Pharmacodynamics

What the drug does to the body

How do drugs work? What do they do?

In this fact sheet, we will look at the fundamental mechanisms of drug action. We will be discussing receptors and how drugs interact with them.

Drugs usually elicit more than one effect...

The desirable effects are why we give the drug, for instance penicillin helps us recover from particular bacterial infections. As with other drugs, it has side effects, effects beyond what we want it to do in the way of killing off an infection. For instance, if you take it orally, it also kills the normal bacterial flora found in the gastrointestinal tract (GIT). This can lead to the overgrowth of the bacteria that are not affected by penicillin, leading to another infection. In this case, the side effect would be an adverse effect.

Sometimes, it is more challenging to decide if a side effect is actually adverse. For instance, Diphenhydramine (Benadryl) is a 1st generation antihistamine, typically used to relieve the symptoms of allergies and colds because it can help dry up the runny eyes and nose associated with those conditions.

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Adverse Drug Reactions (ADRs)

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>&gt;10%</td>
<td>Very common when &gt;10% experience</td>
</tr>
<tr>
<td>1-10%</td>
<td>Common when 1-10% of patients experience the effect</td>
</tr>
<tr>
<td>0.1-1%</td>
<td>Infrequent when only 0.1-1% experience it.</td>
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<tr>
<td>&lt;0.1%</td>
<td>The effect is Rare when experienced by &lt;0.1% of patients</td>
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Receptors include ion channels (image by J Stoffer, from the NIGMS Image Gallery). The ions moved are most commonly sodium, potassium, calcium or chloride.
Focus on G-protein Coupled Receptors (GPCR)…

GPCR are a type of receptor that transduces a chemical signal using a series of second messengers. What this means is, a signal is received in the form of a chemical, like the neurotransmitter acetylcholine (ACh) shown in the diagram at right. When the ACh, or a drug acting like ACh, binds to this receptor, activating it, the conformation of the receptor changes and it releases the second messenger G-protein. The G-protein is actually three proteins that split apart. Depending upon which GPCR this is, the second messengers go off to activate different cascades.

The diagram is showing one of five different “muscarinic” receptors, the name for the ACh GPCR. Once stimulated, this receptor triggers a number of events that lead to the opening of potassium channels, which propagates a nerve impulse. So, this receptor is common on nerves. Other muscarinic receptors trigger gene expression, or the activation of other enzymes. There are a number of different possible outcomes.

Many drugs interact with GPCRs.

Look to your lecture slides to see pictures of different receptors we will discuss

Drugs modulate functions, they don’t create effects!

Not all drugs interact with a receptor, exceptions include:
- Mannitol (an osmotic diuretic)
- Cholestyramine (a bile acid sequestrant)
- Neutralizing antacids

What are receptors?

Simply put, they are the site where a drug interacts. They can be many types of structures, but are usually some kind of protein. Examples:

- Hormone or neurotransmitter receptors
- Enzymes
- Transport proteins, pumps and such
- Structural proteins
- Lipids, glycolipids, glycoproteins, glycolipoproteins
- Nucleic acids (either DNA or RNA) – not proteins, but proteins modulate nucleic acid functions, and can be receptors, too.
What is a ligand?

A ligand is simply a chemical that binds to a receptor. It can be the chemical the body would normally use, like a neurotransmitter, or it could be a drug.

To be “gated” simply means to be opened. If you think of the ligand as a key, and the receptor is a door, then the ligand opens a lock keeping the door closed, allowing it to open. In this case, allowing ions to flow through.

Receptor examples

Ion channels

There are many types of ion channels activated by many different ligands, just as there are many types of GPCRs. Illustrated above is another type of ACh receptor, called the “nicotinic” receptor, it is a ligand-gated ion channel (LGIC) for sodium.

- Antagonists include Pancuronium and Succinylcholine, neuromuscular junction blockers used to paralyze patients prior to surgery or intubation.

The 5-HT3 receptor is a LGIC for sodium also, but it is not a nicotinic receptor.

- Important antiemetic drugs, like Ondansetron, are 5-HT3 antagonists.

The GABA-A receptor is a LGIC for the chlorine ion. The LGIC for sodium stimulate the cell, whereas the GABA-A receptor suppresses the cell activity. GABA is therefore, inhibitory.

- GABA-A agonists include sedative hypnotics like the benzodiazepines Diazepam, Lorazepam, Alprazolam and Midazolam. Phenobarbital, a barbiturate, is also a GABA-A agonist, as are most anesthetics, including Propofol.

Enzyme receptors

Enzymes are the receptor for a number of drugs.

- Drugs such as donepezil, and neostigmine are enzyme inhibitors, in this case inhibiting Acetylcholinesterase.

- Selegiline inhibits monoamine oxidase, the enzyme that breaks down catecholamines and serotonin.

G-Protein Coupled Receptors

The norepinephrine (NE) receptors are called adrenergic. They come in two basic varieties, alpha and beta. Alpha-receptors can be 1 or 2, beta receptors come in three types, 1, 2 & 3.

- \(\alpha\) agonists include drugs to treat shock and hypotension such as Dobutamine, and Epinephrine, and nasal decongestants like Phenylephrine and Oxymetazoline.

- \(\beta\)2 agonists are bronchodilators such as Albuterol used to treat asthma and Chronic Obstructive Pulmonary Disease (COPD).

- \(\beta\) blockers are typically used to treat angina and hypertension or glaucoma. Propranolol, Atenolol and Metoprolol are common beta-blockers.

The dopamine receptors aren’t named; they are numbered like the serotonin and histamine receptors. All the dopamine, histamine and serotonin receptors (except 5-HT3) are GPCR.

Nuclear receptors

Nuclear receptors are usually proteins that modulate (control) gene expression. There are many nuclear receptors, mainly activated by steroid hormones such as cortisol, aldosterone, and the sex steroids.

- Drugs such as dexamethasone, budesonide, fluticasone, Mometasone, birth control pills, and thyroid hormone activate nuclear receptors.

Other receptors

See the lecture notes for more examples.
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But, if you have ever taken diphenhydramine, you know, it puts you to sleep. If you were using it to treat an allergy, this might be considered an adverse side effect because it wouldn’t be safe for you to drive and you would find it hard to concentrate. However, diphenhydramine is also sold as Sominex, an over-the-counter hypnotic, used for a short period of time to help people sleep! Now, the fact that it will dry up secretions will be considered a side effect.

So, keep in mind, that a side effect for one indication may be the USE in another situation.

Drug Generations

As we will see, the most popular classes of medications, including the antihistamines have something called generations. You may have noticed that diphenhydramine is called a 1st generation antihistamine. Fexofenadine (Allegra) is a 2nd generation antihistamine.

If we compare the two, we can see a few things that will generally be true whenever we see “generations.”

1. 1st generation drugs are “older” than 2nd and subsequent generations;
2. 1st generation drugs have more side effects than subsequent generations;
   a. Subsequent generations frequently target FEWER receptors, but not always.
3. Subsequent generations typically have improved efficacy for the target condition (improved dynamics); and,
4. Subsequent generations typically have longer half-lives (you don’t have to take them as often) or otherwise improved kinetics.

Receptor Regulation

The degree to which a receptor is used will often alter how much of the receptor the body produces or how sensitive the receptors are. These processes are generally called “Tolerance.”

For instance, if you take an opioid like morphine for its analgesic properties, initially you will most likely experience nausea and vomiting, sedation, euphoria and respiratory depression along with the analgesia.

Over the course of a few days, your body will down-regulate (desensitize) and internalize (through endocytosis) receptors, thus decreasing the number of receptors available for activation and changing how much drug is required to activate the remaining receptors.

Since there are several different opioid receptors involved in triggering all these effects, and they are regulated in differing ways by the body, you develop tolerance to some effects and not others.

There is no upper limit to an opioid for analgesia. As long as you allow the body to become tolerant to the dangerous side effects like respiratory depression, you can keep upping the dose.

Unfortunately, you will never become tolerant to some of the effects – like constipation or miosis.

There is also the possibility of “up-regulation” where the body produces more of a receptor or increases receptor sensitivity.

To read about opioid tolerance, go to:
Drug interactions with receptors

1. Agonists are drugs that elicit the same effect as a natural ligand. It may not cause the same DEGREE of effect. The DEGREE to which it mimics the natural ligand establishes its efficacy.

   a. An agonist may bind to the receptor for the natural ligand triggering the same result as the ligand.
      - **Dobutamine** is an agonist at β adrenergic receptors. It binds to a receptor for the natural ligand in the sympathetic nervous system, causing an increase in blood pressure.

   b. To be an agonist, the drug need not bind to the SAME place on the receptor as long as it causes the same confirmation change as the natural ligand.
      i. Allosteric agonists bind to a different location on the receptor, but cause the same effect as the natural ligand.
         - **Diazepam** is an allosteric GABA-A agonist. It does not bind to the same place as GABA, the natural ligand, but does elicit the same response.

   c. The drug may not bind to the receptor at all, but be an indirect agonist by increasing the levels of the natural ligand.
      i. The drug may block the metabolism of the ligand;
         - **Donepezil** blocks the breakdown of ACh in the brain making more ACh available.
      ii. It may block the reuptake of the ligand;
         - **Fluoxetine** blocks the reuptake of serotonin in the brain (mostly). It is what is called a selective serotonin reuptake inhibitor (SSRI) antidepressant.
      iii. It may promote release of the ligand.

2. Antagonists

   a. A drug that binds to the receptor and prevents activation.
      - **Pancuronium** blocks the nicotinic receptor in the neuromuscular junction.
      - **Aspirin** binds to and inhibits the enzyme (cyclooxygenase, COX) that produces prostaglandins.
         i. It may block the natural ligand from binding.
         ii. It may compete for the same binding site as the ligand.
         iii. It may bind to another location on the receptor and change the receptor confirmation such that the natural ligand can no longer bind.
         iv. It may cause the breakdown or removal of the receptor.

   b. The drug may be an indirect antagonist.
      i. It may block the release of the ligand.

3. Other interactions

   a. Agonist-like interactions
      i. Induction of protein synthesis and up-regulation of receptors (increased number and/or sensitivity of receptors)

   b. Antagonist-like interactions
      i. Inhibition of protein synthesis and down-regulation of receptors (decreased number and/or sensitivity of receptors).
What are endogenous ligands?

Remembering that a ligand is simply a chemical that binds to a receptor, then the endogenous ligand is the chemical normally produced by the body to specifically activate a given receptor(s). Some examples of endogenous ligands and their receptor(s) include:

- ACh – Muscarinic (GPCR) & Nicotinic (LGIC)
- NE – Alpha and Beta receptors (all GPCRs)
- DA – numbered 1-5 (all GPCRs)
- 5-HT – numbered, only 5-HT3 is LGIC
- Cortisol and other steroid hormones – nuclear receptor (modulates gene expression)

**Neurotransmitters include:**
- ACh = Acetylcholine
- NE = Norepinephrine
- DA = Dopamine
- 5-HT = Serotonin

**Hormones include:**
- Cortisol = glucocorticoid produced by adrenal cortex.

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**Homework and Exercises**

1. Read the “START HERE” announcement in Laulima for updates and instructions.
3. Review the PowerPoints and listen to the audio from the face-to-face lecture on Pharmacodynamics.
4. Complete the SLO Practice Set in Tasks, Tests and Surveys.
5. Complete the online quiz in Laulima.

If you have questions, email me at abeale@hawaii.edu

And, you are always welcome to attend the Face-to-Face section at WCC.