Biological Interactions: Drug and Receptor Interaction, Agonism and Antagonism, Shape and Isomerism, and the Role of Water

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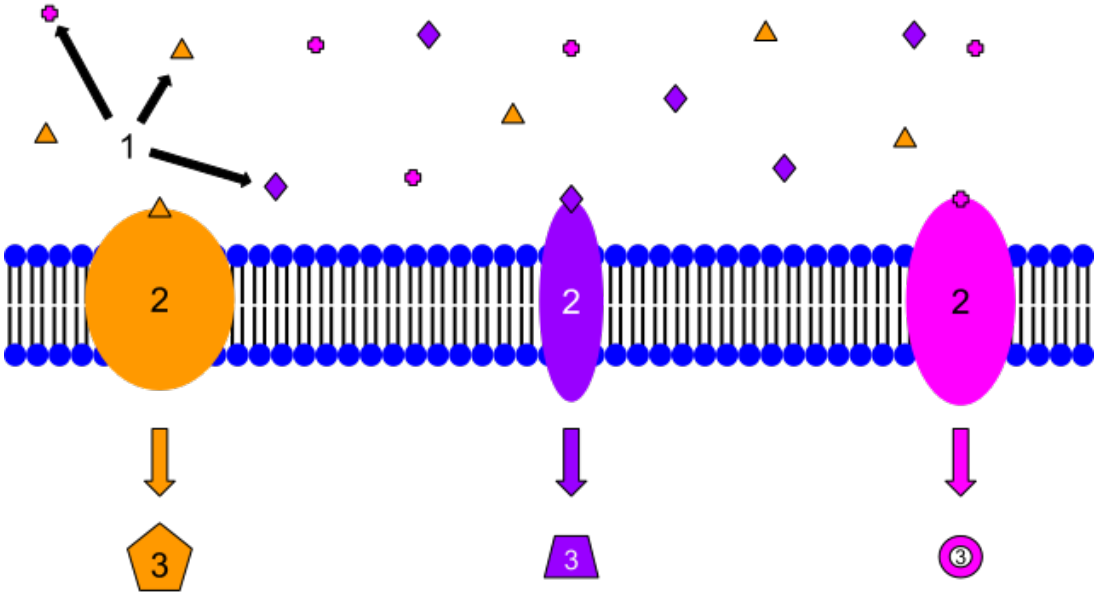
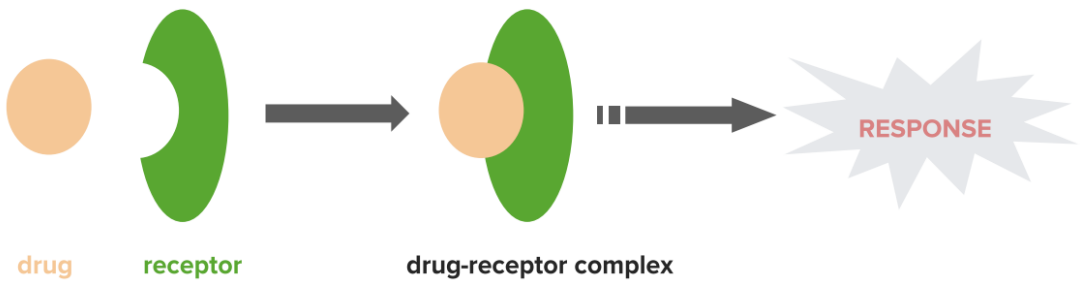
Drug and receptor interaction is an important field of study in medicine. Knowing the chemistry behind these interactions leads to understanding how drugs work in the treatment of different ailments. In this article, the basic chemistry of receptors found in biological membranes is discussed. Also included in this article are the different types of interactions possible between the drug and receptors.



Receptors and Ligands

Note: A receptor is a protein within a cell or in a cell membrane, which responds specifically to a particular neurotransmitter, hormone, antigen, or other substance (ligand). It usually undergoes a conformational or biochemical shift in such a way that it initiates a chain of intracellular events by which the cell reacts to the initial ligand.

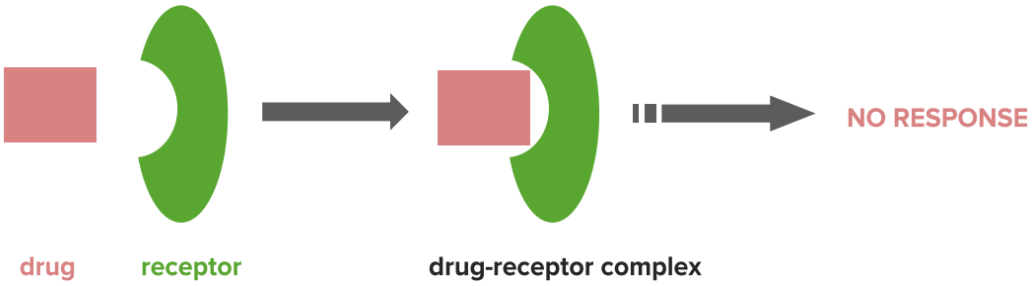


Receptors are **specific areas of proteins and glycoproteins** embedded in the cellular membrane or in the nuclei of living cells. Ligands may selectively bind to these receptors. Binding of ligands is significantly affected by the **stereoelectronic structure of compounds** which will result in specific types of interactions with the receptors.

The ligands usually **selectively bind with the receptors** that have complementary properties with it. When ligands attach to these receptors, a biological response – positive or negative – will occur. **Positive responses** involve promoting or activating physiological processes, such as the opening of ion channels. **Negative responses** occur if the reverse happens. The binding of the ligand to the receptor causes inhibition of physiological processes.

One common ligand is pharmaceutical drugs. Each drug is a ligand for a particular receptor. And drugs, depending on their properties, can be agonistic or antagonistic of a receptor and the specific physiological processes associated with it. **Drugs that result in a positive physiological response are called agonists, while drugs that bind to the receptor but do not cause a response or cause the inhibition of a response, are called antagonists.** For example, muscle relaxants bind to cholinergic receptors, and a naturally occurring agonist at this class of receptors is acetylcholine:

- **Muscle relaxants** bind to **cholinergic receptors** and block it.
- Since the receptor is now blocked, **acetylcholine** cannot bind.
- Since **acetylcholine** cannot act, the muscle cannot contract (or contracts once, but cannot prepare for another contraction).
- Since this type of drug blocked an active site without giving rise to a response, it is an **antagonist.**



Other active sites where drugs can bind include **enzymes.** This apparent contradiction was resolved by the introduction of the idea of a receptor. A receptor is a site where a drug binds and then brings about a physical response.

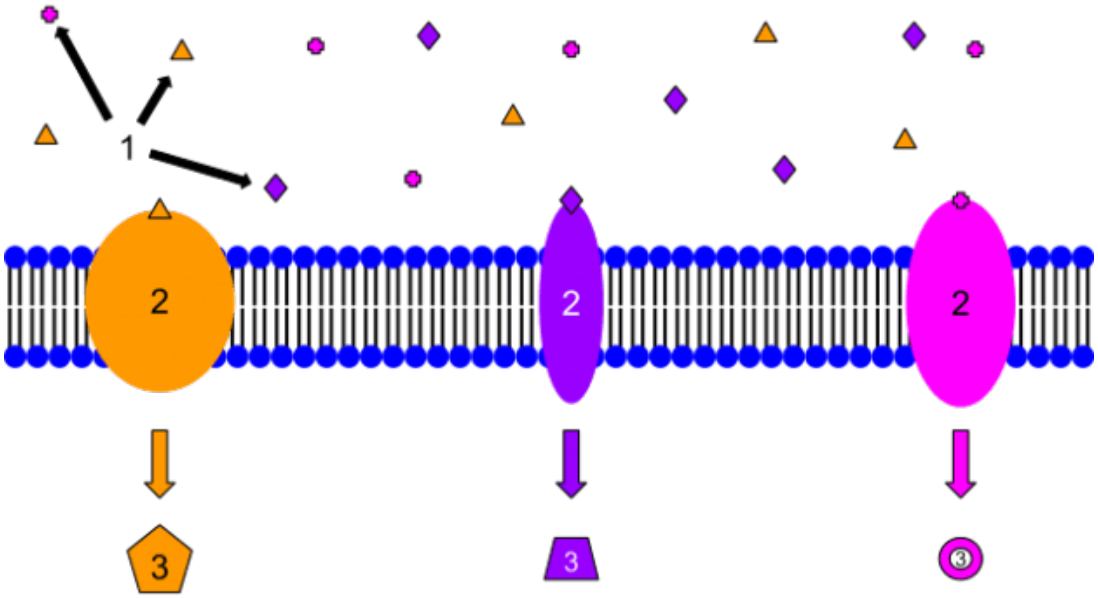


Image: “1. Ligands 2. Receptors 3. Secondary Messengers. These are examples of membrane receptors. Typically, they are proteins that are embedded in the membrane. Although there are many different ligands located outside of the cell, membrane proteins are specific, and only certain ligands will bind to each one. That is why each protein has a different ligand and also induces a different cellular response. The response may be a transcription of a gene, cell growth, or any other cellular actions.” by Isaac Webb. License: CC BY-SA 3.0

Drugs are recognized by their targets via various types of interaction. Drugs binding at the same site but in a different way can give rise to different effects (e.g. agonists and antagonists). Knowledge of these interactions allows us to work out how drugs bind, design new drugs, and predict how they will bind.

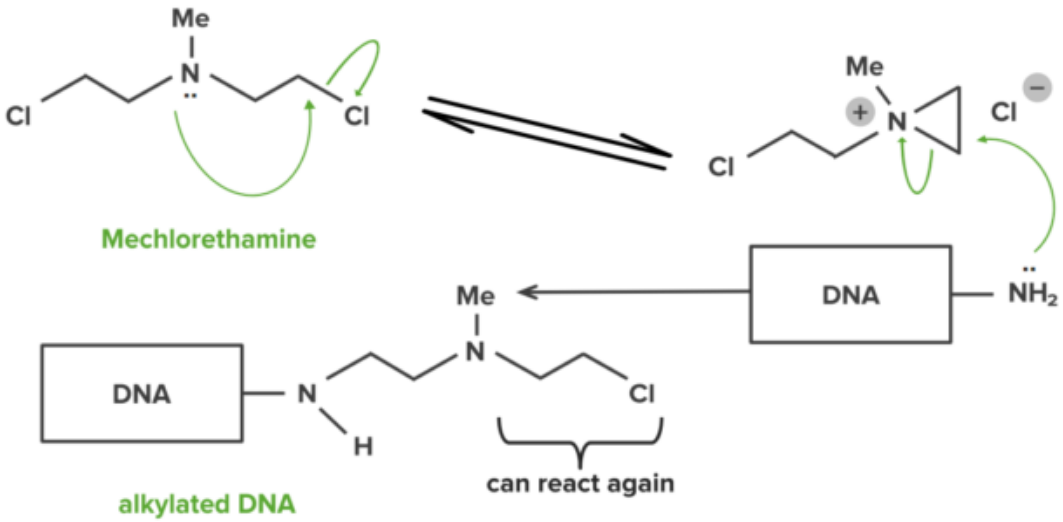
Types of Interaction

The type of binding between ligands and receptors is governed by the **concept of chemical bonding**. Intra- and intermolecular forces of attraction play a big role in understanding the binding chemistry between ligands and receptors. These **interactions include covalent bonding, ionic bonding, and dipole-dipole interactions**. When the ligand approaches the receptor and is within an appropriate distance, a bond is formed and the drug’s mechanism of action occurs (e.g. agonism or antagonism).

Covalent Bonding

A small number of drugs can also make covalent bonds with their targets. Covalent bonds are strong and hence drugs forming them will usually be permanently bound to their target. Some anti-cancer drugs **alkylate** the DNA within tumor cells. The alkylated DNA cannot function and hence the cell dies (e.g. **mechlorethamine)**.

Example of DNA interstrand linking



Ionic interactions are more reversible, compared to its covalent counterpart. This type of bond is effective at greater distances between the charges. The strength of this interaction is dependent on the distance between the charges.

Bond type	Approx. energy/ kJ/ mol
covalent (single)	300—450
ionic	20—40
ion-dipole	up to 150
hydrogen	37
dipole-dipole	5
hydrophobic	4
Van der Waals	1

Electrostatic Interactions

In an electronic dipole, a **polarized bond** is formed. In it, there is a **partially positive end and a partially negative end**. The interaction between the positive and negative ends of different compounds form electrostatic bonds with other polar molecules or ionized compounds.

Dipole-Dipole Interaction

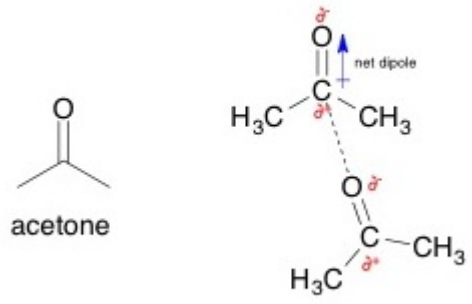


Image: “Dipole-dipole interactions between two acetone molecules, with the partially negative oxygen atom

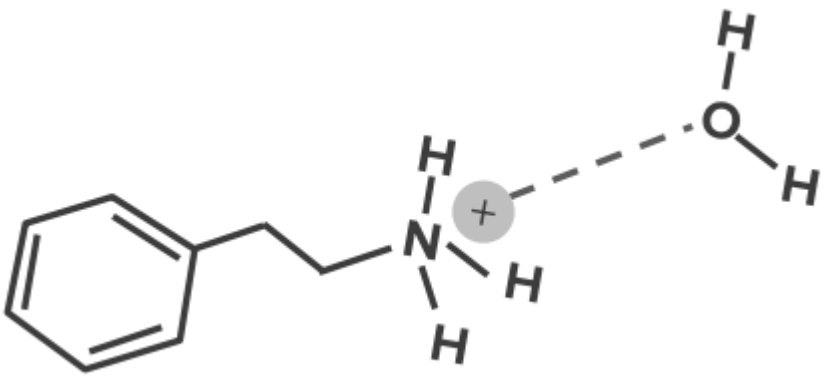
interacting with the partially positive carbon atom in the carbonyl." by AviMole602. License: CC BY-SA 3.0

When **interactions** are **between two polar compounds**, a dipole-dipole interaction will occur. In this type of electrostatic interaction, the partially positive end of the compound will interact with the negative end of the other compound. This specific interaction is **very weak** as there is no formation of permanent bonds.

In many molecules, there are permanent dipoles due to the difference in electronegativities of atoms sharing chemical bonds.

Ion-Dipole Bonds

In ion-dipole interactions, an **ion close to a polar molecule will be attracted to the end of the polar molecule which has a partial opposite charge to it.** When there is an appropriate distance between the two molecules, an electrostatic interaction will happen. This will mean a positive ion will go near the negative end of the polar molecule, while a negative ion will approach the polar molecule in its positive end. Many drug molecules have ionized functional groups. The charges on these groups will bind with permanent dipoles.



This type of bonding plays a key role in the water solubility of a drug.

Charge-Transfer Complexes

This type of complex is formed **between electron donor groups adjacent to electron acceptor groups**. The relative positive or negative molecules transfer portions of its charges to the other molecule. In the process, a weak electrostatic bond is formed.

Hydrophobic Bonding

This is a very weak form of bonding which only occurs when the **non-polar sections of molecules aggregate together in the presence of water because of the low water solubility**. Hydrophobic molecules don't like to interact with polar water molecules, and so when water is present, their tendency is to aggregate and be closer to each other.

Van der Waals Bonding

Van der Waals bonds exist between all atoms. They arise because the electron cloud associated with an atom or molecule is constantly moving so that the electrons are never

evenly distributed. Small, local, **instantaneous dipoles** (charge separations) occur. Diploes behave like small magnets and will attract one another.

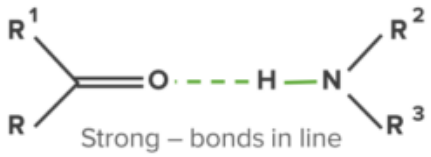
Van der Waals forces are weak. The larger the surface area and the larger the number of electrons in the molecules the larger the interaction will be. These interactions will only occur between molecules very close together: 0.4—0.6 nm apart. The forces drop off quickly if the molecules move apart. **Force equals $1/d^6$ where d is the distance between the molecules**.

These forces are insignificant for individual atoms but can be important in parts of molecules with lots of atoms, especially if the surfaces of the molecules are the right shapes to allow for a close fit.

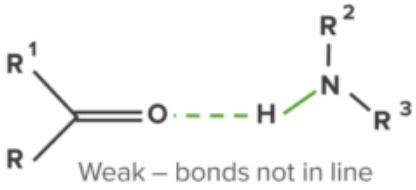
Hydrogen Bonds

Hydrogen bonds are special types of dipole interactions. They are formed when functional groups are present which contain N, O, or S and there is H linked to one of these atoms. For example, between two molecules of water:

- Due to the difference in electronegativity between O and H the O-H bond is polarized.
- Lone pairs of electrons on the oxygen molecule will bond with the hydrogen, which has a partial positive charge.
- The H is effectively shared between the donor and acceptor.
- Donors can form 1 H bond for each H. Acceptors can form 1 H bond for each electron Ione pair. H bonds are directional.



Strong – bonds in line



Weak – bonds not in line

Hydrogen bonds are important not only in drug-target interactions but also in holding together the structure of proteins and DNA.

Ionic Bonding

Ionic bonds, formed between molecules with opposite charges, are strong and can act across long distances. Drugs are often ionized and the active sites in receptors contain charged groups (carboxylic acids and amines).

London Dispersion Forces

London dispersion forces may also cause interactions between a drug and a receptor. The interaction is **very weak** as there is no permanent dipole present in the molecules. This means the positive and negative ends only occur for a very short span of time. They usually arise because of the uneven distribution of electrons at a specific time period.

Shape and Isomerism

In order for drugs to fit an active site, they must first have the correct shape.
Usually, only one isomer of a drug will have the required activity. Most natural molecules

have stereocentres and occur in single optical isomers (e.g. the amino acids which make up proteins, and hence receptors and enzymes).

However, drugs should be administered as a single enantiomer, since the mirror images may have other effects including:

- Producing side effects
- Countering the effect of the drug
- Being metabolized into a toxic product

Geometrical isomerism

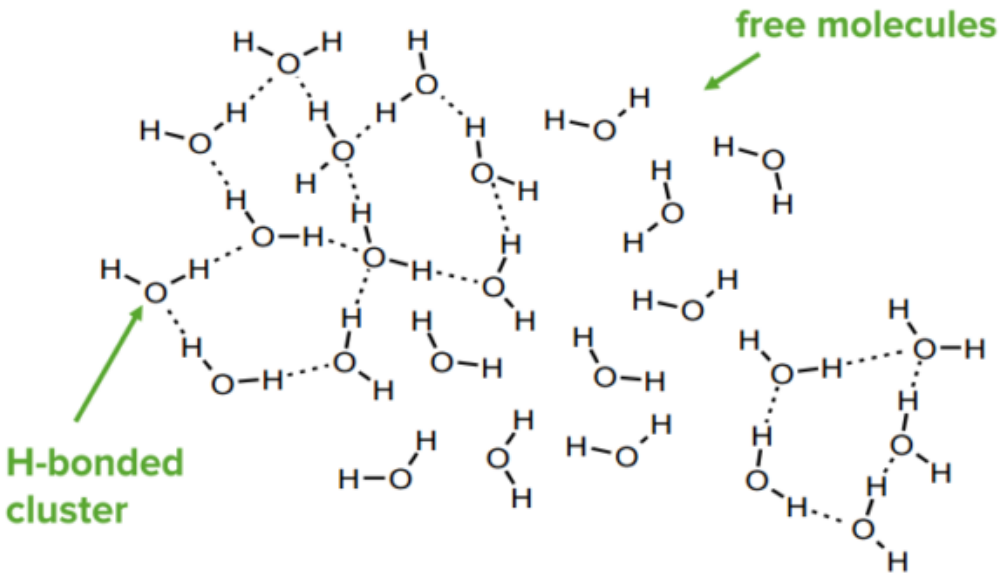
These occur when there is no free rotation around a bond (e.g. double bonds). The functional groups end up in different places.

Conformational isomerism

Molecules can adopt preferred shapes although they can exist in other conformations (e.g. cyclohexane). If the drug has a preferred conformation that fits the active site, then it will usually bind more easily than if it needed to adopt an alternative shape.

The Role of Water

Any system will adopt the lowest energy configuration. In chemical systems, this will mean that the participant will form as many bonds as possible of the strongest type. For example, water molecules will create H-bonds with each other. In ice, each molecule makes 4 H-bonds. In liquid water, H-bonds are continuously forming and breaking—on average each molecule makes 3.4 H-bonds. At any one time, liquid water can have highly H-bonded clusters and areas with few H-bonds.



References

Thomas, G. (2007). Medicinal Chemistry. 2nd ed. John Wiley & Sons Ltd. England.

Patrick, G. (1995). An Introduction to Medicinal Chemistry. Oxford University Press. United

States of America.

Burdge, Julia & Overby Jason (2012). Chemistry Atoms First. USA: McGraw-Hill Companies, Inc.

LeMay, et al. (2002). Chemistry: Connections to Our Changing World.. Pearson education Asia Pte Ltd. Singapore

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