Pharmacology 101 (Part 3) The Grand Finale

In the previous two editions of The Responder we discussed the basics of pharmacology and pharmacokinetics which included the processes of absorption, distribution, metabolism and excretion. In this edition we will focus on the pharmacodynamic phase of pharmacology, which in essence relates to the study of how a drug acts on the body.

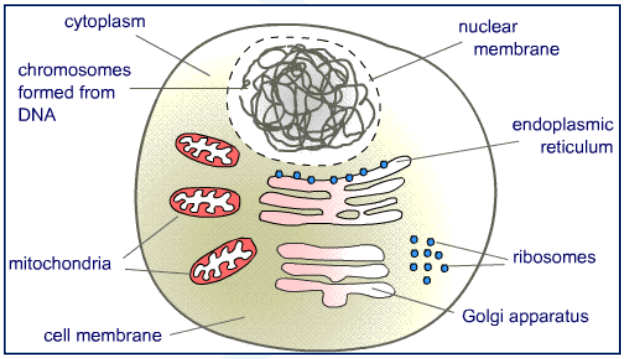
All functions within the body are mediated by control systems which depend on enzymes, receptors on cell walls, carrier molecules, and specific macromolecules such as DNA. Most drugs act by influencing one of these systems at a cellular level.

In general, drugs act by binding to proteins. These protein targets can be divided into four main categories, namely, receptors, ion-channels, enzymes and carrier proteins.

There are however certain drugs that do not bind to proteins. These include anti-tumour medications that bind to DNA and bile sequestrants which bind bile acids in the gastrointestinal tract thereby preventing them from being absorbed.

In order to better understand how drugs work at the cellular level, let's first do a recap on some very basic cellular anatomy.

A bit about cellular structure



There are many billions of cells in the body. Cells make up tissues and tissues form organs. Most cells are specialised to a particular function, e.g., nerve cells conduct nervous impulses, muscle cells contract and glandular cells secrete hormones.

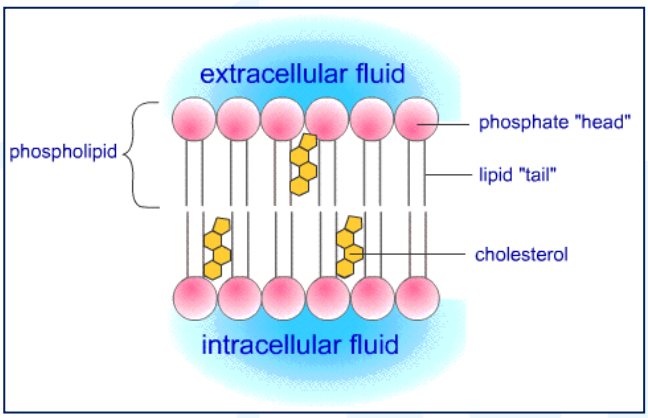
When looking at these cells from the outside, they may all look very different, however when looking inside the cells, it will be seen that they generally contain the same components which carry out the same processes.

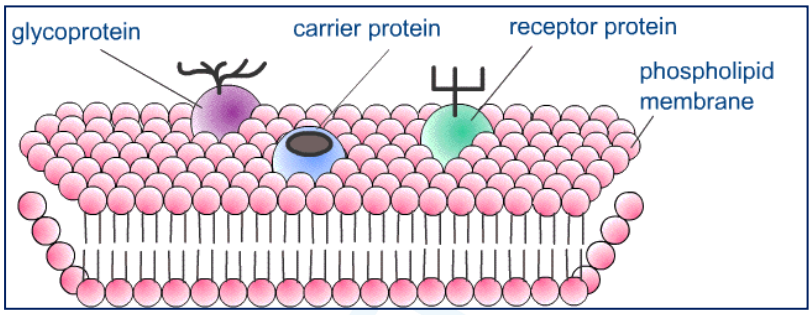
Mitochondria - produce most of the energy for the cell. They use the energy from fuel such as glucose and lipids to produce ATP (adenosine triphosphate) a small packet of energy that powers most of the cells' biochemical processes.

Cytoplasm - is a rich mixture of enzymes, nutrients and electrolytes for the large number of biochemical processes that take place continuously in each cell.

Cell Membrane – is a vital structure that regulates what goes in and out of the cell. It is composed mainly of a phospholipid bilayer interspersed with cholesterol.

Several organelles are involved in the production of proteins. There are tens of thousands of different proteins made by cells. This is why they make such superb targets for drugs.





Some proteins are used within the cell and others are exported from the cell by a process called exocytosis. Many proteins are lodged in the cell membrane as receptors, ion channels or carrier proteins. This group forms a major target for drug interaction.

It is important to note that the phospholipid bilayer is predominantly lipid in character. This in essence means that lipids such as steroid hormones will pass through easily whilst non-lipid materials such as amino acids and ions have to go through carrier proteins and ion channels in the cell membrane. Sometimes energy in the form of ATP is required to move materials in and out of cells through the carrier proteins

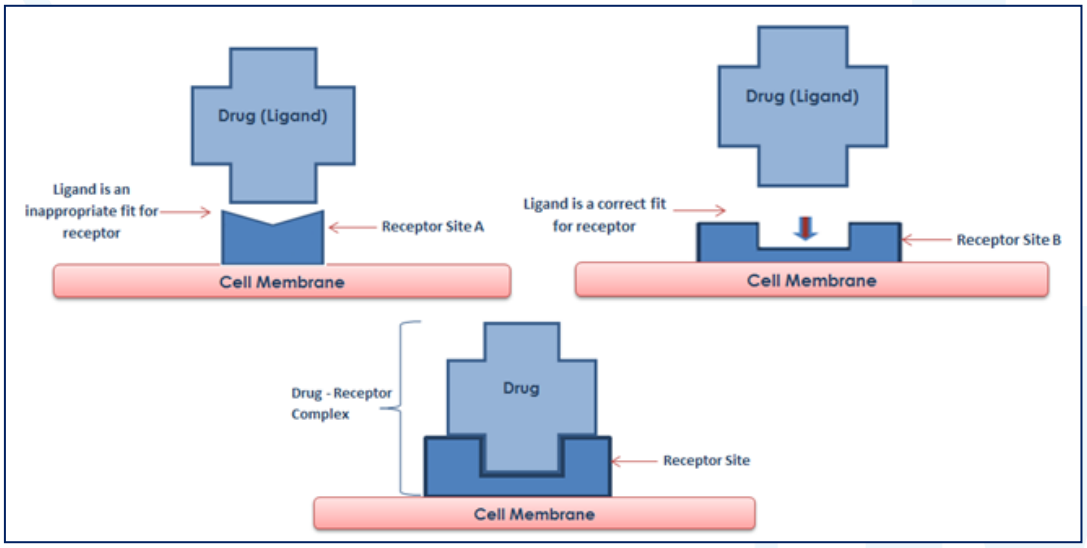
Protein Drug Targets

As mentioned earlier, there are four main protein targets to which drugs bind.

- Receptors
- Ion-channels
- Enzymes, and
- Carrier Proteins

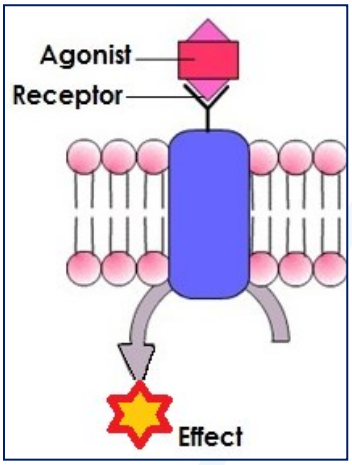
Receptors

Cells generally communicate with each other by releasing chemicals that are detected by target cells. Some communication takes place on a systemic basis e.g. hormones circulate in the blood and are detected by cells distal to the point of release. Other chemicals operate on adjacent cells only and these are generally called mediators or, in the case of nerve cells, neurotransmitters.

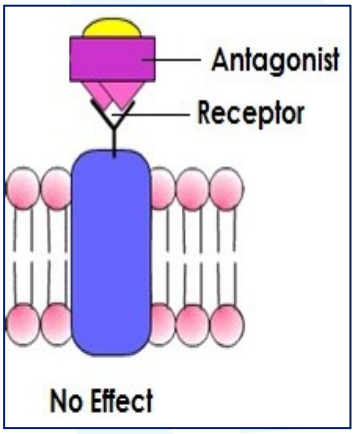


Target cells must have the appropriate receptors to detect and respond to hormones, mediators and neurotransmitters. The collective name for a chemical that binds to a receptor is a ligand.

Receptors are proteins that are specific to the shape of the ligand, much like the way that a lock is specific to a particular key. Only cells that have an appropriate receptor will respond to a particular ligand.



A drug that has an affinity (binds tightly) for a receptor, and that once bound to the receptor can cause a specific response, is called an agonist. For example, Morphine is an opioid agonist that binds to mu receptors in the central nervous system to depress the sensation of pain.



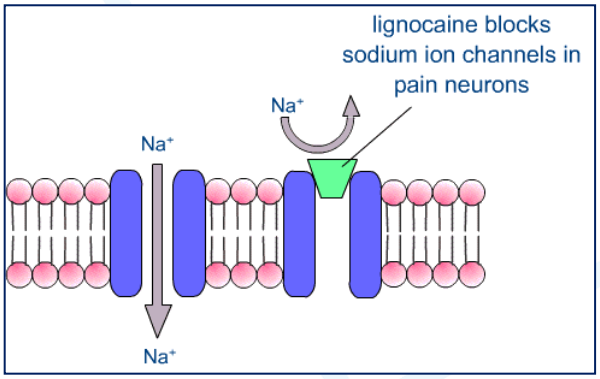
Drugs that bind to receptors and do not cause a response are called antagonists or receptor blockers. These will reduce the likelihood of another drug or chemical binding and hence will reduce or block further drug activity. Antagonists may be competitive, in which case they compete with an agonist for receptor sites and inhibit the action of the agonist.

The action of the drug depends on whether it is the agonist or antagonist which occupies the most receptors. For example, Naloxone is a competitive antagonist for mu receptors and is used to reverse the respiratory depression effects associated with opioid overdose. It will compete with morphine for mu receptors and reverse the effects of an excessive dose of morphine. A non-competitive antagonist will inactivate a receptor so that an agonist cannot have an effect.

It is important to remember that many antagonists have a shorter half-life than the drugs they compete with for receptors. In the clinical setting, it is crucial to reassess the patient continuously to ensure that the effects of the antagonist have not worn off to the point where the adverse effects of the drug you are trying to block (agonist)… return.

Drugs acting on Ion Channels

Ion channels are selective pores in the cell membrane that allow the movement of ions in and out of the cell. Some drugs will block these channels, which ultimately interfere with ion transport and cause an altered physiological response.



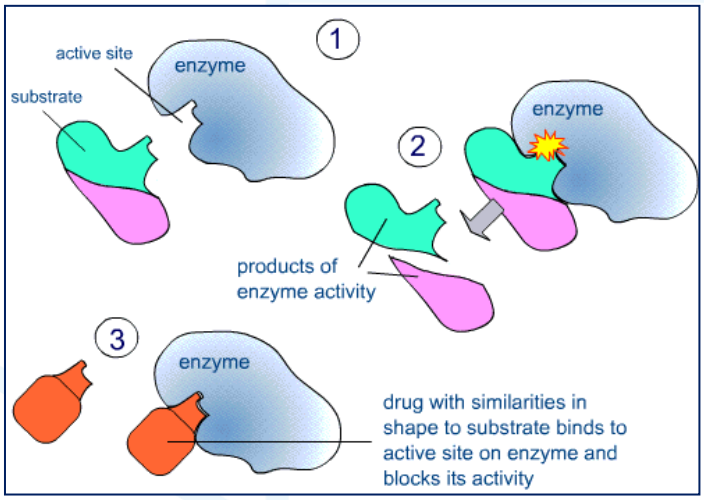
Drugs acting on ion channels can be broadly divided into blockers and modulators.
Blocking drugs physically block the channels and prevent the ion specific to that channel from moving in or out of the cell. An example of this type of action is lignocaine, a local anaesthetic. Lignocaine blocks the Na+ channels in pain neurons and so prevents nervous impulses from carrying the "pain information" to the CNS.

Modulators do not physically block the ion channel but bind to sites on the channel and either enhance or inhibit its normal operation.

Drugs acting on enzymes

There are many thousands of different enzymes active in the body, intracellular and extracellular, responsible for the catalysis of the numerous biochemical reactions necessary for life.

One of the prime targets for those drugs that act on enzymes is the active site where the enzyme interacts with its substrate (the substance on which the enzyme acts). Drugs that have a molecular shape similar to the substrate can bind to the active site and inhibit the action of the enzyme.



Non-steroidal anti-inflammatory drugs (NSAID's) are examples of drugs that act on enzymes. NSAID's inhibit the enzyme cyclo-oxygenase (COX) which catalyses a reaction in the biochemical pathway that results in the production of prostaglandins, important mediators in the inflammatory response.

Carrier proteins as sites for drug action

Ions and less lipid-soluble molecules are transported in and out of cells by carrier proteins. These carrier molecules play an important role in the excretion of drugs by the renal tubule. Among the most commonly prescribed drugs in primary care are several that block carriers.
An example of this is Furosemide, a loop diuretic which inhibits the Na+/K+/Cl- co-transporter in the membrane of the loop of Henle in the nephron of the kidney. This changes the sodium balance in the kidney, so producing large amounts of urine.

Another example is Digoxin which blocks the Sodium-Potassium Pump in cardiac muscle, which slows down heart rate and increases its force of contraction.

And in conclusion…

It is crucial to have a good understanding of the medications in your protocols. It is impossible to make an informed clinical decision if you are unfamiliar with what the drug is going to do or interact with once administered. Remember, once given, you cannot repent on the action. Yes the negative adverse side effects of certain agonists are reversible by administering an antagonist; however by following a careful thought process, you dramatically reduce the need for administering an antagonist to "bail" you out from an inappropriate action.

And that's it…. The basics of pharmacology in a nutshell. There is so much more that can be said, however I think the enormity of the subject, far exceeds the available space in The Responder. I hope you found some value in this series of articles.

The Be Safe Paramedical Pharmacy offers a full range of medications at very competitive prices. Please feel free to contact them at pharmacy@be-safe.co.za

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