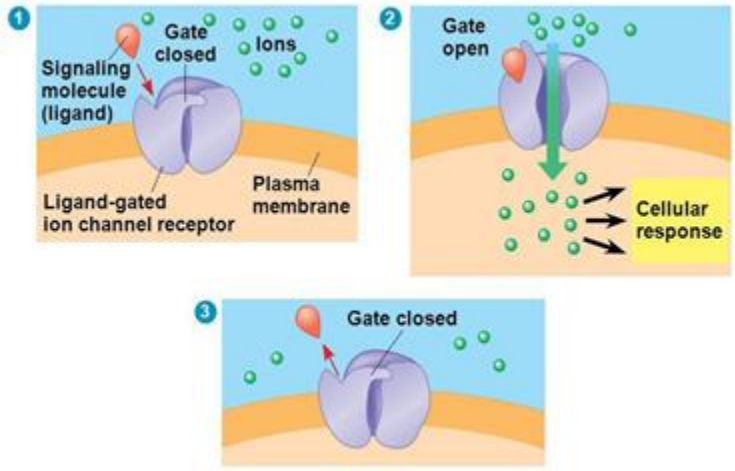
Receptors: are macromolecules mostly proteins, present either on the cell surface, cytoplasm or in the nucleus with which the drug binds and interacts to produce cellular changes.

Most drugs exert effects, both beneficial and harmful, by interacting with the receptors. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction.

It is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

Types and locations of receptors:

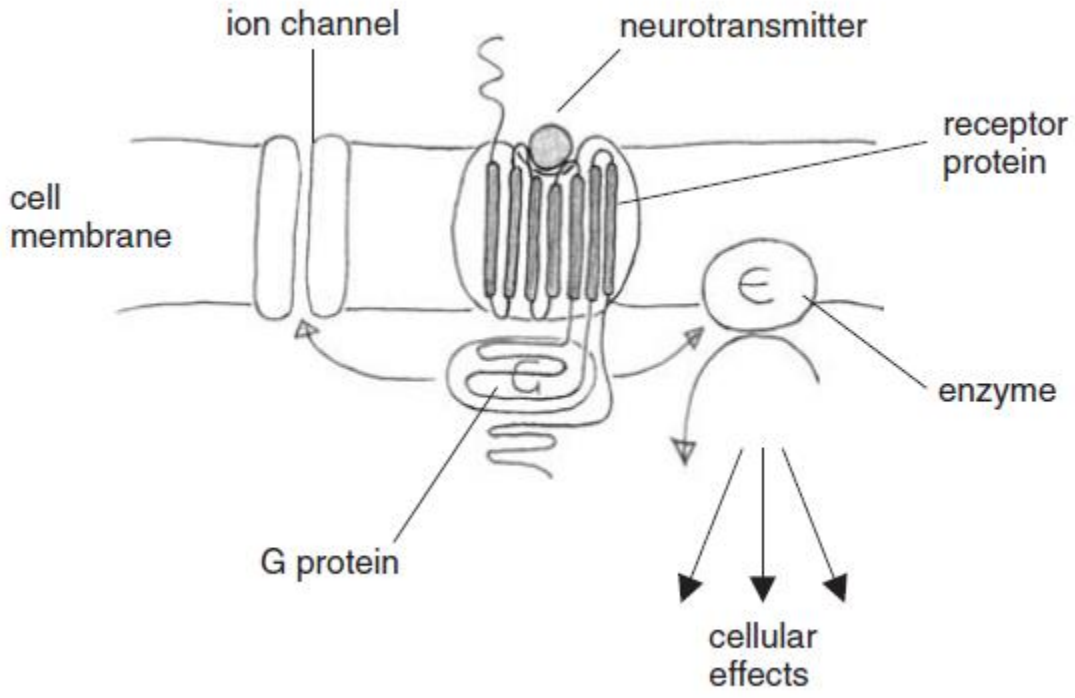
1. Transmembrane ligand-gated ion channels:



- Ionotropic receptors.
- The extracellular portion of ligand-gated ion channels contains the drug-binding site. This site regulates the opening of the pore through which ions can flow across cell membranes (like Na^{+}, K^{+}, Ca^{+2}, and/or Cl^{-}).

- The channel is usually closed until the receptor is activated by an agonist, which opens the channel for a few milliseconds.
- Drug-binding sites are also found on many voltage-gated ion channels where they can regulate channel function. For example, local anesthetics bind to the voltage-gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.
- Ion channels are located within the membrane of all excitable cells (like neurons and muscle cells).

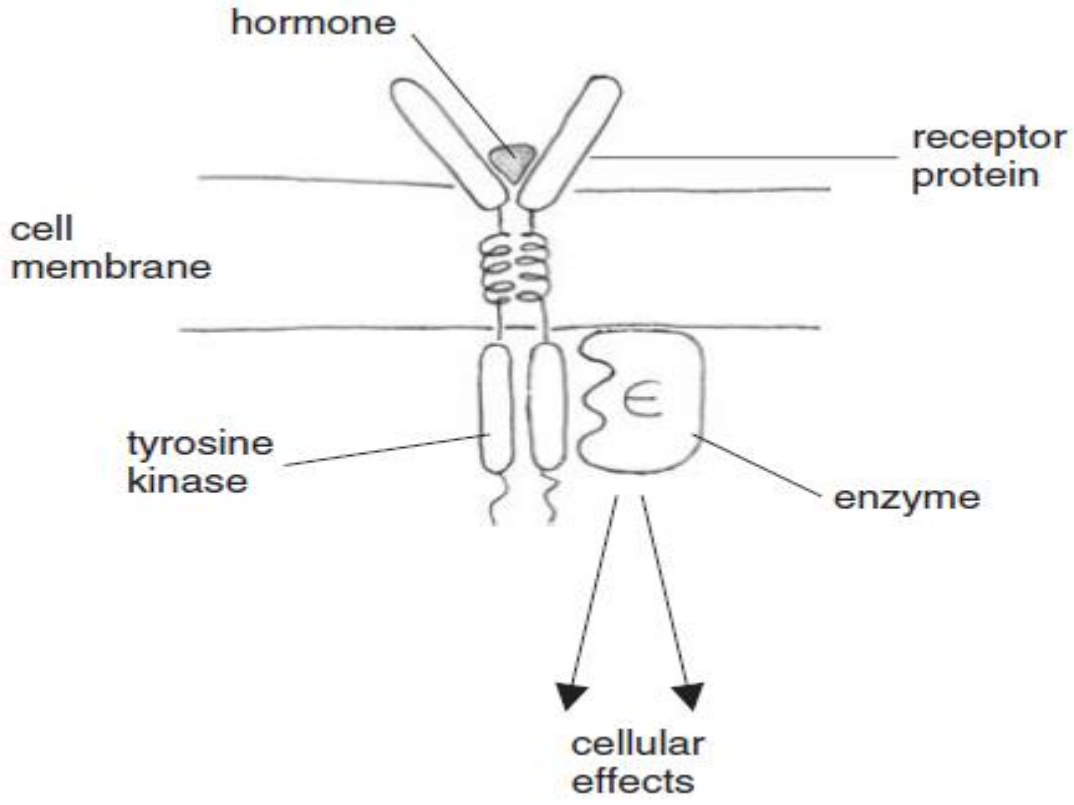
2. Transmembrane G protein–coupled receptors:



- Metabotropic receptors.
- The extracellular portion of this receptor contains the ligand-binding site.
- The intracellular portion interacts (when activated) with a G protein which then interacts with specific cellular effectors, usually an enzyme or an ion channel, that cause further actions within the cell.

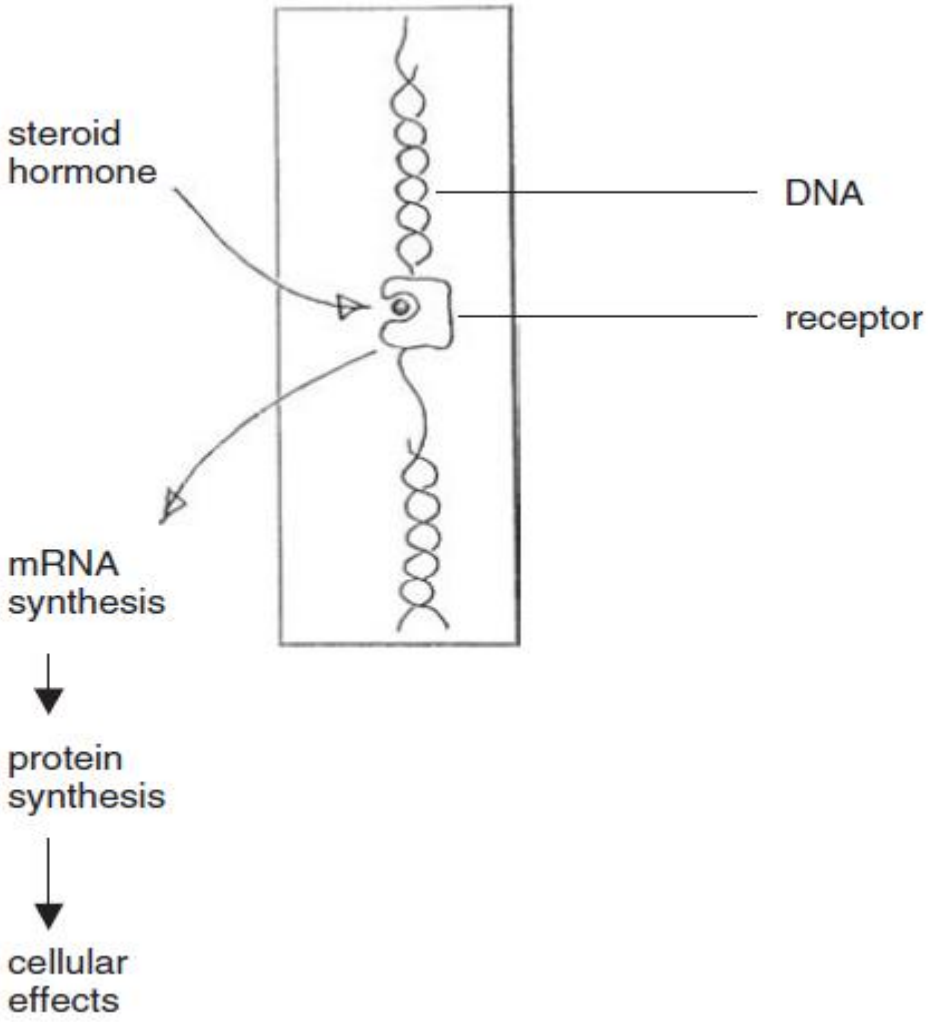
- These responses usually last several seconds to minutes. Often, the activated effectors produce “second messenger” molecules that further activate other effectors in the cell, causing a signal cascade effect.

3. Enzyme-linked receptors:



- These are receptors for insulin and other growth factors, which are directly linked to tyrosine kinase (an enzyme).
- They have large extracellular and intracellular domains.
- The extracellular domain is the binding site for hormone and the intracellular domain includes tyrosine kinase.
- The binding of hormone results in activation of tyrosine kinase.
- Tyrosine kinase then activates cellular enzymes, which in turn stimulate transcription of particular genes. This brings about the cellular response to the original hormone, for example growth.

4. Intracellular receptors:



- These are receptors for steroid hormones and thyroid hormone.
- They are located in the nucleus or the cytoplasm of the cell.
- The hormone first has to enter the cell. Steroid hormones and thyroid hormones pass easily across the cell membrane, as they are lipid soluble.
- Once the hormone binds to its receptor, the receptor is thought to unfold exposing a DNA-binding domain. The receptor molecule then binds to a particular region of DNA and activates certain genes. The result is increased protein synthesis that mediates the cellular response.

Theories of drug receptors interactions:

1. Occupation theory: the response comes from a receptor only when it is occupied by an appropriate ligand (drug).

Maximal response occurs when all the receptors are occupied.

2. Rate theory: the response is proportional to the rate of drug-receptor complex formation.

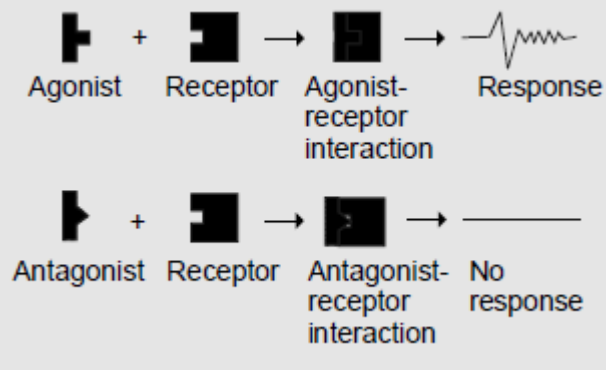
The duration of receptor occupation determines whether a molecule is agonist or partial agonist.

3. Operational model: it is based on the occupancy theory by incorporating both tissue responsiveness and drug efficacy.

Agonist: A drug that is capable of producing pharmacological action after binding to the receptor.

Partial agonist: A drug that binds to the receptor but produces an effect less than that of an agonist.

Antagonist: A drug that binds to receptors but is not capable of producing pharmacological action.



An antagonist has no effect on biological function in the absence of an agonist, but can decrease the effect of an agonist when present. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

Types of antagonism:

- **Competitive antagonism**: In competitive antagonism, both agonist and the antagonist bind reversibly to the same site on the receptor. This type of antagonism can be overcome (reversible) by increasing the concentration of agonist.
- **Noncompetitive antagonism**: could be
  - ✓ Irreversible antagonists: in which the antagonist binds covalently to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist. In contrast to competitive antagonists, addition of more agonist does not overcome the effect of irreversible antagonists.
  - ✓ Allosteric antagonists: An allosteric antagonist binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist.
- **Physiological (functional) antagonism**: Here, two drugs act at different receptors or by different mechanisms on the same physiological system and produce opposite effects. For example, insulin and glucagon on blood sugar, adrenaline and histamine on bronchial smooth muscle—histamine produces bronchoconstriction (via histamine receptors), whereas adrenaline produces bronchodilatation by acting through adrenergic β_2 receptors—hence adrenaline helps to reverse bronchospasm in anaphylactic shock.