PHARMACODYNAMICS II

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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.

1. The relations between dose and response in patients

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

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.

- 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.

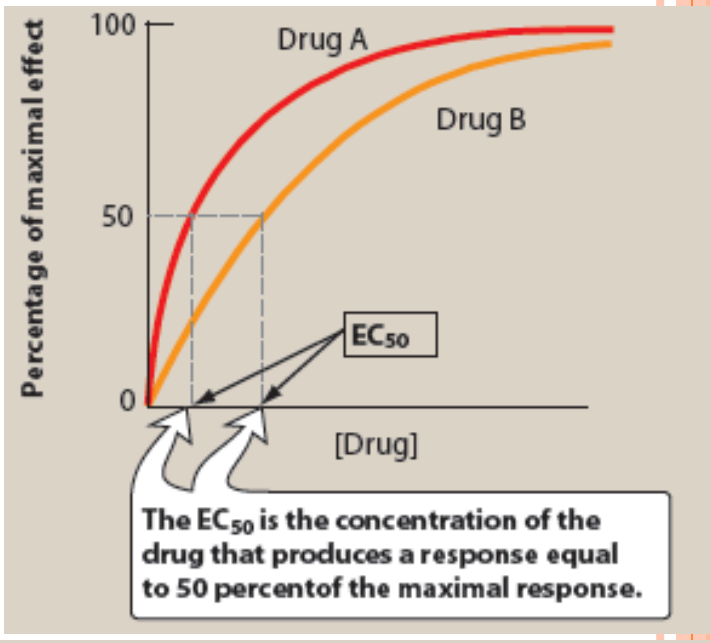
- Two important properties of drugs, can be determined by graded dose–response curves which are

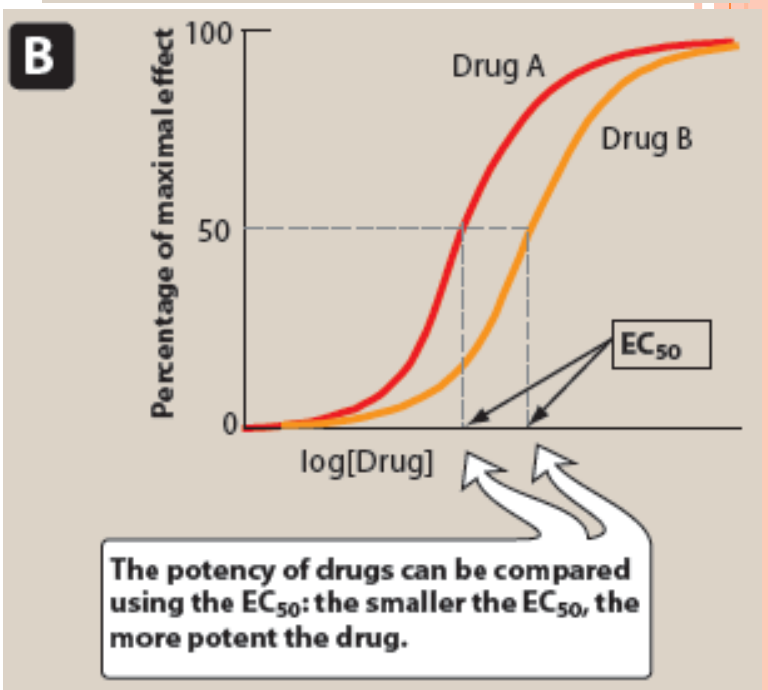
1. Potency
2. Efficacy

1. Potency:

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
3. Affinity: *describes 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

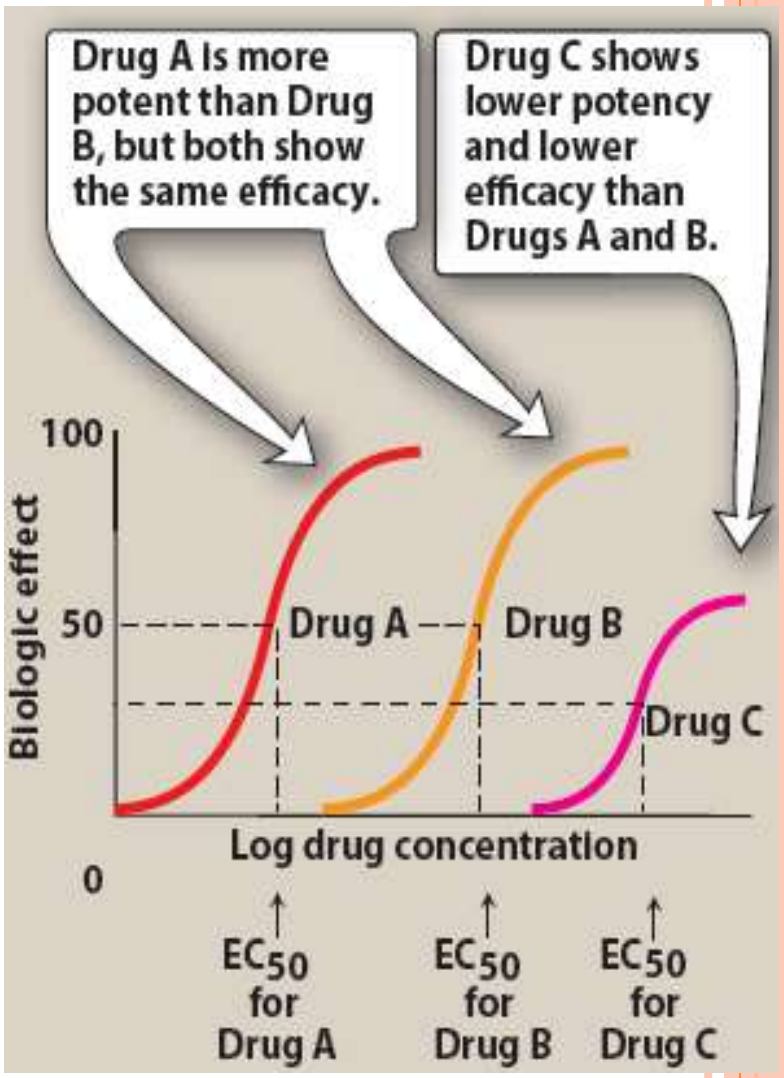
It is the ability of a drug to elicit a response when it interacts with a receptor.

➢**Efficacy is dependent on:**

1. Number of drug–receptor complexes formed
2. the efficiency of the coupling of receptor activation to cellular responses.

➢ 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

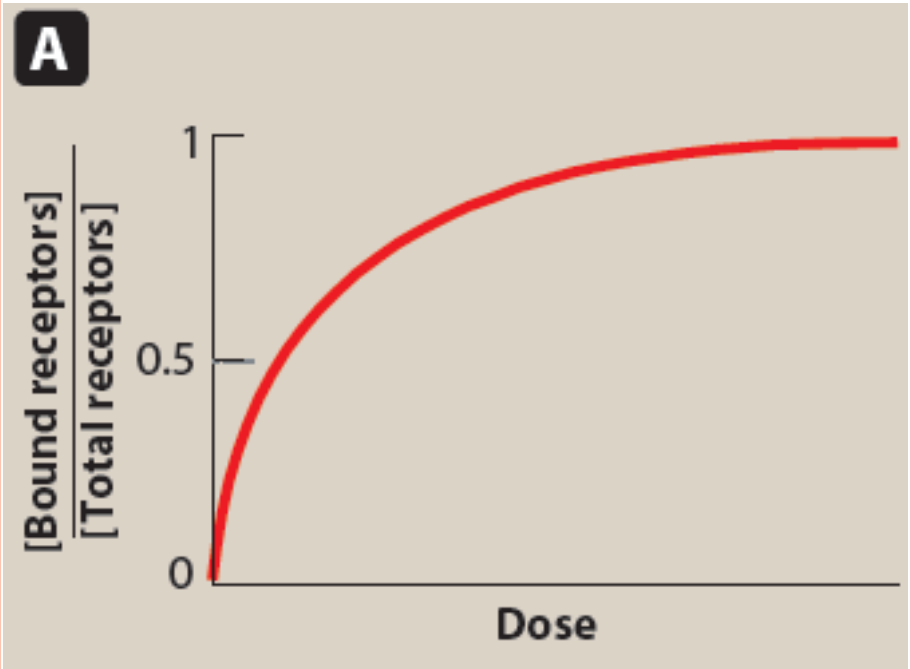


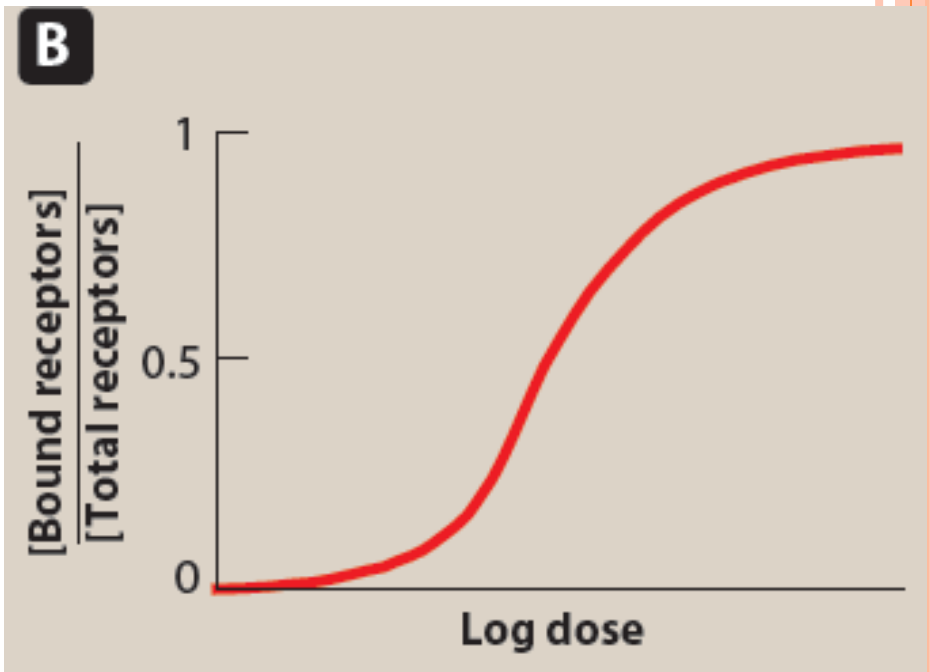
Effect of drug concentration on receptor binding

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





- the relationship between the percentage of bound receptors and the drug concentration:

$$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]}$$

[D] = the concentration of free drug,

[DR] = the concentration of bound drug,

[Rt] = the total concentration of receptors and is equal to the sum of the concentrations of unbound (free)receptors and bound receptors,

Kd = the equilibrium dissociation constant for the drug from the receptor.

- The value of Kd is used to determine the affinity of a drug for its receptor.

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

- The higher the Kd value, the weaker the interaction and the lower the affinity.

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;

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 :

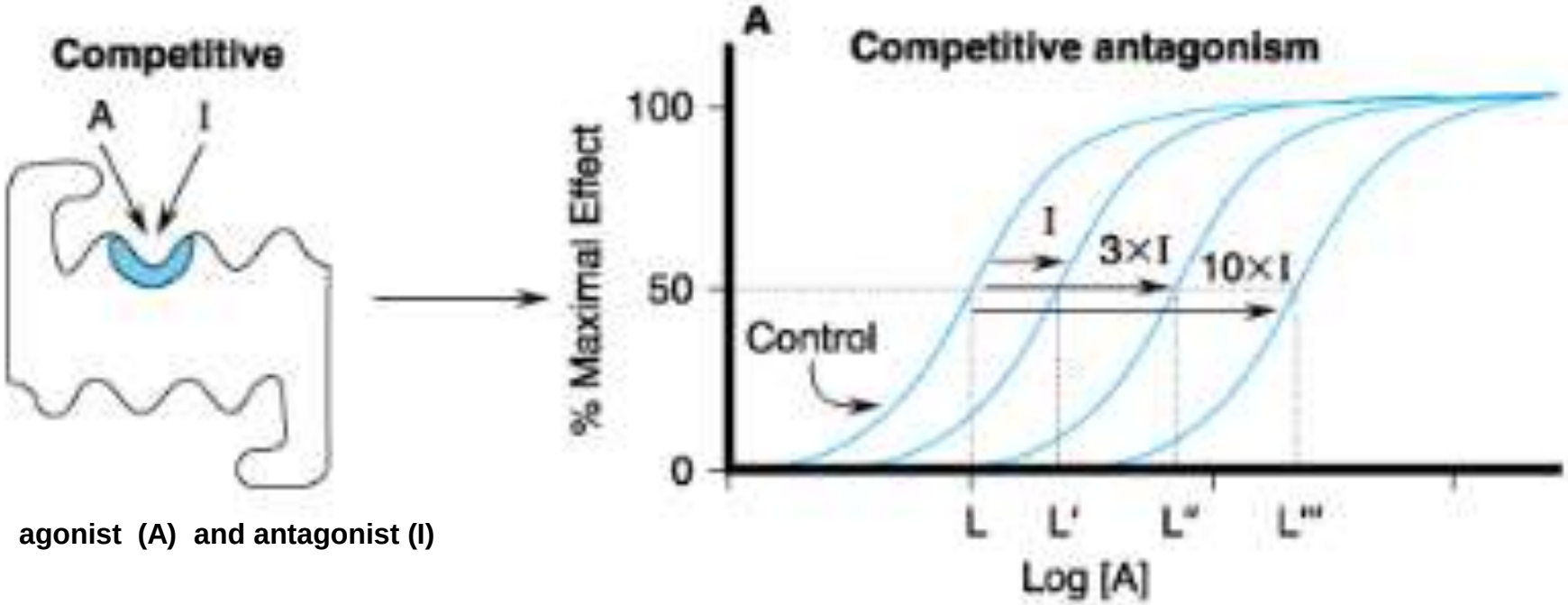
Pharmacological receptor antagonists have affinity for the receptors but ***have no intrinsic activity or efficacy***

There are three main types :

A. Competitive reversible antagonist :

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**.



agonist (A) and antagonist (I)

- The DR curve of agonist is shifted to the right, 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.

➢The affinity of competitive antagonist K_I to its receptors is calculated from :

$$C^*/C = 1 + [I] / K_I$$

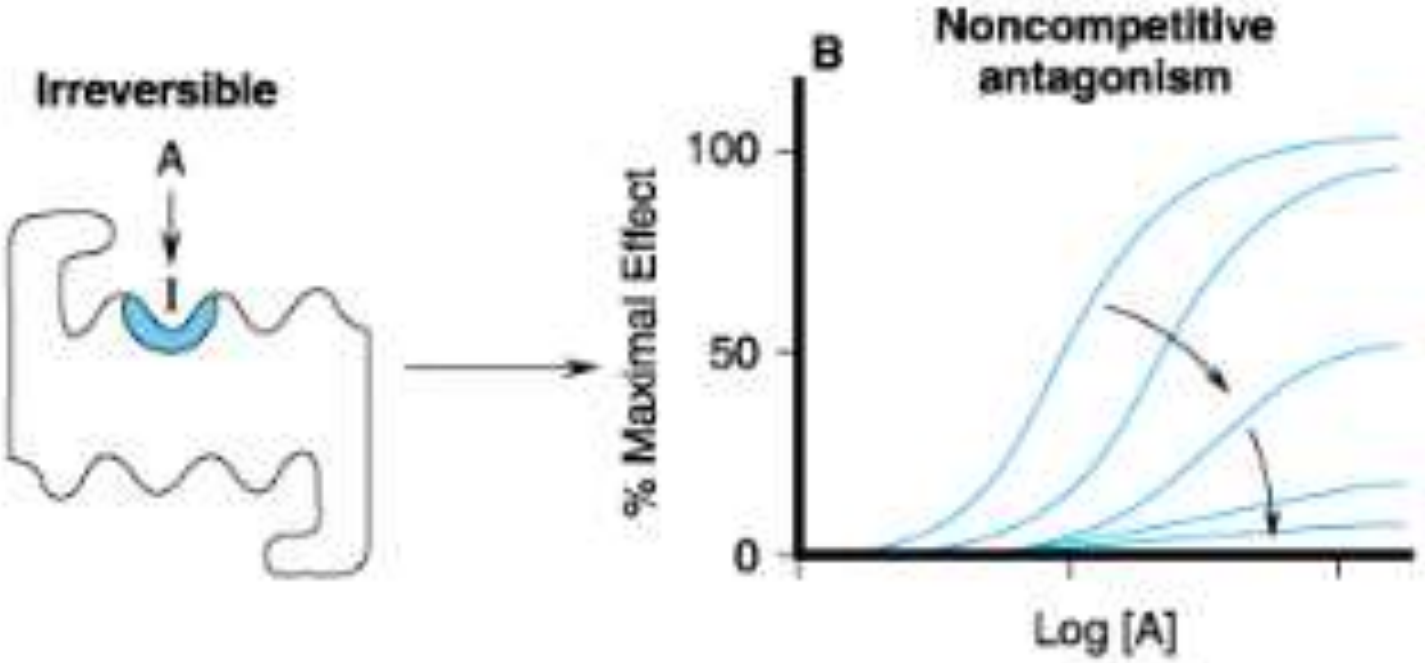
where C* is concentration of agonist that restores response in presence of antagonist concentration [I], and C is agonist concentration giving this response in absence of antagonist.

B. Non-competitive antagonist :

There are two subtypes:

1. Irreversible antagonist :

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 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.

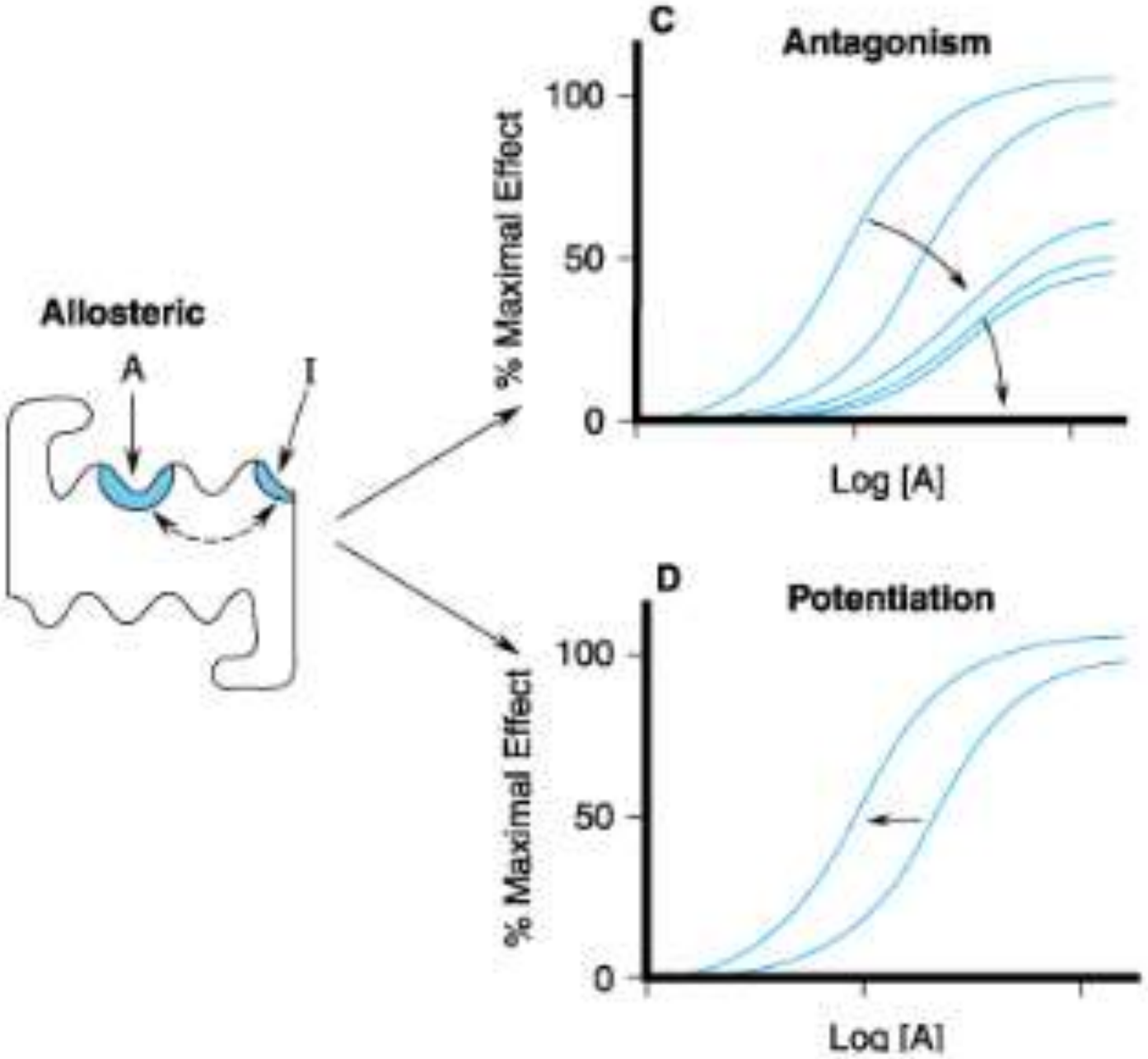
- **The more is the concentration of antagonist, the more is depression of maximal response**

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.

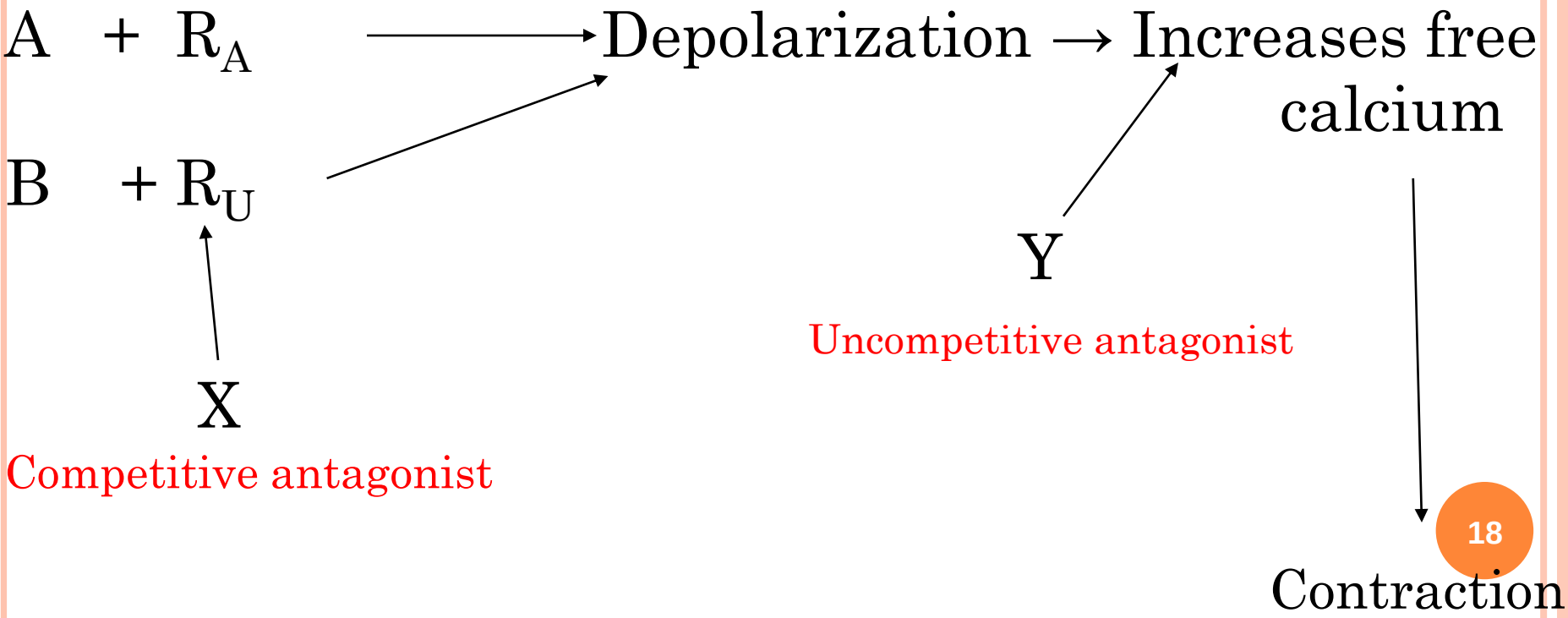
The dose response curve of antagonist is similar to that of irreversible non-competitive antagonist.

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.


Allosteric
A
I
C
Antagonism
% Maximal Effect
100
50
0
Log [A]
D
Potentiation
% Maximal Effect
100
50
0
Log [A]

C. Uncompetitive antagonism :

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



Receptor regulation

1. Receptor up-regulation :

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

It may occur with :

A. Prolonged use of receptor antagonist : here, there is lack of binding of receptor to agonist for long period of time

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 .

- 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.

Tachyphylaxis : it is a **rapidly developing tolerance**

- It is not due to receptor downregulation
- 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 :

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.**

2. 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.

THANKS