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).

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### G-proteins

<table>
<thead>
<tr>
<th>G-proteins</th>
<th>Targets activated</th>
<th>Example of receptor involved</th>
<th>Typical effect</th>
<th>Produced by agonists</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>(G_\alpha)</td>
<td>Phospholipase C</td>
<td>PIP&lt;sub&gt;2&lt;/sub&gt; → IP&lt;sub&gt;3&lt;/sub&gt; → DAG activates protein kinase C</td>
<td>H&lt;sub&gt;1&lt;/sub&gt;-histamine, smooth muscle contraction (↑ IP&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>Histamine Ch. 15</td>
<td>Mepyramine</td>
</tr>
<tr>
<td></td>
<td>Adenylate cyclase</td>
<td>ATP → cAMP activates protein kinase A</td>
<td>(\beta_2)-Adrenoceptor, smooth muscle relaxation (↑ cAMP)</td>
<td>Adrenaline Ch. 11, salbutamol Ch. 24</td>
<td>Propranolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K&lt;sup&gt;+&lt;/sup&gt; channels in cell membrane</td>
<td>M&lt;sub&gt;2&lt;/sub&gt;-muscarnic, increased opening of the channels resulting in hyperpolarisation</td>
<td>Acetylcholine</td>
<td>Atropine</td>
</tr>
</tbody>
</table>

**Fig. 2.2 Examples of G-protein-coupled actions.** The pathways are shown for three different G-proteins. IP<sub>3</sub>, inositol trisphosphate, PIP<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate.
**G-proteins** are attached to the membrane and consist of 3 subunits $\alpha$, $\beta$, and $\gamma$, the last two being closely associated:

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

1. Agonist interacts with receptor
2. The $\alpha$-subunit (+ GDP) interacts with the receptor
3. GTP replaces GDP
4. The $\alpha$-subunit + GTP interacts with the enzyme, activating it. The $\beta/\gamma$ complex also activates a target enzyme
5. GTP is hydrolysed by the GTPase of the $\alpha$-subunit. The agonist dissociates from the receptor
6. The $\alpha$-subunit + GDP re-associates with the $\beta/\gamma$-subunits, to be back where we started

**Fig. 2.3** The mechanism of the G-protein transduction process. Activated enzyme indicated by a blue box.

**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).

**Fig. 2.4** Examples of receptors linked to ion channels (ionotropic receptors). ACh, acetylcholine.

**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).

**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’. 

**Fig. 2.5** The mechanism of the G-protein transduction process. Activated enzyme indicated by a blue box.
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)
MOLECULAR ASPECTS OF DRUG ACTION

**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).

Across a cell membrane. Drugs can modify this action by occupying a binding site (e.g. the action of furosemide (frusemide) on the Na\(^+/K^+\)/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).

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**Fig. 2.7** The action of the sodium pump.

**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).

![Diagram showing voltage-gated Na^+ channels in sensory neurons, local anaesthetics (LAs) blocking the channel, and binding sites for calcium antagonists and KATP channels.](image1)

**Figure 2.9** Examples of drugs acting directly on ion channels.

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

Table 2.1 Drugs acting through alteration of enzyme reactions