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 site where a drug binds and then the receptor brings about a physical response.

Receptors are *specific areas in 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 **s stereoelectronic structure of compounds** which will result in specific types of interactions with the receptors.

The ligands usually **selectively bind with the receptors** with complementary properties with it. When ligands attach themselves to these receptors, a biological response – positive or negative – will occur. **Positive responses** involve promoting or activating physiological responses, 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 responses.

- The drug is a ligand for this receptor
- It is described as an agonist
- In the case of the muscle relaxants, the receptor was identified as being in a family called the cholinergic receptors
- A naturally occurring agonist at this class of receptors is acetylcholine:

![Acetylcholine](image)

The mechanism of drug action involves the drugs attaching themselves to specific receptors, causing stimulation or inhibition of physiological response. Drugs that result in positive physiological response are called **agonists**, while drugs that bind to the receptor but do not cause a response, are called **antagonists**.

- Since the receptor is now blocked, **acetylcholine** cannot bind
- Since **acetylcholine** cannot act, the muscle contracts
- Drugs which block active sites without giving rise to a response are called **antagonists**
- 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 the receptor brings about a physical response.
Response

**Note:** The drugs found to contract muscle were shown to be acting at the same receptors. These were found to bind to the receptors but without giving rise to a physical response.

**Agonism and Antagonism**

Drugs are recognized by their targets by a number of 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 the drug binds and design new drugs and predict how they will bind.

**Types of Interaction**

The binding of ligands to 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 the ligands and the receptors. These interactions include *covalent bonding, ionic bonding, and dipole-dipole interactions*. When the ligand approaches the receptor in an appropriate distance, a bond is formed, and then the drug
This type of bonding is the strongest form of bond that can be formed between a ligand and a receptor. The bond formed is so very strong that detachment of the ligand is very hard and non-spontaneous. This type of interaction is usually not employed in drug action.

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.

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

**Electrostatic Interactions**

In an electronic dipole, a *polarized bond* is formed. In it, there is a *partially positive and 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**

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 with it. When they approach the 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 will have ionized functional groups
- The charges on these groups will bind with permanent dipoles, e.g.

![Image of ion-dipole bond]

- This type of bonding play a key role in the water solubility of a drug

A salt of a weak base and a weak acid is not necessarily very water-soluble.

Charge-Transfer Complexes

This type of complexes 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 Waal’s 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.

Alkene Nomenclature

Van der Waal’s 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: \textbf{Force a }1/d^6\textbf{ where }d = \textit{distance between.}

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 a close fit.

\section*{Hydrogen Bonds}

Hydrogen bonds are special types of dipole interactions. They are formed when there are functional groups present which contains N, O or S and there is H linked to one of these atoms.

E.g. two molecules of water:

\begin{itemize}
  \item Due to the difference in electronegativity between O and H the O-H bond is polarized.
  \item Lone pairs of electrons on the oxygen bond with the hydrogen which has a partial positive charge
\end{itemize}

\textbf{Hydrogen bond donor and acceptor}

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 lone pair. H bonds are directional, i.e.:

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=0.5\textwidth]{hydrogen_bonds.png}};
\end{tikzpicture}
\end{center}

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

\section*{Ionic Bonding}

Ionic bonds, formed between species 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).

\section*{Covalent Bonding}

The majority of the bonds within drugs and their targets will be covalent. 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 \textbf{alkylate} DNA in tumor cells. The alkylated DNA cannot function and hence the cell dies, e.g. \textbf{mechlorethamine}.

\textbf{Example of DNA interstrand linking}
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 as the mirror images may have other effects including:

- producing side effects
- countering the effect of the drug
- being metabolized to a toxic product

Geometrical isomerism

These occur when there is no free rotation about 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 which fits the active site then it will usually bind more easily than if it needed to adopt an alternative shape think.
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 H-bond 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, there will be highly H-bonded clusters and areas with few H-bonds.

Review Questions

The correct answers can be found below the references.

1. Which of the following interactions forms the strongest bond between the drug and the receptor?
   A. Ion-dipole
   B. Covalent bonding
   C. Ionic interaction
   D. Dipole-Dipole

2. Which of the following is responsible for the aggregation of non-polar molecules in hydrophobic bonding?
   A. Acetone
   B. Water
   C. Ethanol
   D. Ethane

References

