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pharmacology sheet

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RELATION BETWEEN DRUG DOSE & CLINICAL RESPONSE

In order to make rational therapeutic decisions, the prescriber must understand how drug-receptor interactions underlie

1. The relations between dose and response in patients

2. The nature and causes of variation in pharmacologic responsiveness

3. The clinical implications of selectivity of drug action.

These relations are exhibited as following:

A. Graded dose–response relationships (individual):

The response is a graded effect, meaning that the response is continuous and gradual

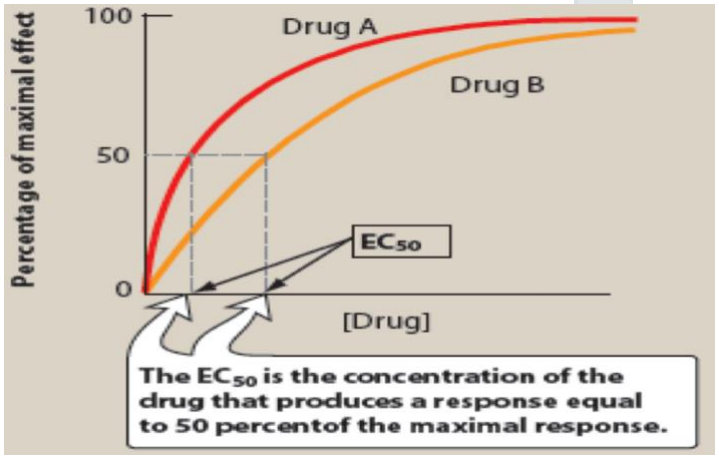
B. Quantal dose–response relationships (population)

describes an all-or-no response

***measuring the frequency of responed persons to a drug.**

A. GRADED DOSE–RESPONSE RELATIONSHIPS

➢The magnitude of the drug effect depends on the drug concentration at the receptor site, which in turn is determined by the dose of drug administered and by factors characteristic of the drug pharmacokinetic profile, such as rate of absorption, distribution, and metabolism.



- **Rate of absorption is called area under care, which means the amount of drug that reaches blood.**

➢As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases.

➢Plotting the magnitude of the response against increasing doses of a drug produces a graph, the graded dose–response curve, that has the general shape described as a rectangular hyperbola.

➢ Two important properties of drugs, can be determined by graded dose–response curves which are :

1. Potency

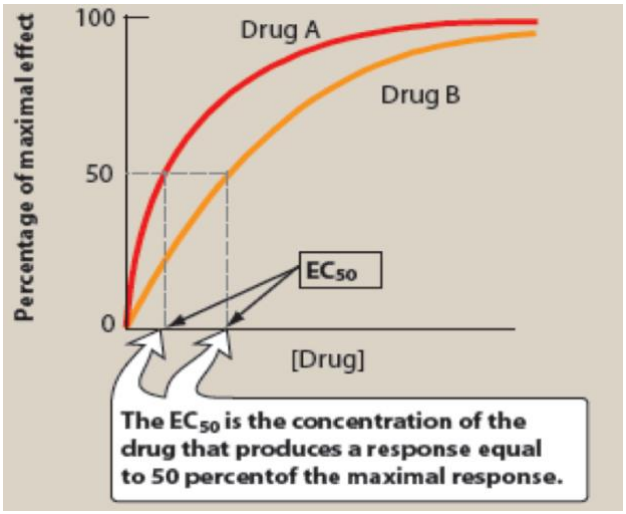
2. Efficacy

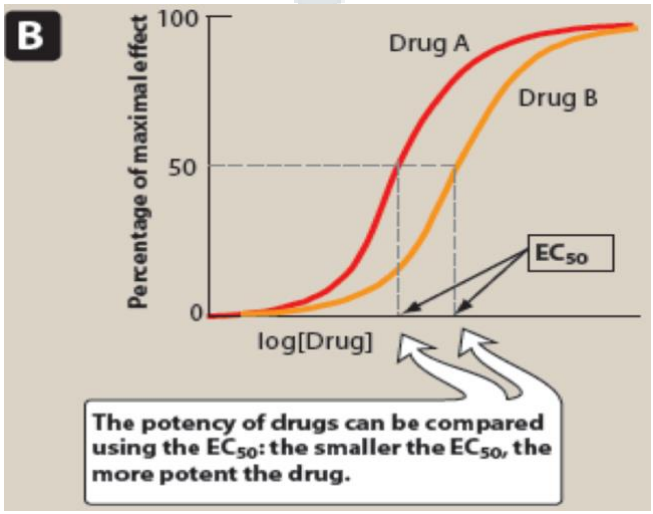
1. POTENCY: (EC50)

A measure of the amount of drug necessary to produce an effect of a given magnitude.

➢ The concentration of drug producing an effect that is 50 percent of the maximum is used to determine potency and is commonly designated as the EC50

➢ Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect.





➢ **Potency is affected by:**

1. Receptor concentration or density in tissue,

2. Efficiency of stimulus-response coupling mechanism in tissue (downstream signaling)

3. Affinity: the strength of the interaction (binding) between a ligand and its receptor.

4. Efficacy

➢ Potent drugs are those which elicit a response by binding to a critical number of a particular receptor type at low concentrations (high affinity) compared with other drugs acting on the same system and having lower affinity and thus requiring more drug to bind to the same number of receptors

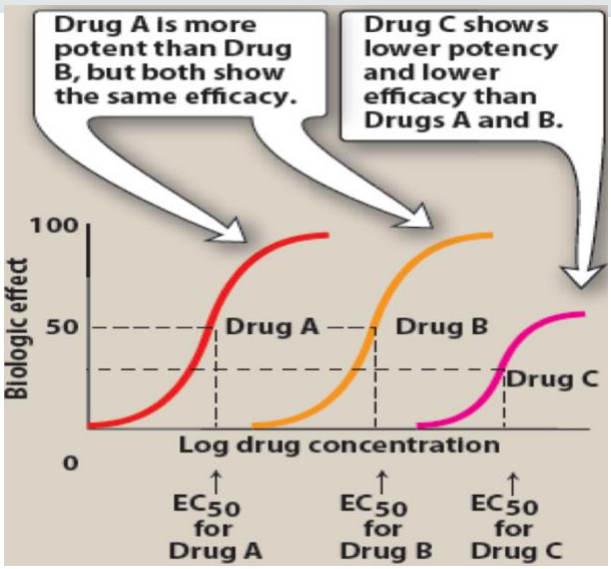
2. EFFICACY

It is the ability of a drug to elicit a response when it interacts with a receptor.

➢Efficacy is dependent on:

1. Number of drug–receptor complexes formed

2. the efficiency of the coupling of receptor activation to cellular responses.



➢**A drug with greater efficacy is more therapeutically beneficial than one that is more potent.**

➢ **Maximal efficacy (Emax) of a drug assumes that all receptors are occupied by the drug, and no increase in response will be observed if more drugs are added**

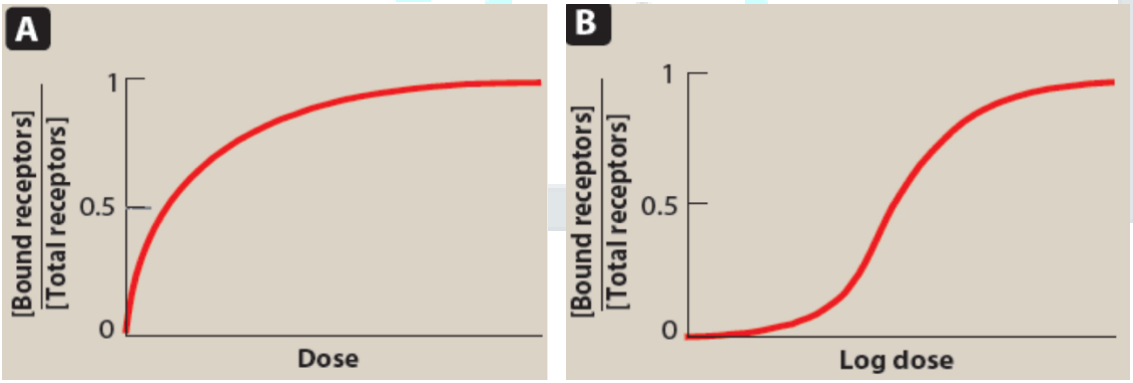
➢**The height of maximal response is used to measure maximal efficacy of agonist drug, and to compare efficacy of similar acting agonists**

EFFECT OF DRUG CONCENTRATION ON RECEPTOR BINDING

The quantitative relationship between drug concentration and receptor occupancy is expressed as follows:

Drug + Receptor ←→ Drug–receptor complex → Biologic effect

➢ **As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity**



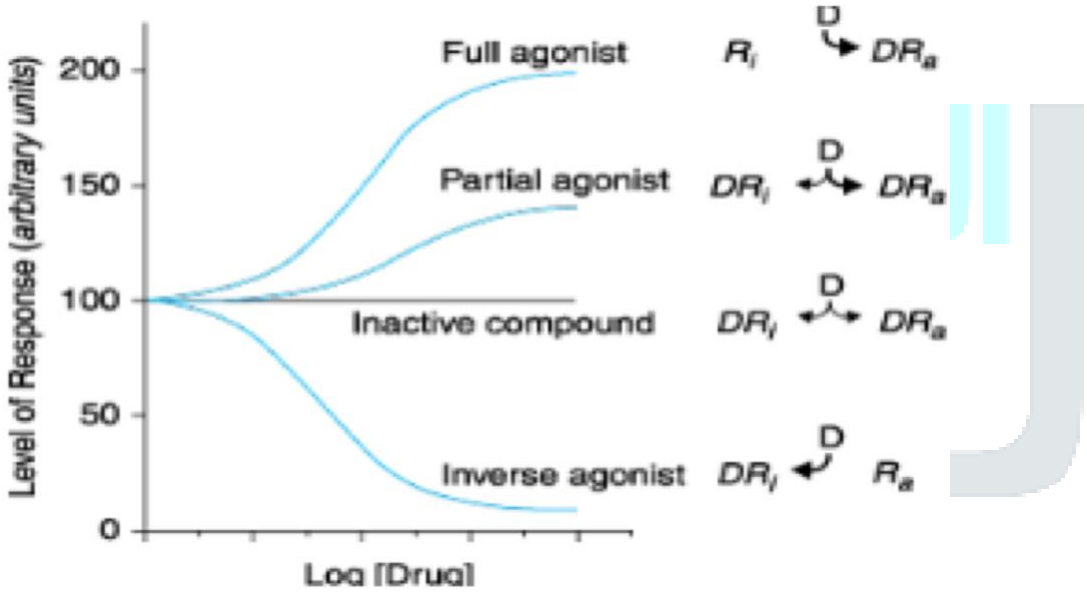
CONCEPT OF DRUG RECEPTOR BINDING & AGONISTS

A receptor can exist in at least two conformational states, active (*Ra*), and inactive (*Ri*). These states are in equilibrium, & the inactive state *Ri* predominates in absence of agonist drug, thus basal activity will be low or absent.

➢ **If a drug that has a higher affinity for *Ra* than *R i* is given, it will drive the equilibrium in favor of active state and thus activate more receptors. Such drug will be an agonist.**

A full or strong agonist is sufficiently selective for the active conformation that at a high concentration it will drive the receptors completely to the active state.

If a different but structurally similar compound binds to the same site on *R* but with only slightly or moderately greater affinity for *Ra* than for *Ri*, its effect will be less, even at high concentrations. Such a drug that has intermediate or low efficacy is referred to *as a partial agonist*



➢**If a drug binds with equal affinity to either conformation of receptor but does not change the activation equilibrium, then it will act as a *competitive antagonist.***

➢**A drug with preferential affinity for *Ri* actually will produce an effect opposite to that of an agonist, and thus named *inverse agonist*. It further reduces the resting level and effect of receptor activity.**

- **agonism are 2 drugs with same effect.**
- **antagonism are 2 drugs work against each other.**

ANTAGONISTS

➢ They are of 3 main types :

1. Chemical antagonist :

This combines with agonist and inactivates it away from tissues or receptors

Examples:

a. Alkaline antacids neutralize HCl in stomach of peptic ulcer patients; such as MgSO4

b. protamine (basic) neutralizes the anti-coagulant heparin (acidic) in plasma

c. chelating agents bind with higher affinity to heavy metals (e.g. lead, mercury, arsenic) in plasma and tissues, preventing their tissue toxicity

2. Physiological antagonist :

➢**This is actually an agonist on the same tissue but produces opposite effect to that of the specific agonist; it acts by mechanisms or receptors that are different from those of the specific agonist .**

➢**Physiological antagonists quickly reverse the action of the specific agonist on the same tissue.**

Examples:

Adrenaline, given IM, is a quick acting physiologic antagonist to histamine (that is released from mast cells or basophils) in anaphylactic shock; it is a life-saving drug in this condition

3. Pharmacological antagonist :

Pharmacological receptor antagonists have affinity for the receptors but have no intrinsic activity or efficacy.

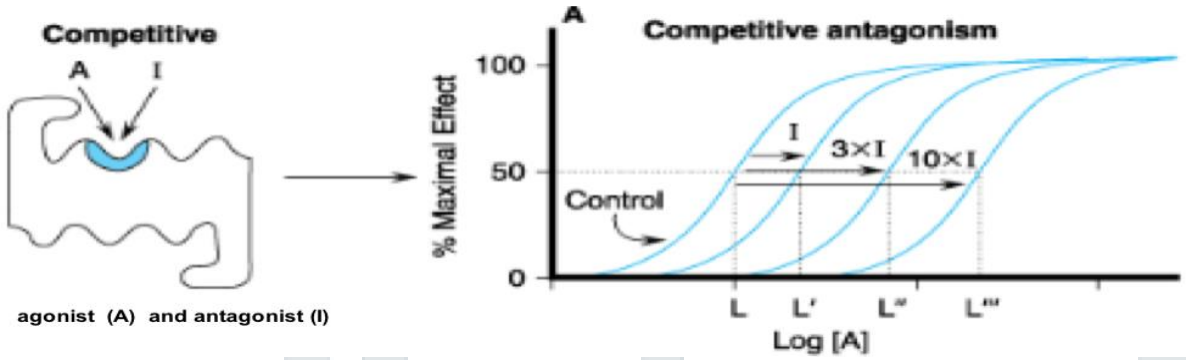
There are three main types :

A. Competitive reversible antagonist :

either electrostatic or hydrophobic bonding

This antagonist , because of similarity in its chemical structure to agonist, competes with agonist for binding to its specific receptors in tissue, and thus decreases or prevents binding of agonist and its effect on tissue.

The antagonist molecules bind to the agonist receptors with reversible ionic bonds, so that it can be displaced competitively from receptors by increasing the concentration or dose of agonist , and thus response of tissue to agonist is restored



➢ The DR curve of agonist is shifted to the right (reduced potency), and the maximal response can be restored by increasing dose of agonist. The more is the concentration of antagonist, the greater is this shift of DR curve of agonist to the right.

Examples:

➢ atropine is a competitive reversible antagonist to Ach at muscarinic receptors;

➢ Beta-blockers are competitive antagonists to adrenaline at beta – adrenergic receptors.

- **Both Ach & adrenaline are called controls in this case.**

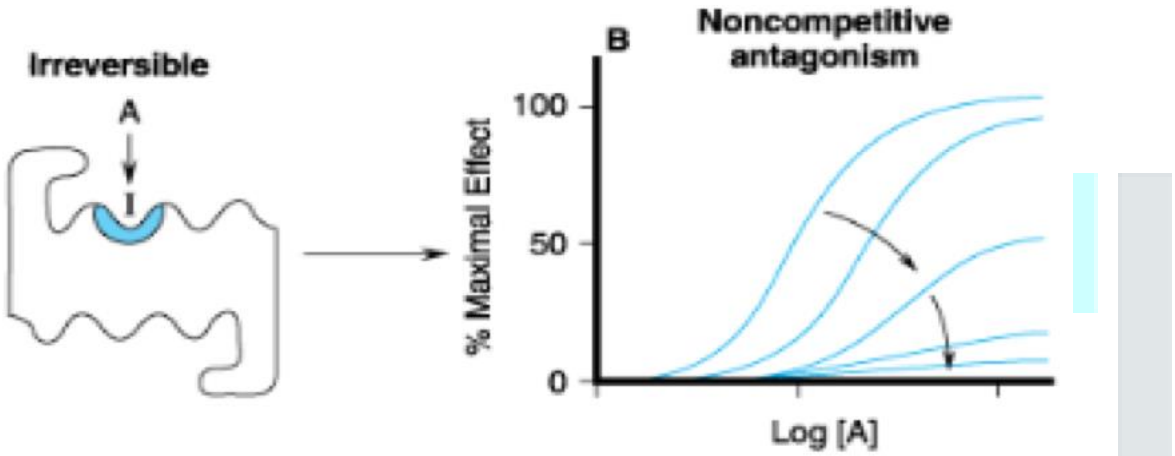
B. Non-competitive antagonist :

There are two subtypes:

1. Irreversible antagonist :

covalently bonded

Here, the antagonist molecules either bind to agonist receptors by strong irreversible covalent bonds or dissociate very slowly from the receptors, so that the effect of antagonist can not be overcome fully by increasing concentration of agonist.



➢ **The dose response curve of agonist is shifted slightly to the right , but the maximal height or response of curve is depressed (decreased efficacy)and can NOT be restored by increasing the dose of agonist . This is due to decrease in number of receptors remaining available to bind to agonist.**

➢ **The more is the concentration of antagonist, the more is depression of maximal response**

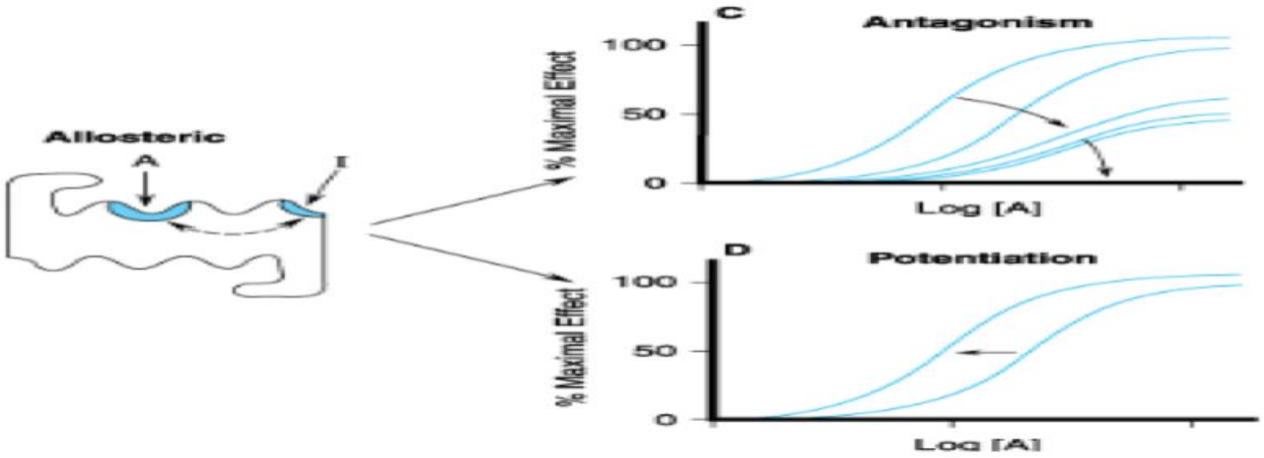
2. Allosteric antagonism :

Here, the antagonist binds to allosteric site on receptor that is different from the site that binds agonist molecules, leading to change in receptor binding or affinity to agonist with subsequent antagonism.

The dose response curve of antagonist is similar to that of irreversible non-competitive antagonist.

Note : Allosteric enhancement : with some receptors, a drug can bind to another allosteric site on agonist receptor leading to increase in binding of agonist to its receptor and thus allosteric enhancement of agonist effect . e.g. Binding of benzodiazepines to GABA-A receptors can enhance the depressant GABA effect on brain neurons.

Ligand (agonist) can't bind with receptor due to conformational change.



increased affinity to the ligand

C. Uncompetitive antagonist:

Here antagonist bind to a receptor different from that of agonist, and is located more distally in the effector mechanism so that the effect of agonist is blocked as well as that of other agonists that produce similar effect by acting on a different receptor i.e. it lacks specificity. The dose-response curve is similar to that of irreversible non-competitive antagonist

affect the work of more than one drug, for instance G-protein coupled receptor. uncompetitive antagonist can inhibit Adenyl cyclase which is in the pathway of G-protein receptor.

RECEPTOR REGULATION

1. Receptor up-regulation :

This means increase in number of receptors and/or affinity of specific receptors (receptor supersensitivity).

It may occur with :

A.Prolongeduseofreceptorantagonist: here, there is lack of binding of receptor to agonist for long period of time, such as beta blockers of adrenaline.

B. Disease : e.g. hyperthyroidism : here excess thyroxine hormone in blood stimulate proliferation of beta-adrenergic receptors in heart which increases risk of cardiac arrhythmia from adrenaline or use of beta- adrenoceptor agonists .

B. Receptor down-regulation (Receptor tolerance):

This means a decrease in number and/or affinity of available specific receptors due to their prolonged occupation by agonist .

- **Common in anti-depressents.**

➢ It occurs with continued use (for days or weeks) of receptor agonist , and is evident as decrease in response to agonist .

➢ In order to restore the intensity of response, the dose of agonist must be increased.

- **it is tested by providing high doses of agonist.**

Tachyphylaxis : it is a rapidly developing receptor tolerance

➢ It is not due to receptor down-regulation

➢ It is associated with repeated use of large doses

of direct receptor agonist, usually at short dose intervals , OR with continuous IV infusion of agonist.

➢ **It may be due to :**

1. Desensitization of receptors :

- **Due to change in receptor conformational structure.**

Change in the receptor: where the agonist-induced changes in receptor conformation result in receptor phosphorylation, which diminishes the ability of the receptor to interact with G proteins

2. Depletion of intra-cellular stores of transmitter

e.g. depletion of noradrenaline stores in vesicles inside sympathetic nerve ending resulting from repeated use of indirect sympathomimetic amphetamine

➢ **In order to restore the response, the agonist drug must be stopped for short time to allow for recovery of receptors or stores of transmitter.**

CAUSES OF VARIATION IN PHARMACOLOGIC RESPONSIVENESS

Individuals usually show variation in intensity of response to drugs due to :

1. Variation in concentration of drug that reaches the tissue receptors : due to pharmacokinetic factors

2. Abnormality in receptor number or function : either genetically-determined or acquired due to up-regulation or down-regulation

3. Post-receptor defect inside cells :

This is an important cause of response variation

4. Variation in Concentration of an Endogenous Receptor Ligand

contributes greatly to variability in responses to pharmacologic antagonists.

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