Dr. Iman Naji **lec 2**

Pharmacodynamic 2

Inverse agonist: drug that produces **effects** which are opposite to those of the agonist, e.g. **β – carbolines** bind to benzodiazepine receptor leading to stimulation and anxiety (opposite to benzodiazepines).

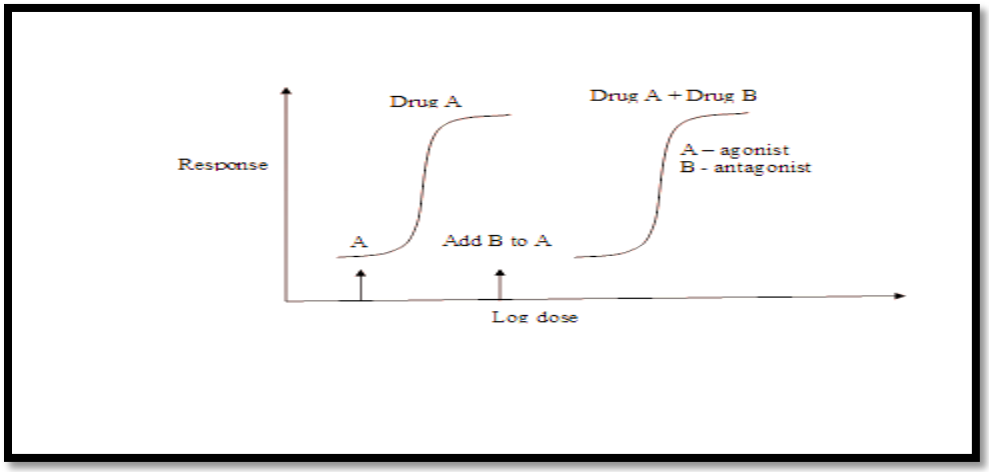
Receptor binding

- **Reversible binding:** weak binding through hydrogen or electrostatic bonds, an agonist can be replaced by antagonist by mass action and vice versa.

1-Competitive antagonism: agonist and antagonist compete to occupy the receptor according to the **law of mass action**. The agonist is said to be **surmountable**.

-If both agonist and antagonist bind to the **same site** on the receptor ,they are said to be competitive e.g **prazosin and noradrenaline at alpha- 1 receptors.**

- In the presence of an antagonist, higher doses of the agonist can produce a parallel DRC shifted to the right. **(increased EC50) without affecting Emax**
-



- **Irreversible binding:** drug binds to the receptor through strong (covalent) bonds effectively, leading to irreversible binding.
- **2-Non – competitive antagonism (concentration independent):**
- -If the antagonist binds to a site other than where the agonist binds ,the interaction is non-competitive or allosteric

When antagonist occupy the receptor, increasing the agonist does not fully restore the response (insurmountable antagonism), restoration of response requires elimination of drug from the body, and synthesis of new receptors.

e.g phenoxybenzamine at alpha receptor

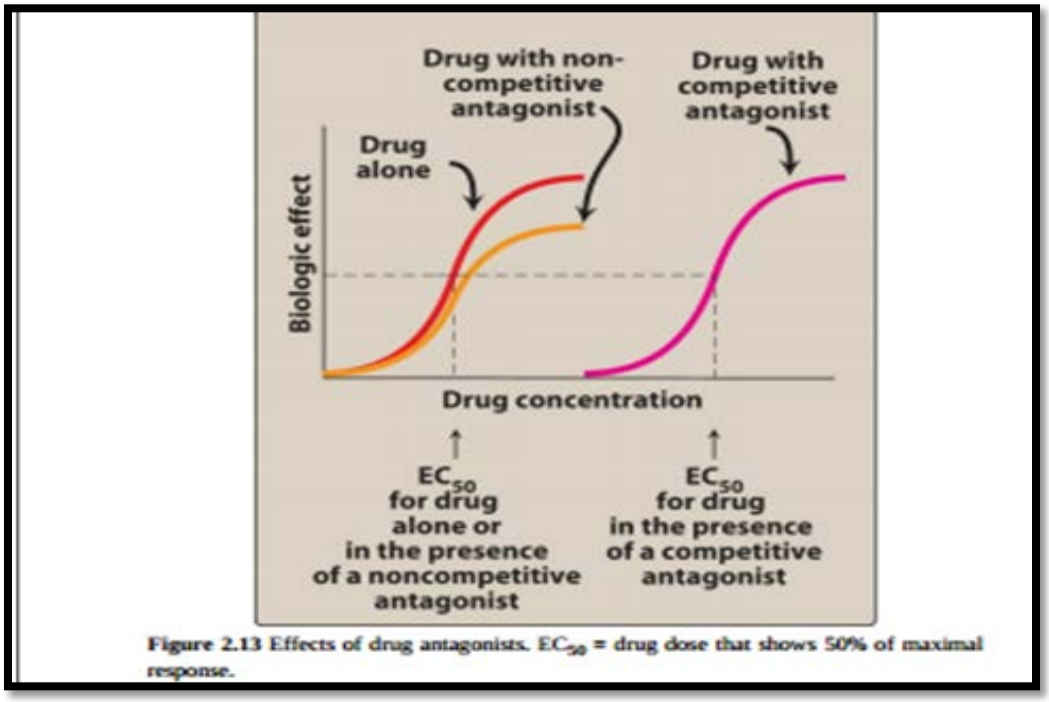


Figure 2.13 Effects of drug antagonists. EC_{50} = drug dose that shows 50% of maximal response.

A fundamental difference between competitive and noncompetitive antagonists is that competitive antagonists reduce agonist potency (increase EC 50) an **noncompetitive antagonists** reduce agonist efficacy (decrease Emax)

3-Allosteric antagonists

An allosteric antagonist binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist. This type of antagonist also causes a **downward shift of the EMax** of an agonist, with no change in the EC50 value.

An example of an allosteric agonist is picrotoxin, which binds to the inside of the GABA-controlled chloride channel. When picrotoxin binds inside the channel, no chloride can pass through the channel, even when GABA fully occupies the receptor.

Antagonism can occur in several ways:

- **Pharmacological:** action of drugs on the same receptor, either competitive **e.g. propranolol + adrenaline on β-receptors**, or non – competitive **e.g. noradrenaline + phenoxy benzamine on α – receptors.**
- **Physiological (functional):** pharmacological effect of a drug is overcome by a second drug by different physiologic mechanism, e.g. bronchoconstriction by **histamine (H_1 receptor)** can be antagonized by **adrenaline** through β_2 – receptor effect. Propranolol ↓ heart rate by blocking β_1 receptors, while atropine ↑ heart rate by blocking vagal activity.
- **Chemical:** antagonism by direct chemical interaction **e.g. antacids + gastric HCl.**

Enzymes: drugs may alter enzyme activity because they resemble a natural substrate and hence compete with it for enzyme.

- **Competitive – reversible – enzyme inhibitors** e.g. ACE inhibitors used in Rx of heart failure and hypertension, enalapril structure is similar to angiotensin I.
- **Non – competitive (irreversible) enzyme inhibitors**: e.g. organophosphorous insecticides, combine with Ach – esterase covalently, recovery of the enzyme activity requires new enzyme formation.

Dose – response curve (D. R. C.)

Drug response is proportional to its concentration at receptor sites which depends on the **dose** given and the **pharmacokinetic parameters**. ↑ the dose will result in proportional ↑ in response. When the dose and response plotted on a semi – log paper a **sigmoid** (S – shaped) DRC will result. The log concentration or dose is plotted on the horizontal X – axis and the response is plotted on the vertical Y – axis.

- Steep rising and prolonged curve indicates that a small change in the dose → a large change in effect of that drug e.g. **Frusemide** diuretic.
- For thiazide diuretics the curve soon reaches plateau, increasing the dose adds no diuretic effect, but adds to toxicity.

From graded DRC we can estimate:

- **Potency**: is the amount or dose of a drug producing a response of a given magnitude,
- the concentration producing an effect that is fifty percent of the maximum is used to determine potency (EC50).
- The **smaller the amount, more potent drug** is. Potency is determined mainly by the **affinity** of the receptor for the drug and **the number of receptors.**

For example, **candesartan** and **irbesartan** are angiotensin receptor blockers that are used to treat hypertension.

The therapeutic dose range f or candesartan is 4 to 32 mg, as compared to 75 to 300 mg f or irbesartan. Therefore, **candesartan** is

more potent than is irbesartan (it has a lower EC 50 value, similar to drug A).

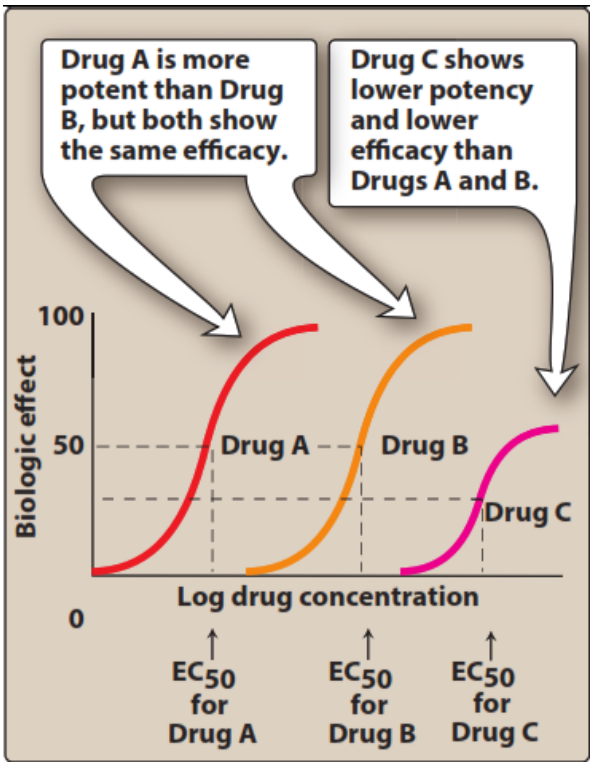
- **Efficacy(intrinsic activity):**. A maximum response induced by agonist.(Emax).
  -Efficacy depends on the number **of drug – receptor complexes** and the **intrinsic activity of the drug** (its ability to activate the receptor and cause a cellular response).

  If the drug binds to the receptors and produces no response so called zero efficacy e.g. antagonist.

Drug + Receptor (**affinity**) → D.R. complexes → (**efficacy**) Response

- **Amiloride** diuretic causes 5% excretion of Na^+ load **(low efficacy).**
- **Frusemide** causes 25% excretion of filtered Na^+ **(high efficacy).**

Efficacy is more important than potency because greater therapeutic benefit may be obtained with a more efficacious drug, a more potent drug may not reach it's receptors in sufficient concentration due to some pathological condition



❖ -Selectivity

• As drugs may act preferentially on particular receptor types or subtypes, such as β1- and β2-adrenoceptors, it is important to be able to quantify the degree of selectivity of a drug.

For example, it is important in understanding the therapeutic efficacy and unwanted effects of the bronchodilator drug salbutamol to recognize that it is approximately **10 times** more effective in stimulating the β2- adrenoceptors in the airway smooth muscle than the β1-adrenoceptors in the heart.

• In pharmacological studies, selectivity is likely to be investigated by measuring the effects of the drug in vitro on different cells or tissues, each expressing only one of the receptors of interest.

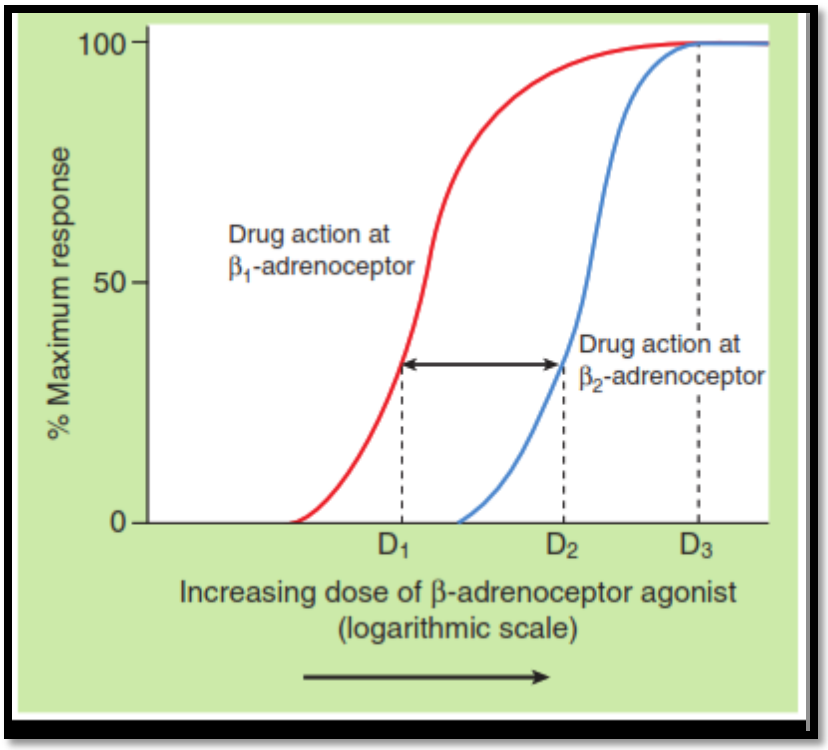
An example might be dobutamine, which is used to selectively stimulate β1-adrenoceptors on the heart in heart failure.

• The degree of receptor selectivity is given by the ratio of the doses of the drug required to produce a given level of response via each receptor type.

It is clear from the Fig. that the ratio is highly dose-dependent and that the selectivity disappears at extremely high drug doses, because the dose then produces the maximal response of which the biological tissue is capable. It should be remembered that many drugs and most neurotransmitters can bind to more than

one type of receptor, thereby **causing both desired therapeutic effects and**

undesired side effects.



❖ Intrinsic Activity

• Intrinsic activity describes the ability of the bound drug to induce the conformational changes in the receptor that induce receptor signaling.

It determines drug ability to fully or partially activate the receptors.

• Although affinity is a prerequisite for binding to a receptor, a drug may bind with high affinity but have low intrinsic activity.

A drug with zero intrinsic activity is an antagonist

❖ Therapeutic index (T.I.):

Is the ratio between the dose that produces unwanted or **toxic** effect in 50% of patients to the dose that produces **therapeutic** effect in 50% of patients.

- T.I. is a measure of drugs safety. A large value indicates a wide margin between toxic and effective (therapeutic) doses i.e. safe drug. While small or narrow T.I. means that the difference between the toxic and therapeutic doses is small and such drugs need careful monitoring e.g. digoxin, lithium, phenytoin.
- **The therapeutic window**, a more clinically useful index of safety, describes the dosage range between the minimum effective therapeutic concentration or dose, and the minimum toxic concentration or dose. For example, if the average minimum therapeutic plasma concentration of theophylline is 8 mg/L and toxic effects are observed at 18 mg/L, the therapeutic window is 8–18 mg/L.
  • Although high TI values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases. In these cases, the risk of experiencing side effects is not as great as the risk of leaving the disease untreated.
- **• Warfarin ,oral anticoagulant (example of a drug with a small therapeutic index):** As the dose of warfarin is increased, a greater fraction of the patients respond (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond. However, at higher doses of warfarin, anticoagulation resulting in hemorrhage.
- **• Penicillin, an antimicrobial (example of a drug with a large therapeutic index):** For drugs such as penicillin, it is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse side effects.

Tolerance:

- Is the gradual reduction in response to drugs following continued drug administration.
- Higher doses are needed to produce the previous effect obtained with a smaller first dose.
- Tolerance may be due to:
    1. Down regulation of receptors e.g. morphine.
    2. Generation of free radicals e.g. GTN in Rx of angina.
    3. ↑ Metabolism due to enzyme induction as with alcohol taken regularly.
- **Natural tolerance:** due to inherited factors e.g. warfarin.
- **Cross – tolerance:** occurs between drugs of similar structure e.g. benzodiazepines, alcohol, barbiturates, anesthetics, antibiotics.

Tachyphylaxic:

Is a rapid loss of efficacy or response due to frequent repeated administration, more rapid than tolerance.

e.g. rapid loss of bronchodilator effect of ephedrine due to depletion of neurotransmitters.