PHARMACODYNAMICS – DRUG RECEPTOR INTERACTIONS

8.1 THEORIES OF DRUG RECEPTOR INTERACTIONS

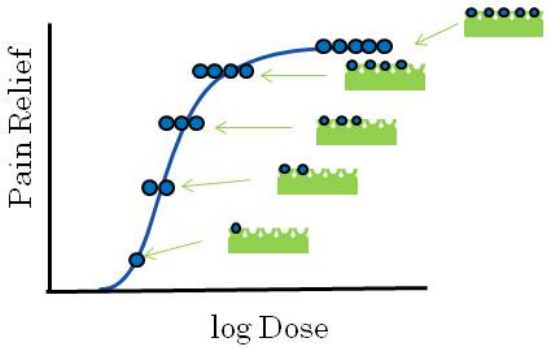
- In the last module we learned that most drugs work by binding to receptors.
- Is simply occupying the receptor enough to have a response?
- What if two drugs occupied the same number of the same receptor, would the response be the same?
- There are two receptor theories that we use to describe drug receptor interactions:

    1) The simple occupancy theory
    2) The modified occupancy theory

1) <u>The simple occupancy theory</u>

- The simple occupancy theory states:

1) The intensity of a drug's response is proportional to the number of receptors occupied.
2) The maximal response occurs when all the receptors are occupied.



- This implies that two drugs that act at the same receptor should produce the same effect. This is not true! We know this because there are many drugs that act at the same receptor yet have different efficacies.

2) <u>The modified occupancy theory</u>

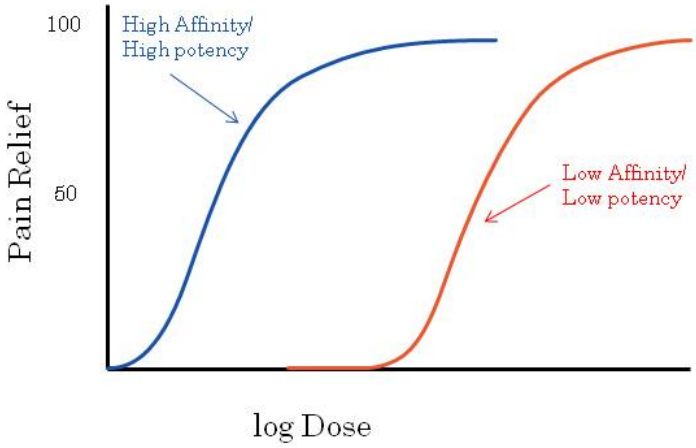
- The modified occupancy theory identifies that some characteristics of drug receptor interactions cannot be accounted for by the simple occupancy theory.
- The modified occupancy theory states:

1) The intensity of a drug's response is proportional to the number of receptors occupied.
2) Two drugs occupying the same receptor can have different binding strengths (i.e. affinity).
3) Two drugs occupying the same receptor can have different abilities to activate the receptor (i.e. intrinsic activity).

- In summary, in addition to accounting for the number of receptors occupied, the modified occupancy theory takes into account the affinity of the drug for the receptor and the ability of the drug to activate the receptor.

Modified Occupancy Theory – Affinity

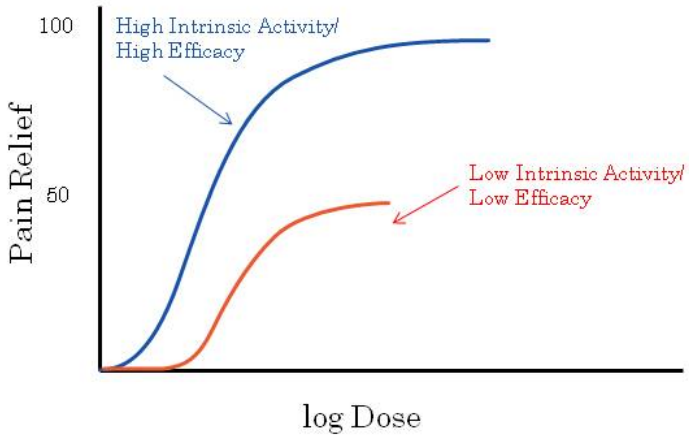
- Affinity is the attraction that a drug has for its receptor.
- Drugs with a high affinity are highly attracted to their receptor and therefore bind to the receptor effectively even at low concentration.
- Drugs with low affinity are weakly attracted to their receptor and therefore bind ineffectively to the receptor even at high concentration.



- The affinity of a drug is the primary determinant of a drug's potency. Drugs with high affinity for their receptor have high potency whereas drugs with low affinity for their receptor have low potency.

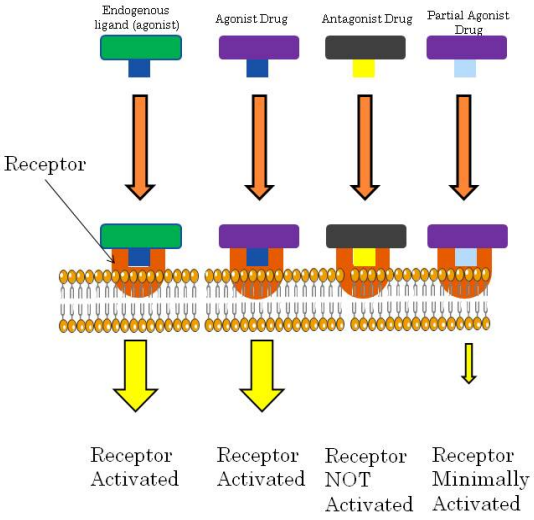
Modified Occupancy Theory – Intrinsic Activity

- Intrinsic activity is the ability of a drug to activate the receptor.
- Drugs that have high intrinsic activity cause intense receptor activation.
- Drugs with low intrinsic activity only minimally activate the receptor.
- The intrinsic activity of a drug is reflected in its efficacy, whereby drugs with high intrinsic activity have high maximal efficacy and drugs with low intrinsic activity have low maximal efficacy.



8.2 CLASSIFICATION OF DRUG RECEPTOR INTERACTIONS

- After a drug binds to a receptor it can either activate the receptor or block other ligands from binding to the receptor.



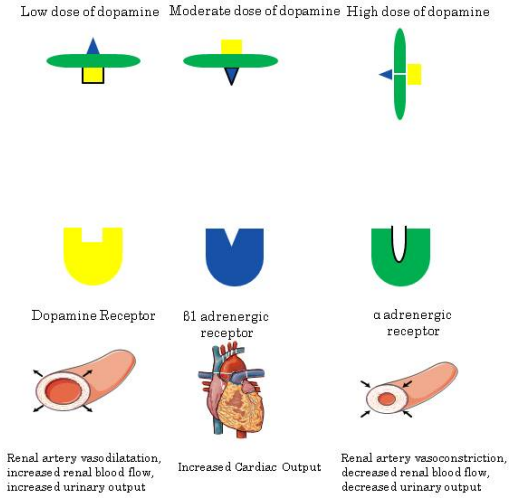
Agonist –a molecule that binds to a receptor and activates it. Agonists mimic the action of endogenous ligands

Antagonists – molecules that bind to a receptor but do not activate it.

Partial Agonists – molecules that bind to the receptor but have minimal ability to activate it.

Agonists

- Since agonists are molecules that activate receptors, endogenous molecules that activate receptors are considered agonists. Some of these include neurotransmitters and hormones.
- Drugs that we design as agonists are often targeted to mimic the action of the body's endogenous molecules.
- Agonists can be thought of as having both affinity AND intrinsic activity since they are able to bind and activate a receptor.
- It is important to note that the action of an agonist does not always increase a physiological response (i.e. heart rate). Agonists may cause either increased or decreased physiological response depending which receptor is activated.
- Some agonists can bind to different receptors (remember specificity) and therefore may cause different effects depending on the dose. A good example of this is dopamine, an endogenous neurotransmitter that we also give as a drug.



Antagonists

- Antagonists bind to receptors but do not activate them.
- Antagonists can be thought of as having affinity BUT NO intrinsic activity.
- Despite not activating receptors, antagonists can have profound pharmacological effects.
- Antagonists generate their effect by preventing the binding of endogenous molecules and other agonist drugs.
- Would an antagonist do anything if there was no agonist present? NO! The pharmacological effect of an antagonist is dependent on the presence of an agonist.
- The activity of antagonists can be used to treat drug overdose.

Examples of Antagonist Drugs	Action
Beta Blockers	Block the binding of endogenous epinephrine to beta 1 receptors in the heart; slows beating of the heart
Antihistamines	Block the binding of histamine to H1 histamine receptors in the nasal mucosa; prevents symptoms of allergy
Gastric Acid Reducers	Block the binding of histamine H2 histamine receptors in the gut; decreases gastric acid secretion.
Opioid Receptor Blockers	Block the binding of opioids to opiate receptors; useful for treating opiate overdose.

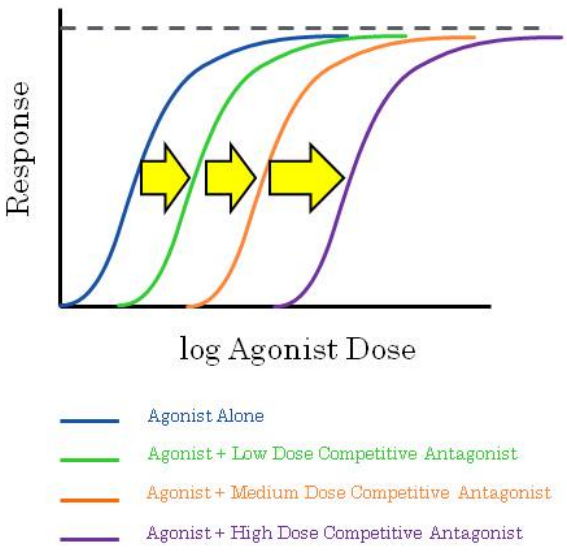
Types of Antagonists

- Antagonists can be classified as either competitive, irreversible or allosteric depending on where the binding occurs and what the nature of the binding is.

1) Competitive Antagonists – Binding occurs at the same site as the agonist and is reversible.
2) Irreversible Antagonists – Binding occurs at the same site as the agonist but is irreversible.
3) Allosteric Antagonists – Binding occurs at a different site than the agonist.

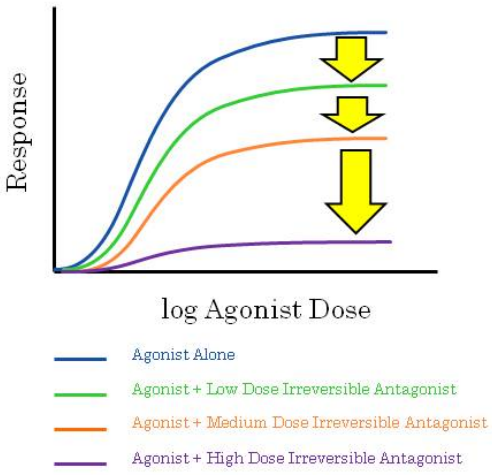
1) Competitive Antagonists

- Compete for binding with an agonist at the same binding site.
- Binding is reversible.
- If the antagonist and agonist have equal affinity, the one with the highest concentration will occupy the binding site.
- Because the binding is reversible, the effect of a competitive antagonist can be overcome by increasing the concentration of the agonist.



2) Irreversible Antagonists

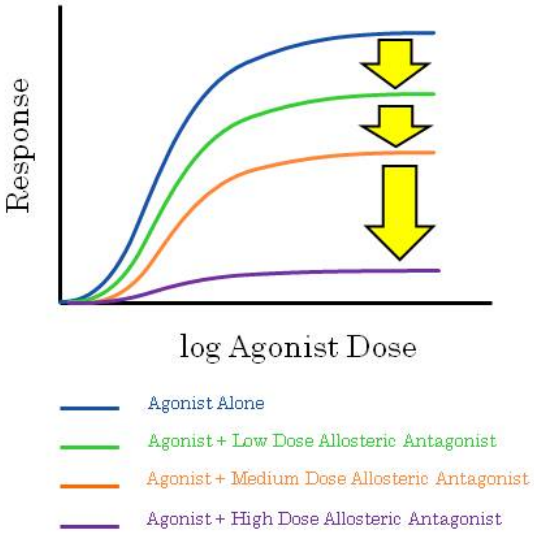
- Irreversible antagonists bind to the same receptor site as the agonist.
- Binding is irreversible and therefore non-competitive.
- Remember that the intensity of response depends on the agonist binding to the receptor. If the antagonist permanently blocks receptor sites, it effectively decreases the maximal response the agonist may have.
- The effects of irreversible antagonists cannot be overcome by increasing the dose of agonist.
- Does this mean the effects last forever? NO! Our body is constantly degrading old receptors and making new ones. The effect of irreversible antagonists lasts until the receptor is replaced.



- Because the agents are irreversible in nature they are very seldom used in therapeutics.

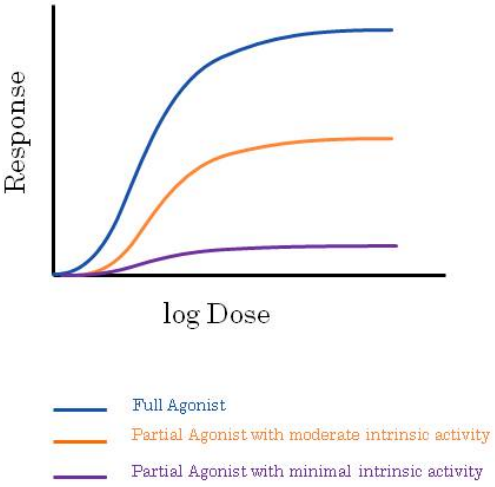
3) Allosteric Antagonists

- Allosteric antagonists bind to a different site on the receptor than the agonist does.
- Binding of the allosteric antagonist changes the conformation of the receptor so the agonist is no longer able to bind.
- The binding of an allosteric antagonist is reversible but not competitive.
- The binding is non-competitive because the agonist and allosteric inhibitor bind to different sites on the receptor.
- Similar to irreversible antagonists, the effects of allosteric antagonists cannot be overcome by increasing the dose of agonist.
- Allosteric antagonists effectively decrease the maximal response that the agonist may elicit.



Partial Agonist

- Partial agonists are agonists that have only minimal or moderate intrinsic activity.
- The maximal efficacy that a partial agonist can produce is less than that of a full agonist.
- Partial agonists are also able to act as antagonists. How is this possible? Remember that a partial agonist has only minimal or moderate activity to activate a receptor. Therefore binding of a partial agonist will cause minimal or moderate activation of the receptor but will also block the binding of a full agonist.

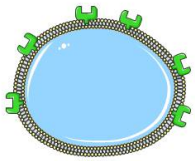


8.3 DRUG TOLERANCE AND RECEPTOR REGULATION

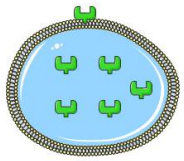
Regulation of Cell Surface Receptor Expression

- The number of receptors on the cell surface is not constant and can change with exposure to drugs.
- For most drugs, their action depends on the receptor being present on the cell surface (exception: intracellular receptors/transcription factors which are normally found inside the cell).

Receptors on Cell Surface



Receptors Inside the Cell



Drug Tolerance

- When patients are continually exposed to agonists, the response to the agonist may decrease. This is known as tolerance.
- There are 3 types of drug tolerance:

1) Desensitization – Continuous exposure to an agonist can cause receptor desensitization. In receptor desensitization, the receptor is internalized into the cell or destroyed. The net effect is a decrease in cell surface receptor expression and decreased drug effects.
2) Metabolic Tolerance – Continuous exposure to some drugs results in the induction of drug metabolizing enzymes. Induction of drug metabolizing enzymes may cause a decrease in the plasma concentration of the drug. *(remember Module 4?)*
3) Tachyphylaxis – A rapid decrease in the response to a drug. Some drugs require a drug free period between administrations to prevent rapidly developing tolerance.

Receptor Upregulation

- Continuous exposure to an antagonist has the opposite effect of tolerance.
- In this case the cell is said to become hypersensitive or supersensitive.
- This occurs because the cell synthesizes more receptors.
- Therefore there are a greater number of receptors at the cell surface and the response increases.