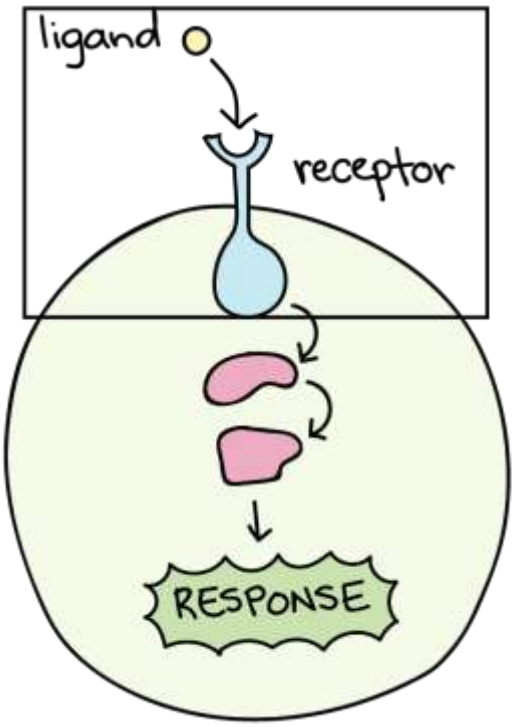
Ligands & receptors

Types of signalling molecules and the receptors they bind to on target cells. Intracellular receptors, ligand-gated ion channels, G protein-coupled receptors, and receptor tyrosine kinases.

Introduction

Just as a journey of a thousand miles begins with a single step, so a complex signalling pathway inside of a cell begins with a single key event – the binding of a signalling molecule, or **ligand**, to its receiving molecule, or **receptor**.

Receptors and ligands come in many forms, but they all have one thing in common: they come in closely matched pairs, with a receptor recognizing just one (or a few) specific ligands, and a ligand binding to just one (or a few) target receptors. Binding of a ligand to a receptor changes its shape or activity, allowing it to transmit a signal or directly produce a change inside of the cell



Stages of signal transduction: ligand-receptor binding, signal relay, response.

This article focuses on the first stage (signal reception).

In this section, we'll look at different types of receptors and ligands, seeing how they interact to turn information from outside the cell into a change inside the cell.

Types of receptors

Receptors come in many types, but they can be divided into two categories: intracellular receptors, which are found inside of the cell (in the cytoplasm or nucleus), and cell surface receptors, which are found in the plasma membrane.

Intracellular receptors

Intracellular receptors are receptor proteins found on the inside of the cell, typically in the cytoplasm or nucleus. In most cases, the ligands of intracellular receptors are small, hydrophobic (water-hating) molecules, since they must be able to cross the plasma membrane in order to reach their receptors. For example, the primary receptors for hydrophobic steroid hormones, such as the sex hormones estradiol (an oestrogen) and testosterone, are intracellular.

When a hormone enters a cell and binds to its receptor, it causes the receptor to change shape, allowing the receptor-hormone complex to enter the nucleus (if it wasn't there already) and regulate gene activity. Hormone binding exposes regions of the receptor that have DNA-binding activity, meaning they can attach to specific sequences of DNA. These sequences are found next to certain genes in the DNA of the cell, and when the receptor binds next to these genes, it alters their level of transcription.

In the process of **gene expression**, a cell reads out the information contained in a gene, or segment of DNA, to produce a functional product – in many cases, a protein. Expression of a eukaryotic protein-coding gene can be divided into two main stages:

1. Transcription, in which the DNA sequence of the gene is copied into an RNA molecule. The RNA molecule is modified in the nucleus to make a mature messenger RNA, or mRNA.
2. Translation, in which the information in the mRNA molecule is used to construct a protein with a specific amino acid sequence.

Different types of cells express different sets of genes, and a single cell may change its pattern of gene expression over the course of its lifetime. Changes in gene expression alter the set of proteins produced by the cell, which can, in turn, change the cell's behaviour, metabolism, and even cellular identity.

You can learn more about gene expression and its stages in the video on transcription and translation.

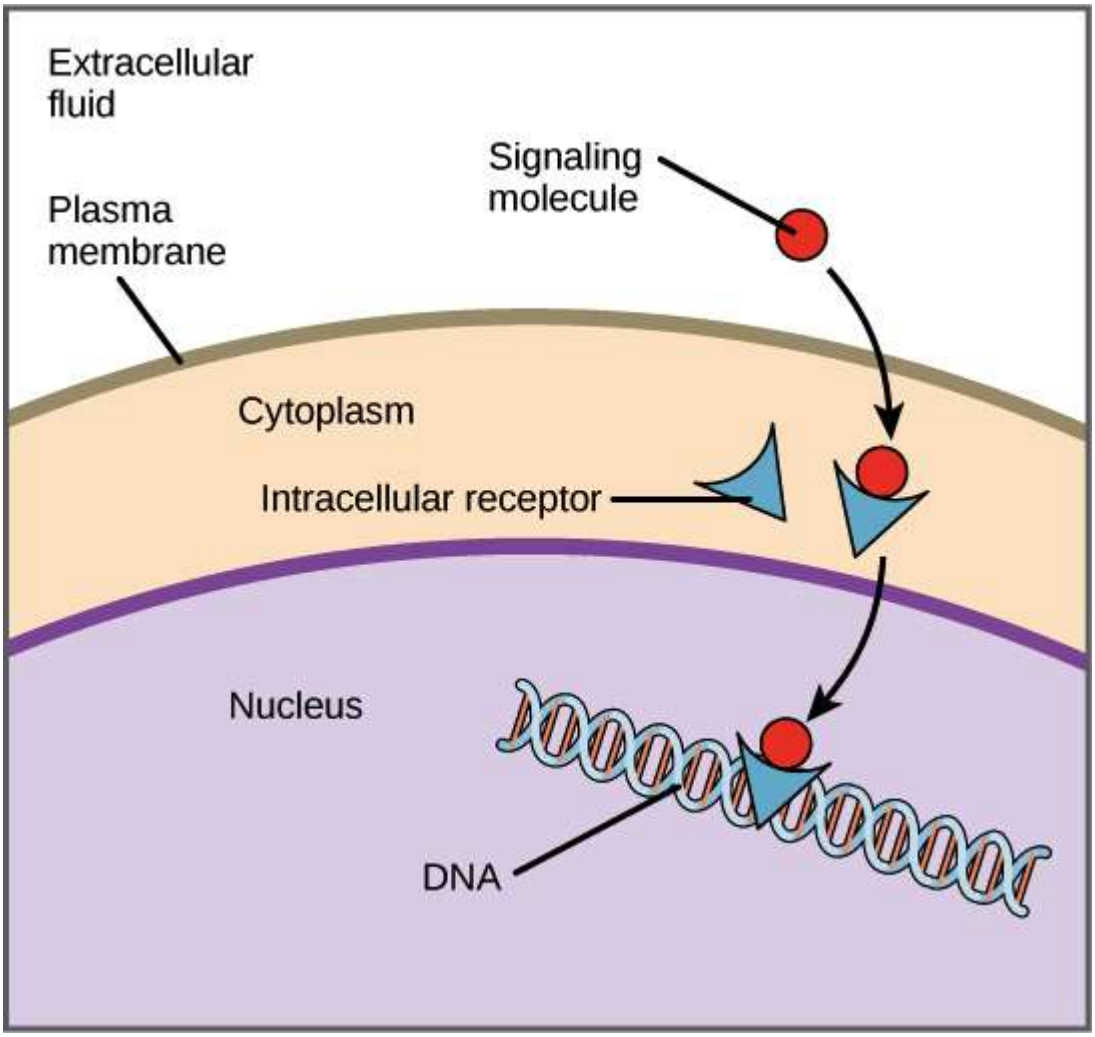


Diagram of a signalling pathway involving an intracellular receptor. The ligand crosses the plasma membrane and binds to the receptor in the cytoplasm. The receptor then moves to the nucleus, where it binds DNA to regulate transcription.

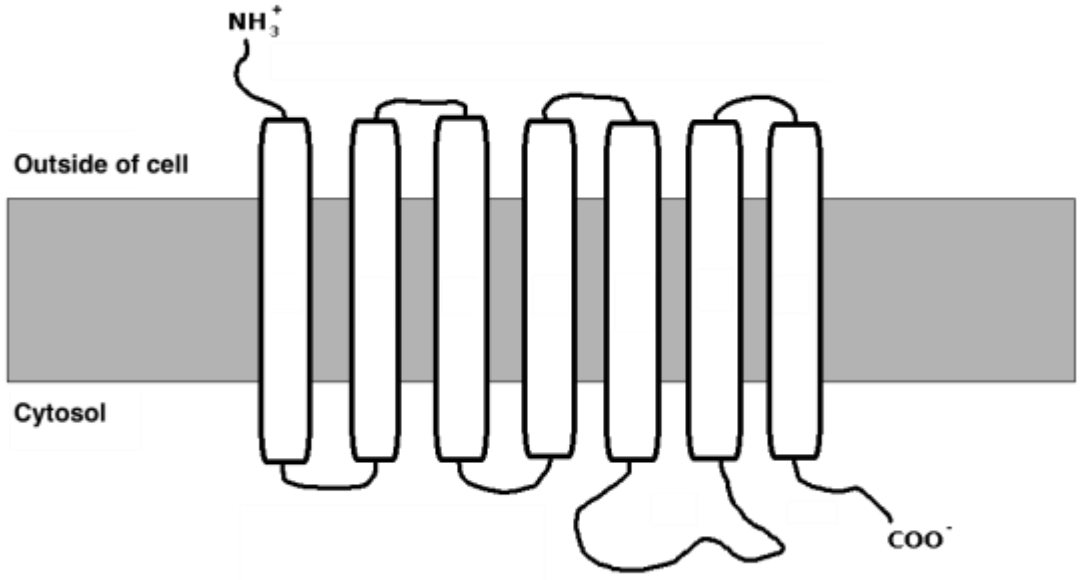
Many signalling pathways, involving both intracellular and cell surface receptors, cause changes in the transcription of genes. However, intracellular receptors are unique because they cause these changes very directly, binding to the DNA and altering transcription themselves.

Cell-surface receptors

Cell-surface receptors are membrane-anchored proteins that bind to ligands on the outside surface of the cell. In this type of signalling, the ligand does not need to cross the plasma membrane. So, many different kinds of molecules (including large, hydrophilic or "water-loving" ones) may act as ligands.

A typical cell-surface receptor has three different **domains**, or protein regions: an extracellular ("outside of cell") ligand-binding domain, a hydrophobic domain extending through the membrane, and an intracellular ("inside of cell") domain, which often transmits a signal. The size and structure of these regions can vary a lot depending on the type of receptor, and the hydrophobic region may consist of multiple stretches of amino acids that criss-cross the membrane.

This diagram shows a G protein-coupled receptor (GPCR), a type of receptor we'll examine in more detail later in the article. GPCRs have seven membrane-spanning domains, as shown by the seven segments crossing the grey region that represents the plasma membrane.



GPCR with seven trans membrane domains. N-terminus is outside the cell and C-terminus is inside.

There are many kinds of cell-surface receptors, but here we'll look at three common types: ligand-gated ion channels, G protein-coupled receptors, and receptor tyrosine kinases.

Ligand-gated ion channels

Ligand-gated ion channels are ion channels that can open in response to the binding of a ligand. To form a channel, this type of cell-surface receptor has a membrane-spanning region with a hydrophilic (water-loving) channel through the middle of it. The channel lets ions to cross the membrane without having to touch the hydrophobic core of the phospholipid bilayer.

When a ligand binds to the extracellular region of the channel, the protein's structure changes in such a way that ions of a particular type, such as Ca_2+, can pass through. In some cases, the reverse is actually true: the channel is usually open, and ligand binding causes it to close. Changes in ion levels inside the cell can change the activity of other molecules, such as ion-binding enzymes and voltage-sensitive channels, to produce a response. Neurons, or nerve cells, have ligand-gated channels that are bound by neurotransmitters.

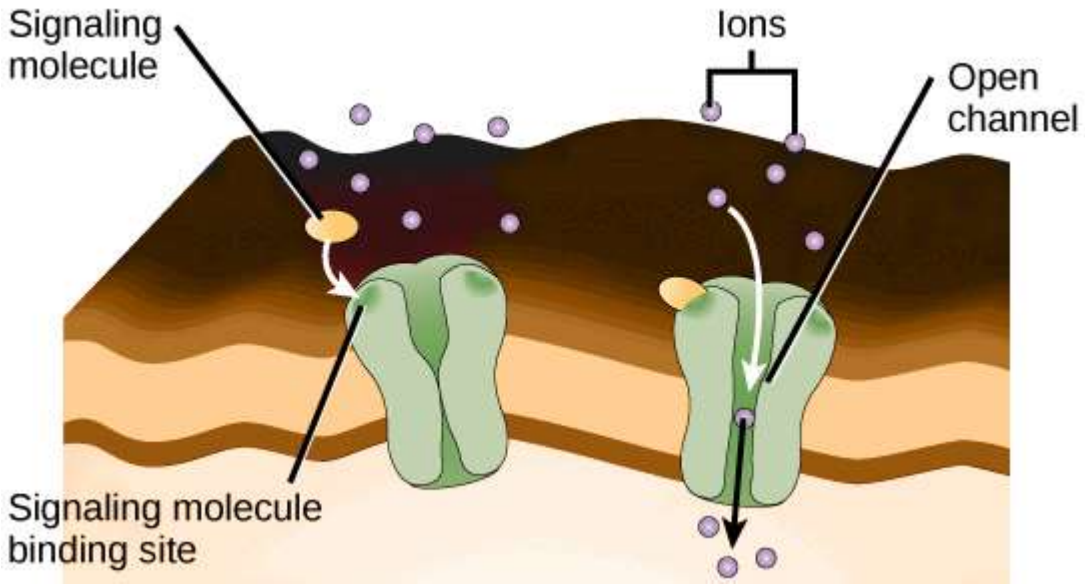


Diagram of a ligand-gated ion channel. When the ligand binds to a closed ion channel in the plasma membrane, the ion channel opens and ions can pass through it, moving into or out of the cell (down their concentration gradient).

Image modified from "Signalling molecules and cell receptors: Figure 4," by OpenStax College, Biology (CC BY 3.0).

G protein-coupled receptors

G protein-coupled receptors (**GPCRs**) are a large family of cell surface receptors that share a common structure and method of signalling. The members of the GPCR family all have seven different protein segments that cross the membrane, and they transmit signals inside the cell through a type of protein called a G protein (more details below).

GPCRs are diverse and bind many different types of ligands. One particularly interesting class of GPCRs is the odorant (scent) receptors. There are about 800 of them in humans, and each binds its own “scent molecule” – such as a particular chemical in perfume, or a certain compound released by rotting fish – and causes a signal to be sent to the brain, making us smell a smell!

When its ligand is not present, a G protein-coupled receptor waits at the plasma membrane in an inactive state. For at least some types of GPCRs, the inactive receptor is already docked to its signalling target, a **G protein**.

G proteins come in different types, but they all bind the nucleotide guano sine triphosphate (GTP), which they can break down (hydrolyse) to form GDP. A G protein attached to GTP is active, or “on,” while a G protein that’s bound to GDP is inactive, or “off.” The G proteins that associate with GPCRs are a type made up of three subunits, known as **heterotrimeric G proteins**. When they’re attached to an inactive receptor, they’re in the “off” form (bound to GDP).

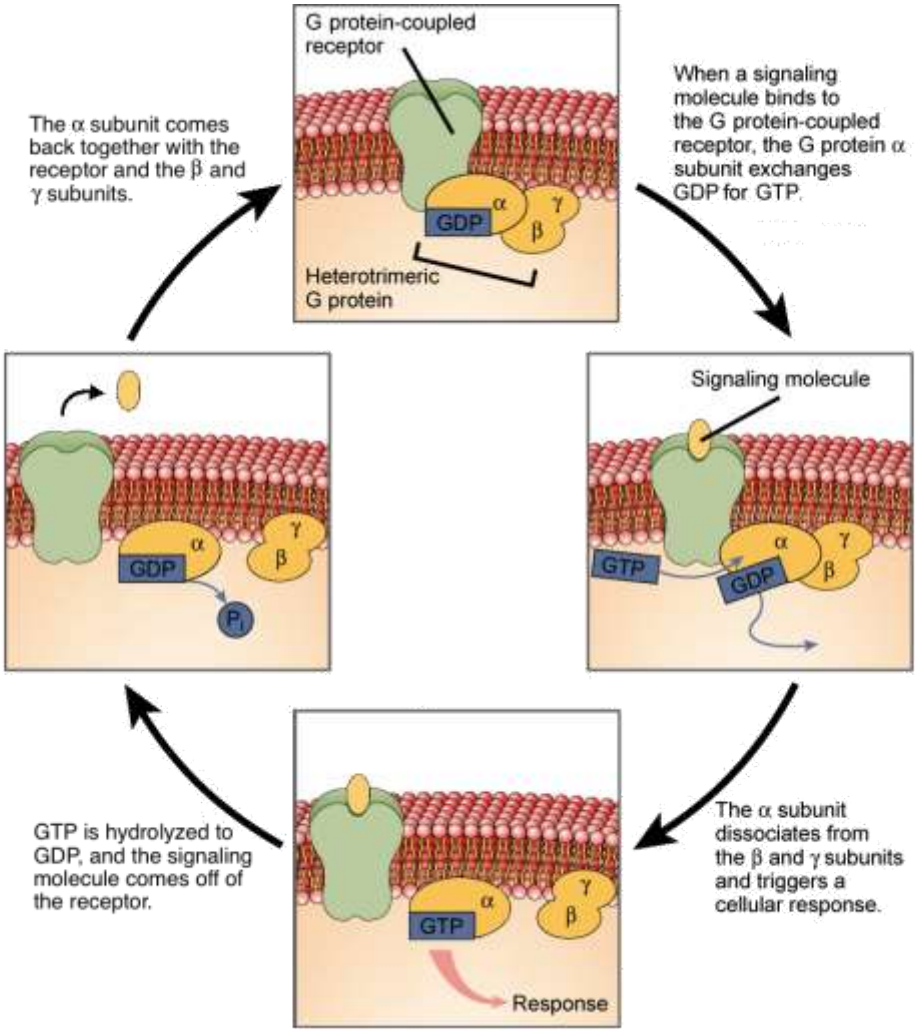


Diagram of the cycle of GPCR signalling.

1. When a signalling molecule binds to the GPCR, the G protein alpha subunit exchanges GDP for GTP.
2. The alpha subunit dissociates from the beta and gamma subunits and interacts with other molecules, ultimately triggering a cellular response. (The beta and gamma subunits may, in some cases, also participate in signalling.)
3. GTP is hydrolysed to GDP, and the signalling molecule comes off of the receptor.
4. The alpha subunit comes back together with the receptor and the beta and gamma subunits.

The cycle can then repeat when a new ligand-binding event takes place.
Image modified from "Signalling molecules and cell receptors: Figure 5," by OpenStax College, Biology (CC BY 3.0).

Ligand binding, however, changes the picture: the GPCR is activated and causes the G protein to GDP for GTP. The now-active G protein separates into two pieces (one called the α subunit, the other consisting of the β and γ subunits), which are freed from the GPCR. The subunits can interact with other proteins, triggering a signalling pathway that leads to a response.

Eventually, the α subunit will hydrolyse GTP back to GDP, at which point the G protein becomes inactive. The inactive G protein reassembles as a three-piece unit associated with a GPCR. Cell

signalling using G protein-coupled receptors is a cycle, one that can repeat over and over in response to ligand binding.

G protein-coupled receptors play many different roles in the human body, and disruption of GPCR signalling can cause disease.

Some disease-causing bacteria release toxins that interrupt G protein-coupled receptor signalling, leading to illnesses like pertussis, botulism, and cholera.

In cholera, for example, the water-borne bacterium *Vibrio cholerae* makes a toxin called choleragen, which binds to cells lining the small intestine. The toxin then enters the intestinal cells, where it modifies a G-protein that controls the opening of ion channels, locking it in a permanently active state. Because the G-protein cannot turn itself off, the ion channels remain open much longer than they should, causing ions to pour out of the cells (with water following by osmosis). This small change in a GPCR signalling pathway causes the diarrhoea, severe fluid loss, and potentially fatal dehydration seen in cholera victims.

Giving cholera patients a simple solution of salt and glucose can prevent dehydration and save lives. Learn why in the article on active transport.

Receptor tyrosine kinases

Enzyme-linked receptors are cell-surface receptors with intracellular domains that are associated with an enzyme. In some cases, the intracellular domain of the receptor actually *is* an enzyme that can catalyse a reaction. Other enzyme-linked receptors have an intracellular domain that interacts with an enzyme.

Receptor tyrosine kinases (**RTKs**) are a class of enzyme-linked receptors found in humans and many other species. A **kinase** is just a name for an enzyme that transfers phosphate groups to a protein or other target, and an receptor tyrosine kinase transfers phosphate groups to specifically to the amino acid tyrosine.

How does RTK signalling work? In a typical example, signalling molecules first bind to the extracellular domains of two nearby receptor tyrosine kinases. The two neighbouring receptors then come together, or dimerize. The receptors then attach phosphates to tyrosines in each other's intracellular domains. The phosphorylated tyrosine can transmit the signal to other molecules in the cell.

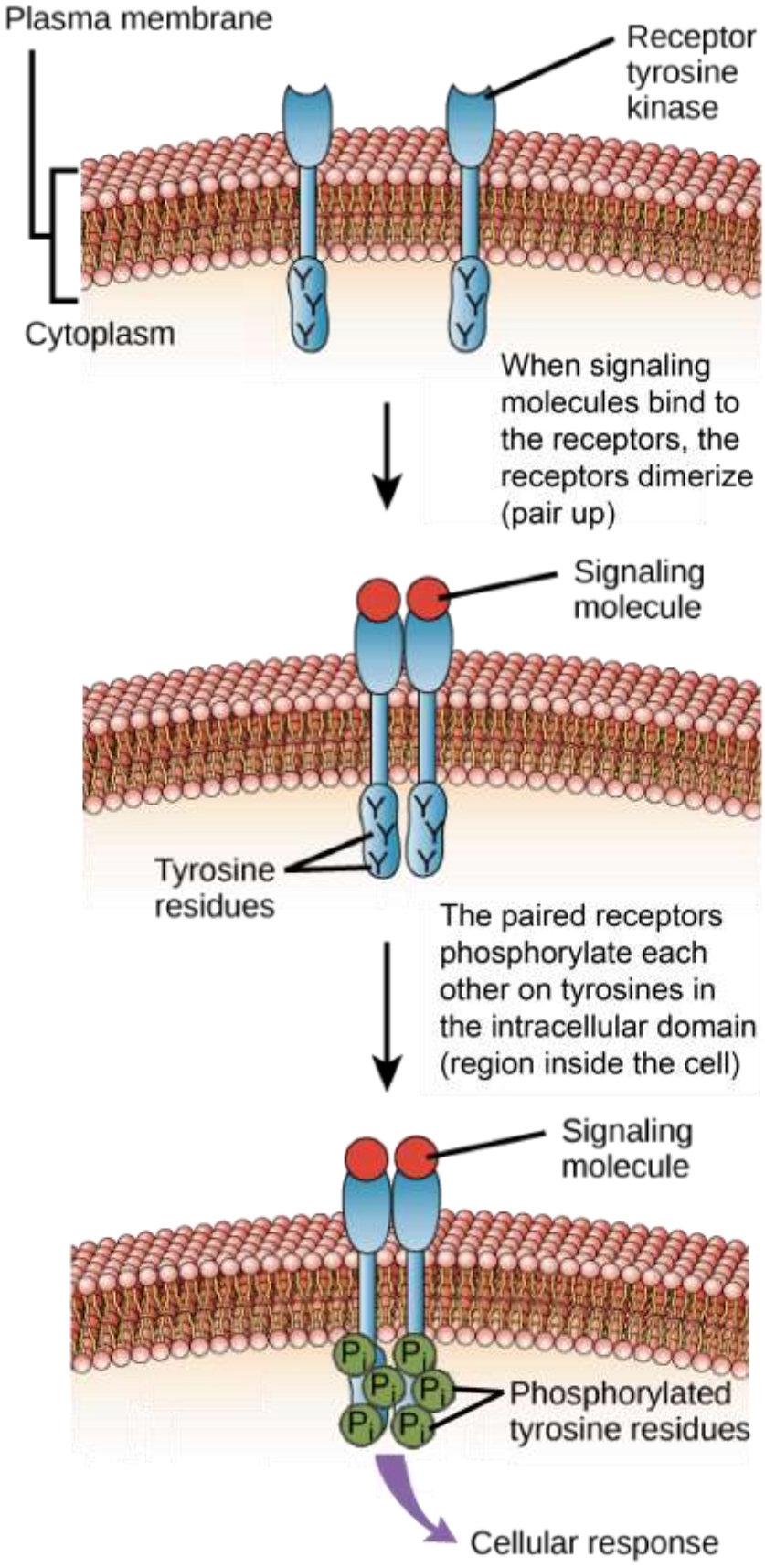


Diagram of receptor tyrosine kinases, showing ligand binding and receptor auto phosphorylation.

When signalling molecules bind to two nearby receptors, the receptors dimerize (pair up).

The paired receptors phosphorylate one another on tyrosine residues in the intracellular domain (the portion of the protein inside of the cell.

The phosphorylated receptors can interact with other proteins in the cell to trigger signalling pathways leading to a response.

In many cases, the phosphorylated receptors serve as a docking platform for other proteins that contain special types of binding domains. A variety of proteins contain these domains, and when one of these proteins binds, it can initiate a downstream signalling cascade that leads to a cellular response.

Receptor tyrosine kinases are crucial to many signalling processes in humans. For instance, they bind to **growth factors**, signalling molecules that promote cell division and survival. Growth factors include platelet-derived growth factor (PDGF), which participates in wound healing, and nerve growth factor (NGF), which must be continually supplied to certain types of neurons to keep them alive8^88start superscript, 8, end superscript. Because of their role in growth factor signalling, receptor tyrosine kinases are essential in the body, but their activity must be kept in balance: overactive growth factor receptors are associated with some types of cancers.

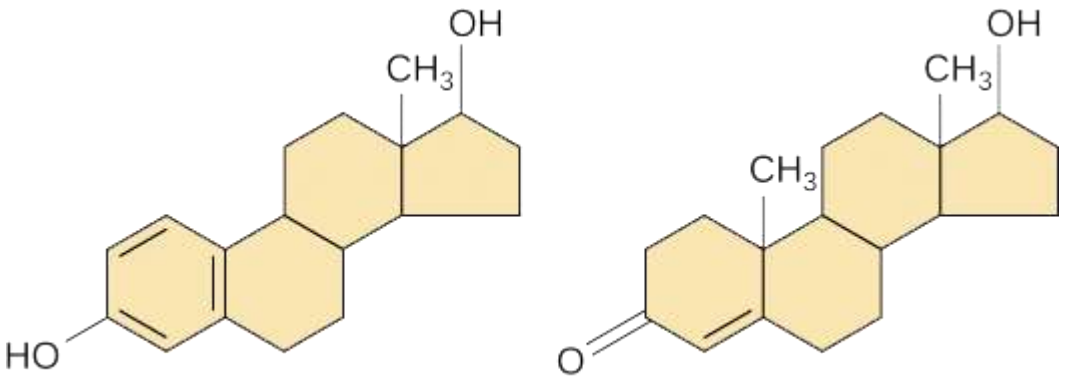
Types of ligands

Ligands, which are produced by signalling cells and interact with receptors in or on target cells, come in many different varieties. Some are proteins, others are hydrophobic molecules like steroids, and others yet are gases like nitric oxide. Here, we'll look at some examples of different types of ligands.

Ligands that can enter the cell

Small, hydrophobic ligands can pass through the plasma membrane and bind to intracellular receptors in the nucleus or cytoplasm. In the human body, some of the most important ligands of this type are the **steroid hormones**.

Familiar steroid hormones include the female sex hormone estradiol, which is a type of oestrogen, and the male sex hormone testosterone. Vitamin D, a molecule synthesized in the skin using energy from light, is another example of a steroid hormone. Because they are hydrophobic, these hormones don't have trouble crossing the plasma membrane, but they must bind to carrier proteins in order to travel through the (watery) bloodstream.



Estradiol **Testosterone**

Chemical structures of estradiol and testosterone. Both have four fused hydrocarbon rings. The two hormones differ in the double bond patterns of the rings and in the functional groups attached to them.

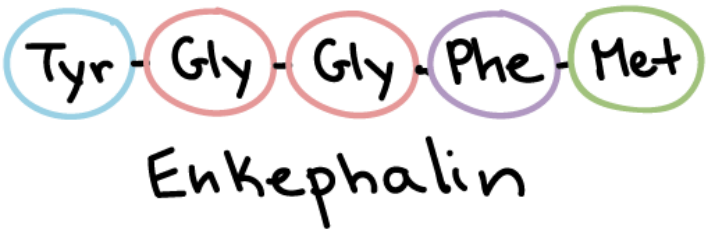
Nitric oxide (NO) is a gas that acts as a ligand. Like steroid hormones, it can diffuse directly across the plasma membrane thanks to its small size. One of its key roles is to activate a signalling pathway in the smooth muscle surrounding blood vessels, one that makes the muscle relax and allows the blood vessels to expand (dilate). In fact, the drug nitro-glycerine treats heart disease by triggering the release of NO, dilating vessels to restore blood flow to the heart.

NO has become better-known recently because the pathway that it affects is targeted by prescription medications for erectile dysfunction, such as Viagra.

Ligands that bind on the outside of the cell

Water-soluble ligands are polar or charged and cannot readily cross the plasma membrane. So, most water-soluble ligands bind to the extracellular domains of cell-surface receptors, staying on the outer surface of the cell.

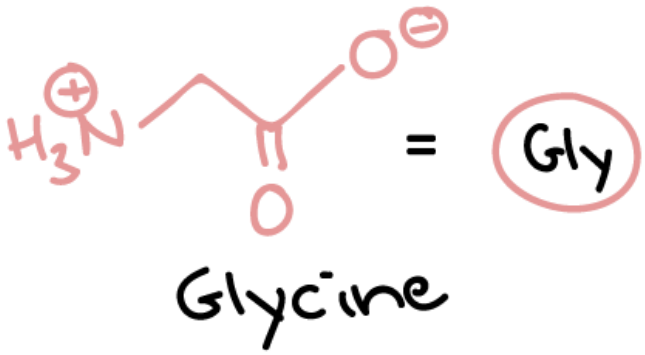
Peptide (protein) ligands make up the largest and most diverse class of water-soluble ligands. For instance, growth factors, hormones such as insulin, and certain neurotransmitters fall into this category. Peptide ligands can range from just a few amino acids long, as in the pain-suppressing encephalin, to a hundred or more amino acids in length.



Encephalin: a short peptide ligand of sequence Tyr-Gly-Gly-Phe-Met.

As mentioned above, some neurotransmitters are proteins. Many other neurotransmitters, however, are small, hydrophilic (water-loving) organic molecules. Some neurotransmitters are

standard amino acids, such as glutamate and glycine, and others are modified or non-standard amino acids.



Glycine: an amino acid.