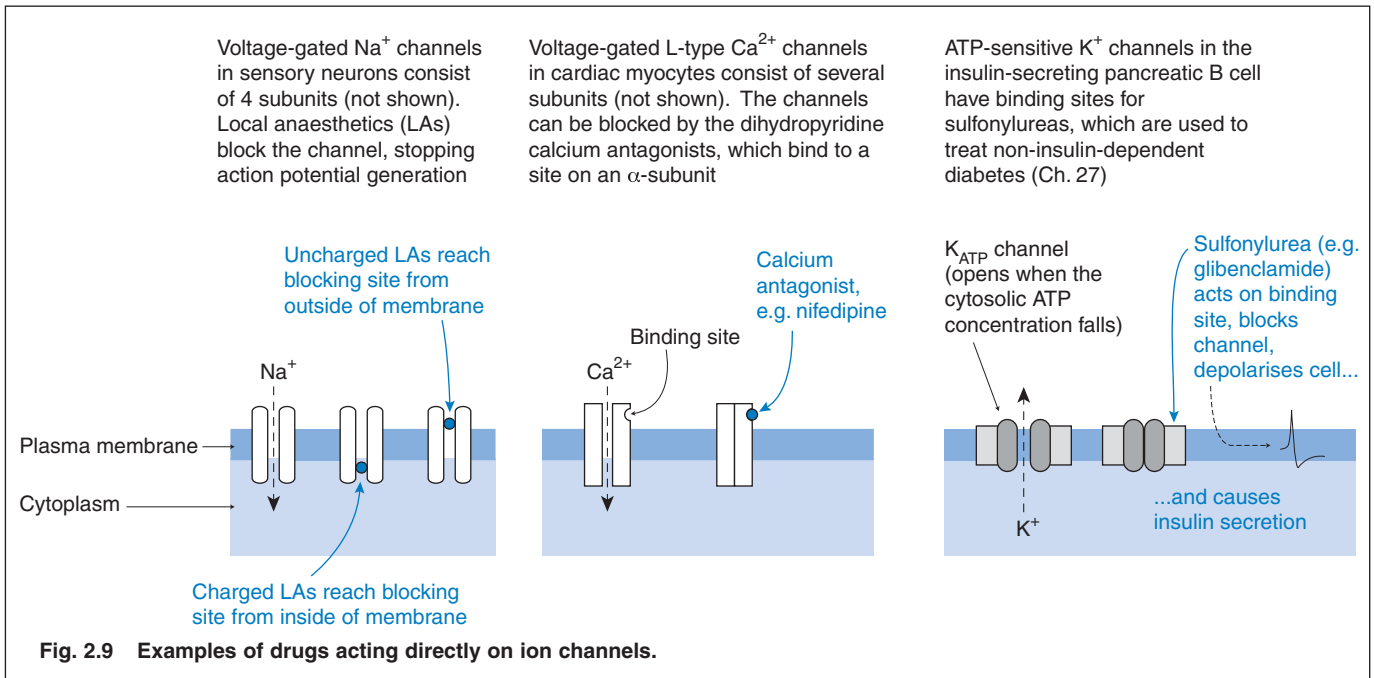


Fig. 2.8 Examples of (A) a symporter, and (B) an antiporter.

ION CHANNELS AS TARGETS FOR DRUG ACTION

Some drugs produce their actions by directly interacting with ion channels. Three examples are given in Figure 2.9. Note that these ion channels transport ions across the plasma membrane. They are not receptors and should be distinguished from ion channels that function as ionotropic receptors (see above).



ENZYMES AS TARGETS FOR DRUG ACTION

Drugs can produce effects on enzyme reactions by substrate competition or by reversibly or irreversibly modifying the enzyme. Some examples are given in Table 2.1.

Table 2.1 Drugs acting through alteration of enzyme reactions

Substrate	Enzyme	Products	Inhibitor	Uses
Acetylcholine	Acetylcholine esterase	Choline; acetate	Neostigmine	Myasthenia gravis and to reverse neuromuscular block
Arachidonate	Cyclooxygenase	Prostanoids	Aspirin	Heart disease and inflammation
Angiotensin (AT)I	AT converting enzyme	AT II	Captopril	Hypertension, heart failure, post-infarct
Hypoxanthine	Xanthine oxidase	Uric acid	Allopurinol	Gout
HMG-CoA	HMG-CoA reductase	Mevalonic acid	Simvastatin	To lower blood cholesterol
Folate	Dihydrofolate reductase	Tetrahydrofolate	Trimethoprim	With cotrimoxazole as antibacterial
Thymidine	Viral reverse transcriptase		Zidovudine	HIV infection
Deoxyribonucleotides	DNA polymerase	DNA	Cytarabine	Anticancer drug