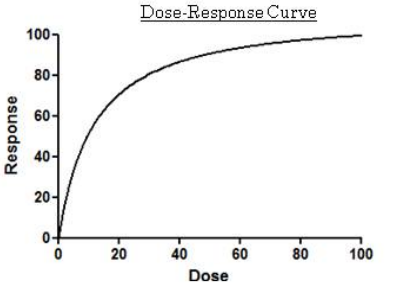
PHARMACODYNAMICS – DOSE RESPONSE RELATIONSHIPS

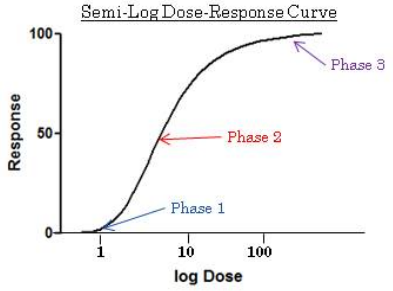
7.1 INTRODUCTION

- Pharmacodynamics is the study of what the drug does to the body.
- In pharmacodynamics we study the biochemical and physiological effects of drugs and the mechanisms by which drugs produce effects.
- In therapeutics it is important to combine knowledge of pharmacokinetics and pharmacodynamics in order to provide optimal pharmacotherapy.

7.2 DOSE RESPONSE CURVES

- In the pharmacokinetics section you learned that increasing the dose of a drug results in increased plasma concentrations.
- In pharmacodynamics you will see that increasing the dose increases the response to the drug.
- To evaluate the pharmacodynamics of drugs, we look at dose-response curves.
- Dose-response curves are monotonic, which means that the response increases as the dose increases.
- Importantly, dose response curves are not linear. For this reason we usually look at the dose response curve as a semi-logarithmic plot.



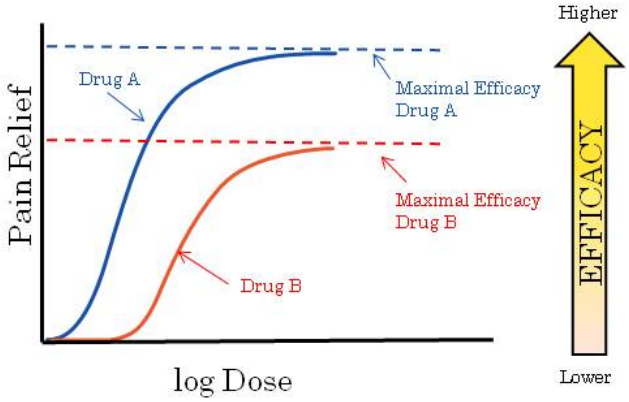


Phases of the semi-logarithmic dose-response curve

Phase 1 – Doses are too low to elicit a clinically relevant response.
Phase 2 - The response is graded and nearly linear.
Phase 3 – Larger doses do not lead to greater response. Larger doses may cause toxicity.

Efficacy

- Is a measure of how effective a drug is at a given dose.
- Maximal efficacy represents the maximum effect that a drug is capable of achieving.
- Maximal efficacy is read off the dose response curve by looking at the maximum height.

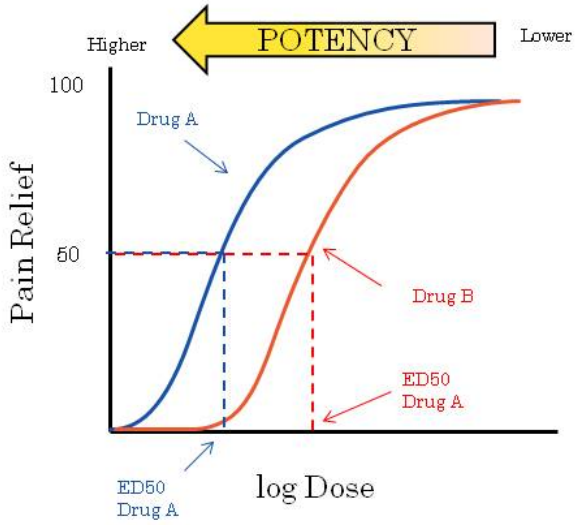


Do we always choose the drug with the highest efficacy to treat patients?

NO! We choose the drug and dose that are therapeutically effective with the fewest side effects. Health care professionals often titrate the dose of a drug. This means they start with a low dose of the drug and slowly increase the dose while monitoring the patient's response.

Potency

- Potency refers to the amount of drug required to elicit a pharmacological response.
- High potency does NOT mean more therapeutically effective.
- In order to compare potency, the drugs must produce the same therapeutic effect. For example, you can't compare the potency of a medication used for pain relief with one that lowers blood pressure.
- A more potent drug will require a smaller dose to achieve the desired effect than a less potent drug.
- Potency is determined by comparing the dose required to produce the half maximal response. This is called the ED50.

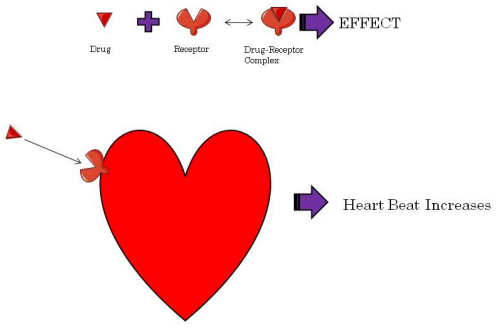


- Drugs with a lower ED50 are said to be more potent than drugs with a high ED50.

7.3 DRUG RECEPTORS

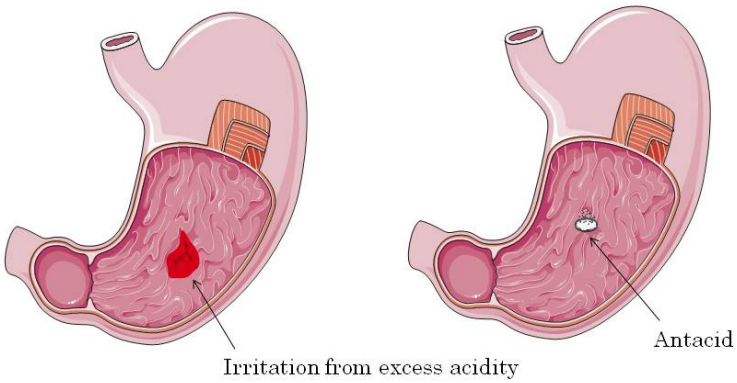
How do Drugs Produce Effects?

- Most drugs act at on cellular macromolecules (i.e. receptors, enzymes etc.).
- The majority of drug targets are receptors but drugs also act on enzymes, ion channels and transport proteins.
- Typical drug action involves the binding of the drug molecule to the macromolecule target. The complex is then able to produce a biological effect.
- Drugs typically mimic an endogenous compound in the body. For example, norepinephrine binds to receptors in the heart and increases heart rate. There are drugs that mimic the action of norepinephrine by binding to the same type of receptor.



Do all Drugs Act on Cellular Targets?

- No! Although most drugs do act on cellular targets, there are a few that do not.
- The best example of drugs that don't act on cellular targets are antacids.
- Antacids are drugs that neutralize stomach acid to provide symptomatic relief from some gastrointestinal disorders.
- Antacids are simply bases that neutralize stomach acid, therefore they do not bind to any cellular target.



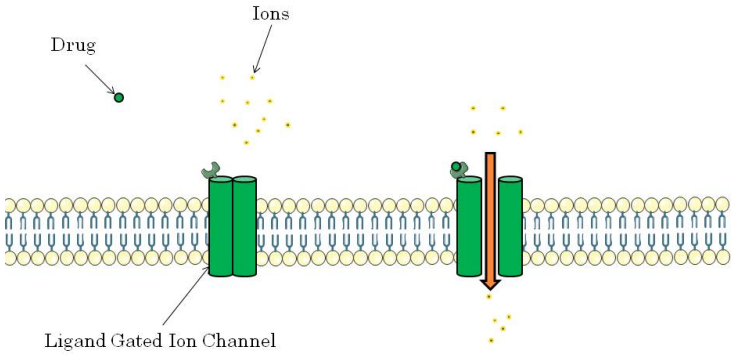
Types of Drug Receptors

- A receptor is a protein that a drug binds to and produces a measurable response.
- The majority of receptors are proteins that are able to translate extracellular signals into biological responses.
- The 4 most important types of receptors are:

1) Ligand gated ion channels
2) G-protein coupled receptors
3) Enzyme linked receptors
4) Intracellular receptors

1) Ligand gated ion channels

- The movement of ions into or out of a cell can cause instantaneous changes in function.
- As ions are unable to directly cross the cell membrane they utilize specialized channels.
- Ligands (i.e. drugs or endogenous molecules) control the opening and closing of ion channels.
- Many neurotransmitters bind to these types of receptors.
- The GABA receptor is an important example of a ligand gated ion channel.



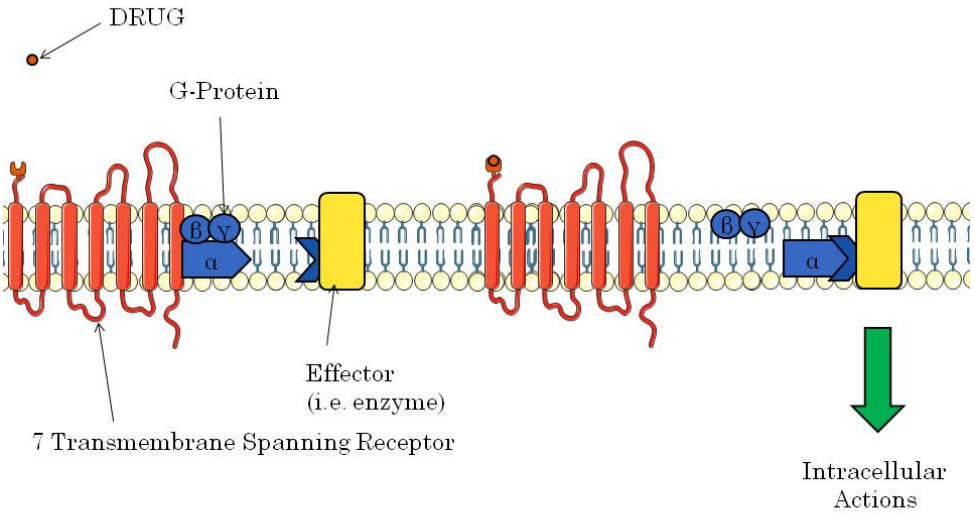
- When GABA (a neurotransmitter) binds to the GABA receptor, it causes the opening of a channel that allows the ion chloride to flow into the cell.
- Drugs that are part of the benzodiazepine class are also able to bind to the GABA receptor and allow chloride to enter the cell. *We'll see benzodiazepines in Module 14!*
- Activation of the GABA receptor causes sedation and muscle relaxation mediated by the increased intracellular chloride.
- Responses to these receptors are very rapid having a duration of milliseconds.

2) <u>G-protein coupled receptors (GPCRs)</u>

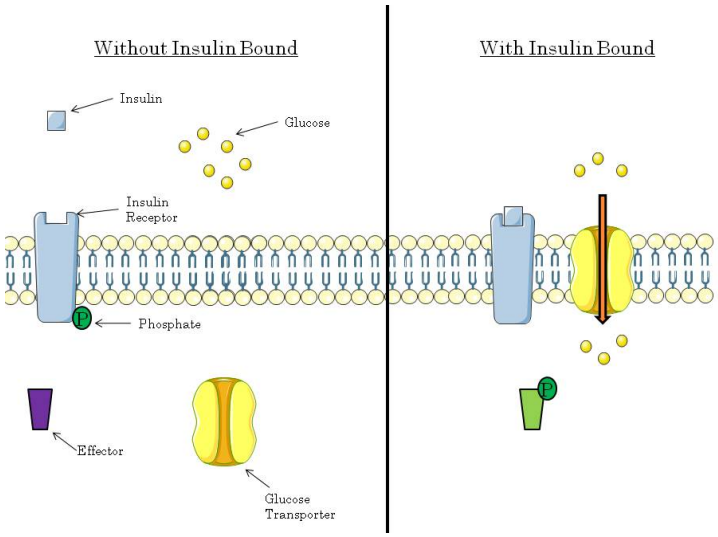
- Approximately 50% of currently marketed drugs mediate their effects through actions on GPCRs.
- GPCRs have three components:

    1) A seven transmembrane spanning protein receptor.
    2) A G-protein which has three subunits.
    3) An effector molecule (i.e. an enzyme).

- Binding of a ligand to a GPCR causes activation of the G-protein.
- The G-protein then dissociates from the receptor and activates the effector.
- Activation of GPCRs result in a response that lasts from seconds to minutes in duration.
- Endogenous neurotransmitters such as norepinephrine, serotonin and histamine mediate their effects by binding to GPCRs.



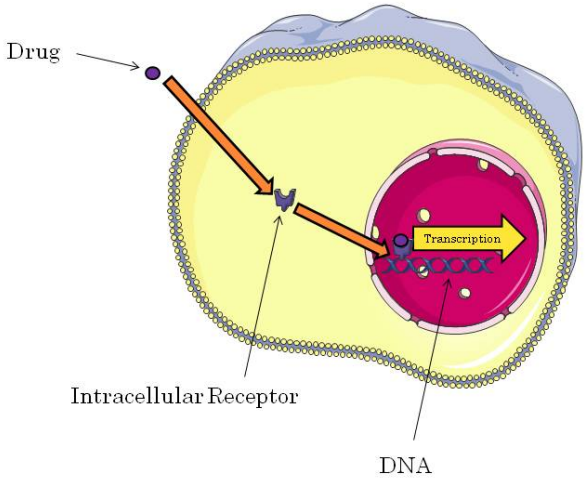
3) Enzyme linked receptors



- Enzyme linked receptors span the cell membrane with the ligand binding domain on the outside of the cell and the enzyme's catalytic site on the inside.
- Binding of a ligand on the outside of the cell activates the enzyme on the inside of the cell.
- Responses to enzyme linked receptors occur very rapidly (seconds).
- An example of an enzyme linked receptor is the insulin receptor.
- Binding of insulin to the insulin receptor causes enzyme mediated phosphorylation and activation of an intracellular effector.
- The phosphorylated effector causes an increased translocation of glucose transporters to the cell membrane.
- The net effect of insulin binding to its receptor is increased cellular glucose uptake and utilization.

4) Intracellular receptors

- These receptors reside completely inside the cell and are also called transcription factors.
- In order to access these receptors, ligands must be able to cross the cell membrane either by diffusion or via a drug transport protein.
- Binding of the ligand causes translocation of this complex to the nucleus and binding to DNA.
- When the ligand/receptor complex binds to DNA, transcription of messenger RNA is stimulated.
- Protein synthesis occurs hours or days later.
- Ligands to these receptors are typically highly lipid soluble. Endogenous examples include the steroid hormones testosterone and estrogen.



NOTE: *in the animation for this lecture, the drug SHOULD bind the receptor and THEN move into the nucleus. This will be changed in the next version of the course.*

7.4 DRUG RECEPTOR SELECTIVITY

- Selectivity is an important characteristic of a drug.
- A classical view of drug-receptor selectivity is the lock and key hypothesis.
- The lock can be thought of as the receptor. The lock requires a key with a specific size and unique shape to open it.
- The drug can be thought of as the key. If it has the right shape and size, it can open the lock.
- Drugs that are selective will bind to only one receptor and therefore will be less likely to produce side effects.
- Note that even if drugs bind to only one receptor, they still may have side effects. Why? The target for therapy may be in the brain but the receptor may be located in the brain and in the intestine. Therefore side effects in the intestine may occur.