References:

- Basic & clinical pharmacology by Katzung
- Lippincott’s illustrated reviews by Finkel, Cubeddu & Clark
- Clinical pharmacology by Laurence
Learning Objectives

At the end of pharmacodynamic lectures you should be able to

1. Describe the relationship between drug dose and response, and between log (drug dose) and response

2. Define ‘competitive’ and ‘non-competitive’ antagonism, and indicate, on appropriate graphs, how these may be distinguished

3. Describe the different types of receptor-effector coupling with reference to: a) ion channels; b) second messengers; c) protein kinases; and d) intracellular receptors
4. Describe what is meant by the terms ‘efficacy’ and ‘affinity’ in describing agonist potency and how these relate to the concepts of ‘spare receptors’ and ‘partial agonists’.
Major Receptor families:
A) Ligand-gated ion channel
B) G protein-coupled receptor
C) Enzyme-linked receptors
D) Intracellular receptors
The recognition of chemical signals by G protein-coupled membrane receptors triggers an increase (or, less often, a decrease) in the activity of adenylyl cyclase.
MAJOR RECEPTOR FAMILIES:

a) LIGAND-GATED ION CHANNEL:

Are responsible for regulation of the flow of ions across cell membrane.

The activity of these channels is regulated by the binding of a ligand to the channel.

The Response is very rapid (few milliseconds).

For example: Nicotinic receptors and aminobuteric acid (GABA) receptors.

Stimulation of the nicotinic receptors by Acetylcholine results in Na\(^+\) influx generation an action potential & activation & contraction of skeletal muscle cells.

Benzodiazepines enhances the stimulation of GABA receptors, this will result in increased CI\(^-\) influx & hyper-polarization of the receptive cell.
Change in the membrane potential leading to an intra-cellular effect
B) G PROTEIN-COUPLED RECEPTORS:
These are comprised of a single peptide that has
seven membrane-spanning regions.

- These receptors are linked to a G Protein (Gs and others) having three subunits, alpha (α) subunit (binds guanosine triphosphate GTP) and a beta-gamma (βγ) subunit.

- Binding of appropriate ligand to extracellular region of the receptor activates the G Protein, so that GTP replaces guanosine diphosphate GDP on the alpha subunit.
• Dissociation of G Protein occurs, and both the alpha-GTP subunit and the βY subunit interact with other cellular effectors (an enzyme or an ion channel).

• Effectors then change the concentration of the 2nd messenger that are responsible for further actions within the cell.

• Stimulation of these receptors results in responses last several "seconds to minutes".
SECOND MESSENGERS:

• Are essential in conducting and amplifying signals coming from G Protein-Coupled receptors.

• A common pathway turned on by Gs and other types of G Protein, is the activation of adenylyl Cyclase by α-GTP subunit, which results in the production of cAMP a second messenger that regulates protein phosphorylation.
• G Protein also activates phospholipase C (responsible for the generation of two other 2nd messengers, "inositol-1,4,5 triphosphate" and "diacylglycerol").

• These effectors are responsible for the regulation of intracellular free Calcium concentration and other proteins as well.

• This family of receptors transduces signals derived from: Odor, Light, Noradrenaline, dopamine, 5-HT and Acetylcholine
C) ENZYME LINKED RECEPTORS:

- These receptors have cytosolic enzyme activity as an integral component of their structure or function.
- Binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity.
- Duration of responses to stimulation of these receptors is in order of "minutes to hours".
Examples of these receptors are the Insulin receptors and others having a Tyrosine Kinase activity as part of their structure.

When the ligand binds to the receptor subunit, the receptor undergoes conformational changes (converting from its inactive form into an active Kinase form).

The activated receptor autophosphorylates "= phosphorylates itself" and phosphorylates Tyrosine residues on specific proteins.

The addition of a phosphate group can modify the 3D structure of the target protein, by acting as a molecular switch.
• **Example:** when insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself in turn the phosphorylated receptor phosphorylates target molecules (insulin receptor substrate peptides) that activates other important cellular signals \( \{1P_3\} \) and the Mitogen-activated protein kinase system leading to multiplication of the initial signal.
• **SPARE RECEPTORS:**
  • Some receptor types characterized by their ability to amplify signal duration and intensity (G Protein Linked Receptors).

• Two phenomena account for the amplification of the ligand-receptor signal:
  • A single ligand-receptor complex can interact with many G Protein, thereby multiplying the original signal many folds.
  • The activated G Proteins persist for longer duration than the original ligand-receptor complex.
    Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximum response. (99% of insulin receptors are spare receptors).
• **DESENSITIZATION OF RECEPTORS:** (de-sensitize-ation means make something less sensitive)

• Repeated or continuous administration of an agonist (or an antagonist) may lead to changes in the responsiveness of the receptor.

• Repeated administration causes "tachyphylaxis", receptors are still present but unresponsive to the ligand.

• Also occur when receptors are "down-regulated" (due to molecular changes in the receptors, endocytosis then sequestered from further agonist interaction).
• Receptors may be recycled to surface, restoring sensitivity or may be further processed and degraded, decreasing the total number of receptors available.

• Some receptors require rest period after stimulation before they can be activated again. During this recovery phase they are said to be "Refractory" or "Unresponsive".
Repeated administration of an agonist (such as epinephrine) over a short time period results in diminished response of the cell.

Following a period of rest, administration of the drug results in a response of the original magnitude.

Desensitization of receptors.
• **DRUG RECEPTORS BINDING FORCES:**

• They're either:

• 1- **Weak forces** like a) $\text{H}^+$ bonds, b) Van Der Wall and, c) electrostatic bonds. These bindings are **REVERSIBLE**.

• 2- **Strong forces**: or Covalent bonds. These bonds are **IRREVERSIBLE**.
THEORIES OF DRUG-RECEPTOR INTERACTIONS:

1) OCCUPATION THEORY:

"RESPONSE TO AN AGONIST IS A FUNCTION OF THE NUMBER OF RECEPTORS OCCUPIED BY THAT AGONIST"

This means:

- This response will increase as the concentration increases. This is true until all receptors are occupied.

- So further increase in the dose (concentration) of the drug causes an increase in response till reaching maximum response after that there is no further increase in response because no more receptors left available for binding with the drug.
$E_{max}$:

maximum response when all receptors are "occupied".
2) **RATE THEORY:**

"RESPONSE TO AN AGONIST IS PROPORTIONAL TO THE RATE OF ASSOCIATION OF AGONIST WITH RECEPTORS"

This means that the more the dose the more the rate of association and the more the response until it reaches the maximum response.
Note:
Agonist drugs have "fast" rates of association and dissociation with receptors, while antagonists have "low" rate of both and accordingly antagonists have small or no effect.
Thank you