PHARMACODYNAMICS II

Quantitative aspects of drugs

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llos

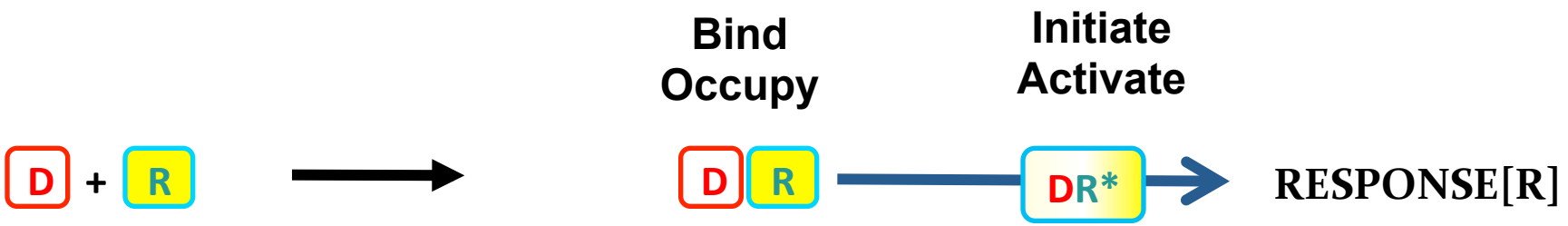
Determine quantitative aspects of drug receptor binding.

Recognize concentration binding curves.

Identify dose response curves and the therapeutic utility of these curves.

Classify different types of antagonism

QUANTIFY ASPECTS OF DRUG ACTION



Relate concentration [C] of D used (x- axis) to the binding capacity at receptors (y-axis)

Concentration-Binding Curve

Relate concentration [C] of D used (x-axis) to response produced (y-axis)

Dose Response Curves

AFFINITY

EFFICACY

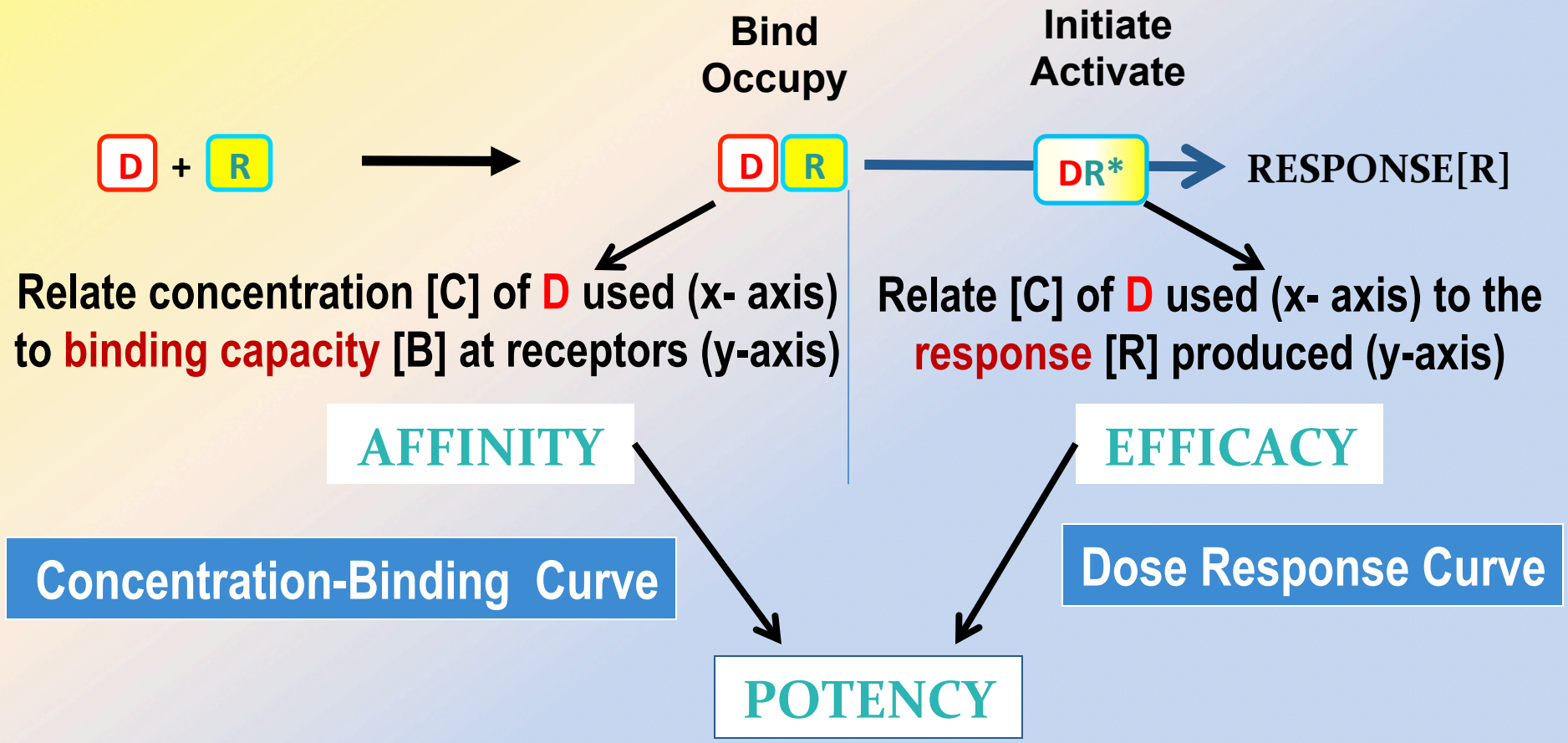
POTENCY

The **tendency of a drug to bind to the receptors** is governed by its ***affinity.***

AFFINITY

The **ability for it, once bound, to activate the receptor is** denoted by its ***efficacy.***

EFFICACY



Concentration binding curves

Is a correlation between **drug concentration [C]** used (x- axis) and **drug binding** capacity at receptors [B] (y-axis).

i.e. Affinity :

is relation between concentration & drug binding

Concentration-Binding curves are used to determine:

- **B_{max} (the binding capacity)**

is the total density of receptors in the tissues.

- **K_{D50}**

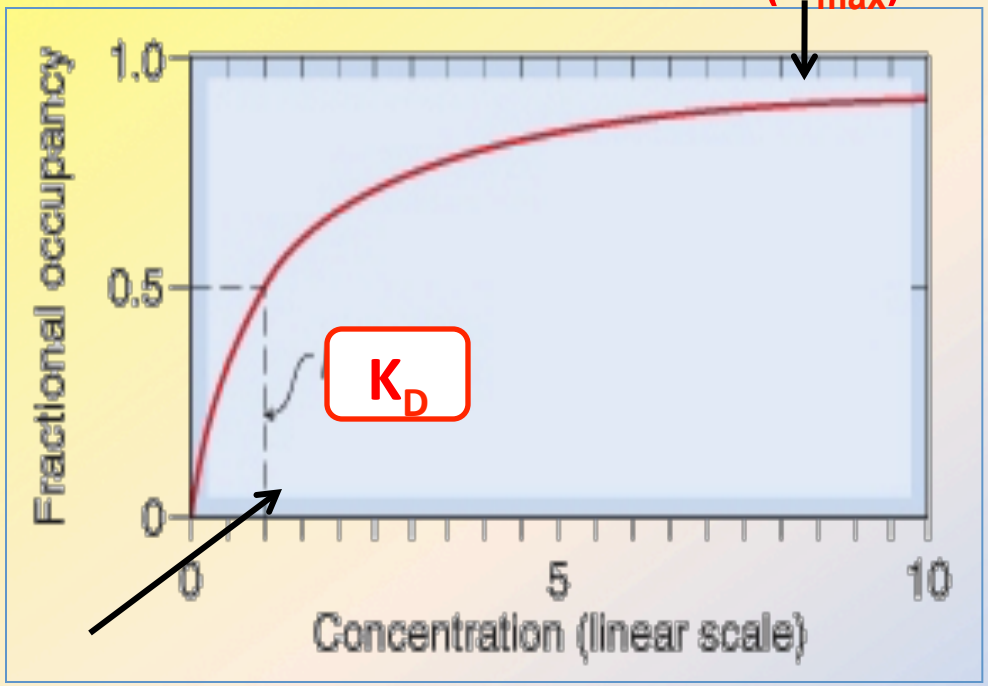
is the concentration of the drug required to occupy 50% of receptors at equilibrium.

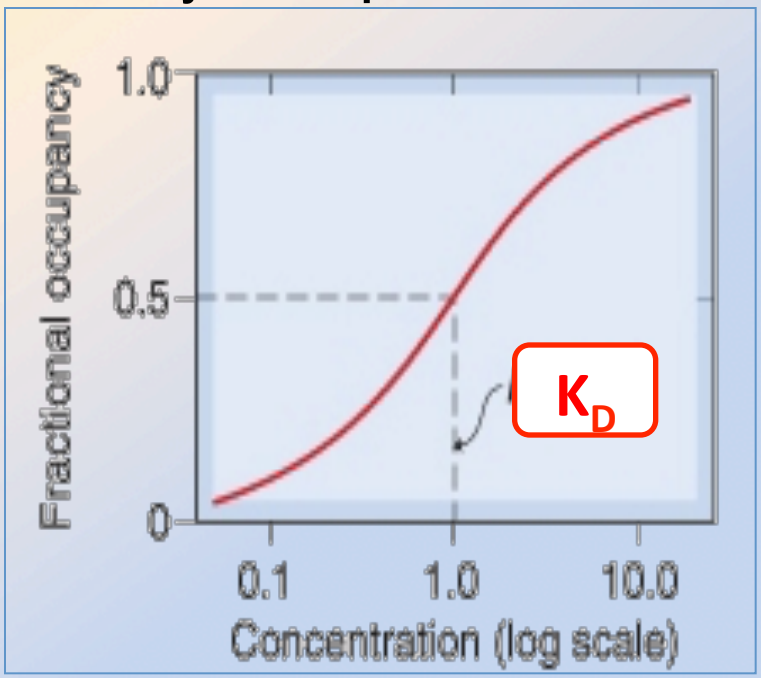
- **The affinity of drug for receptor**

The higher the affinity of D for receptor, the lower is the K_D **i.e. inverse relation**

Concentration-Binding Curve

(B_{max}): Total density of receptors in the tissue





(k_D)= [C] of D required to occupy 50% of receptors at equilibrium

Dose -response curves

- Used to study how response varies with the concentration of the drug or dose.
- Is a correlation between **drug concentration** [D] used (x- axis) and **drug response** [R] (y-axis).
- **i.e. relation between concentration & Response**

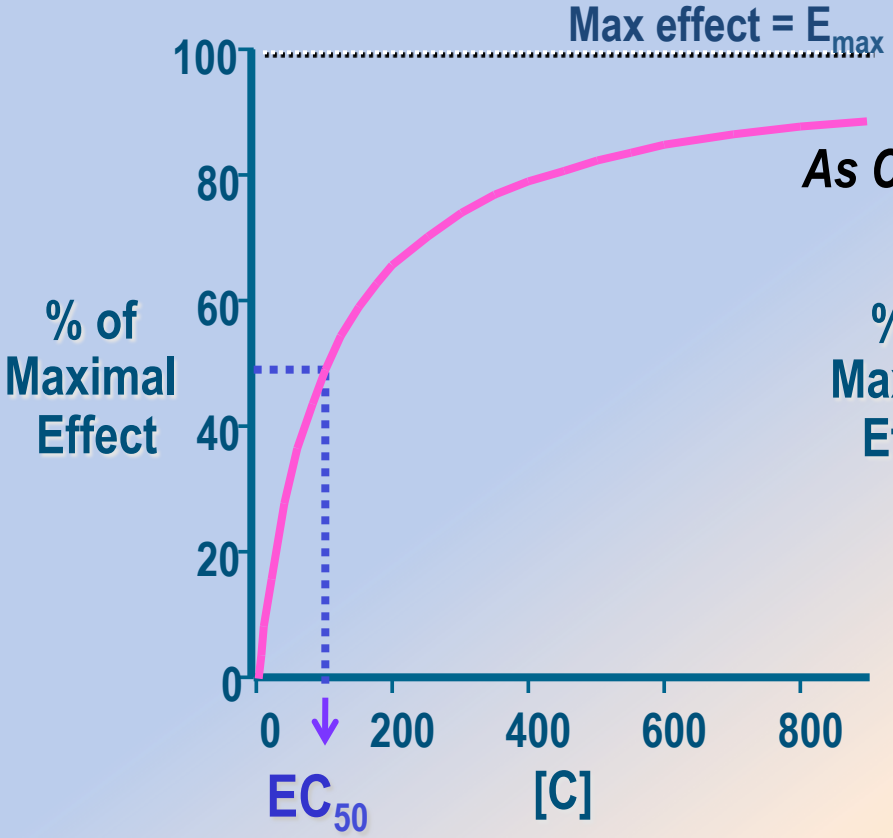
TYPES of Dose -response curves

- ✓Graded dose-response curve
- ✓Quantal dose-response curve

Graded Dose-response Curve

- Relate drug concentration to response.
- Gradual increase in response by increasing the dose
- Response is gradual and continuous.
- e.g. ↓blood pressure, heart rate, blood glucose level, cholesterol,…
- Curve is usually sigmoid in shape

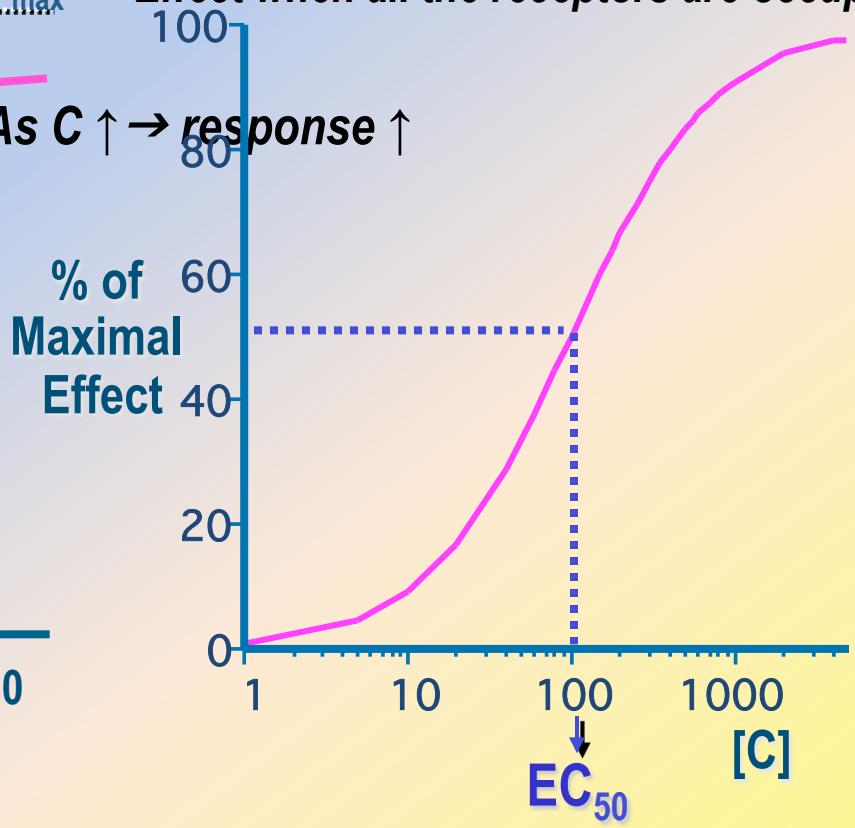
GRADED DOSE RESPONSE CURVE



C that gives the half-maximal effect

Effect when all the receptors are occupied by D

As C ↑ → response ↑



Graded dose-response curves are used to determine:

Graded dose-response curves are used to calculate:

- **Efficacy**
- **E_{max}**
- **EC_{50}**
- **Potency**

Maximum Efficacy (E_{max}): is the maximal biological response produced by a drug.

Median Effective concentration (EC_{50}):

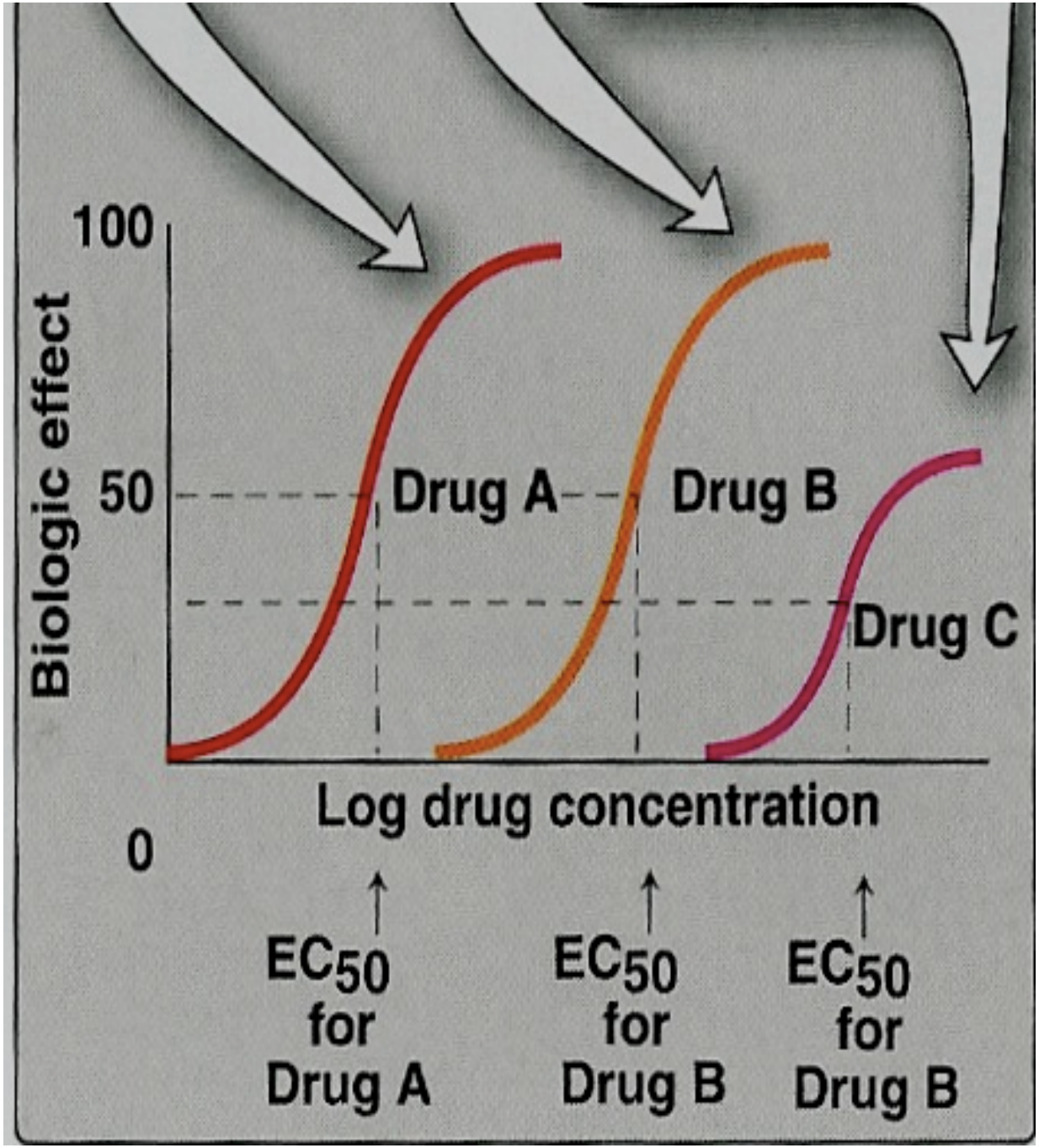
- is the concentration of the drug that produces a response equal to 50% of the maximal response (**E_{max}**).

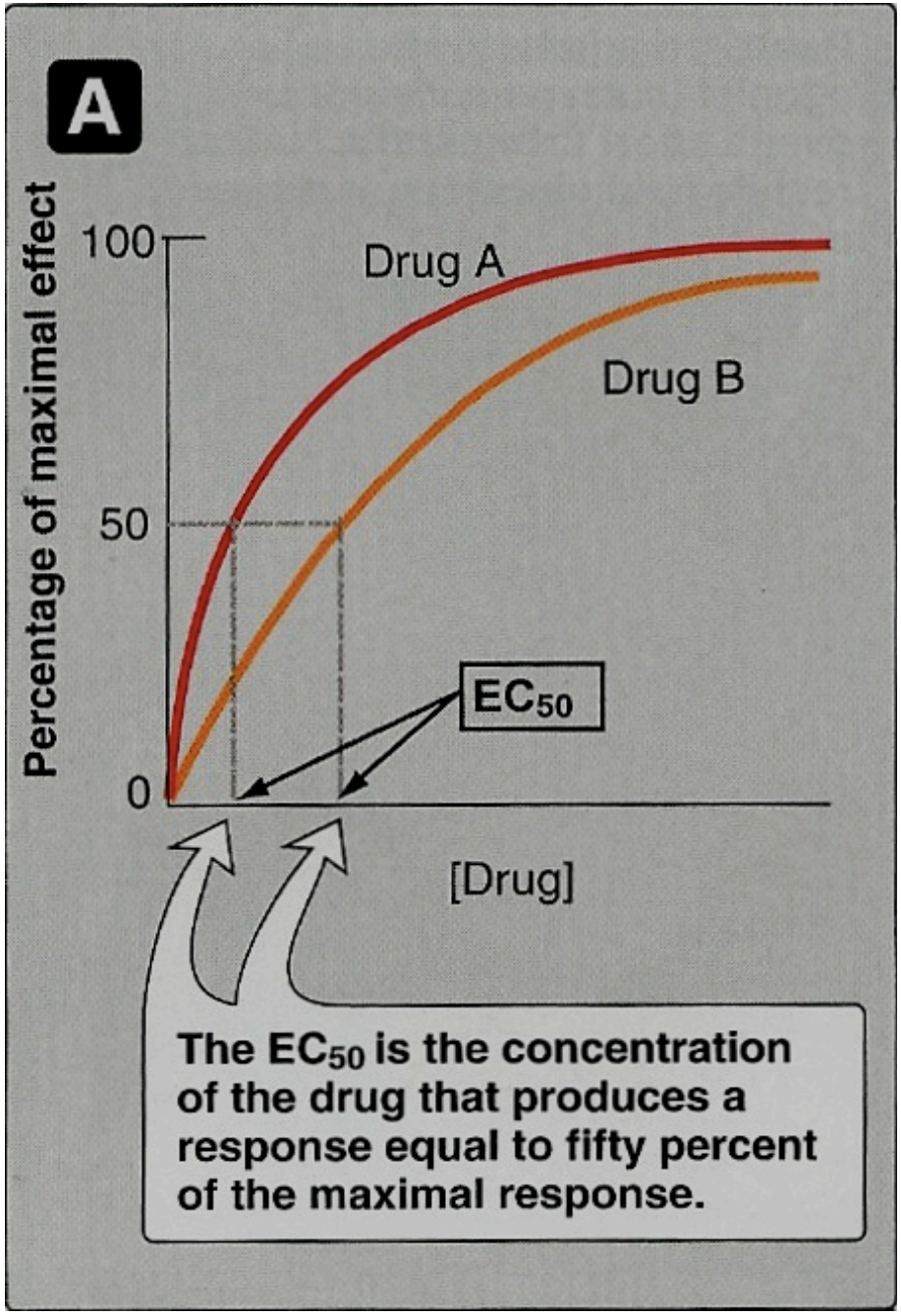
Graded dose-response curves are used to determine:

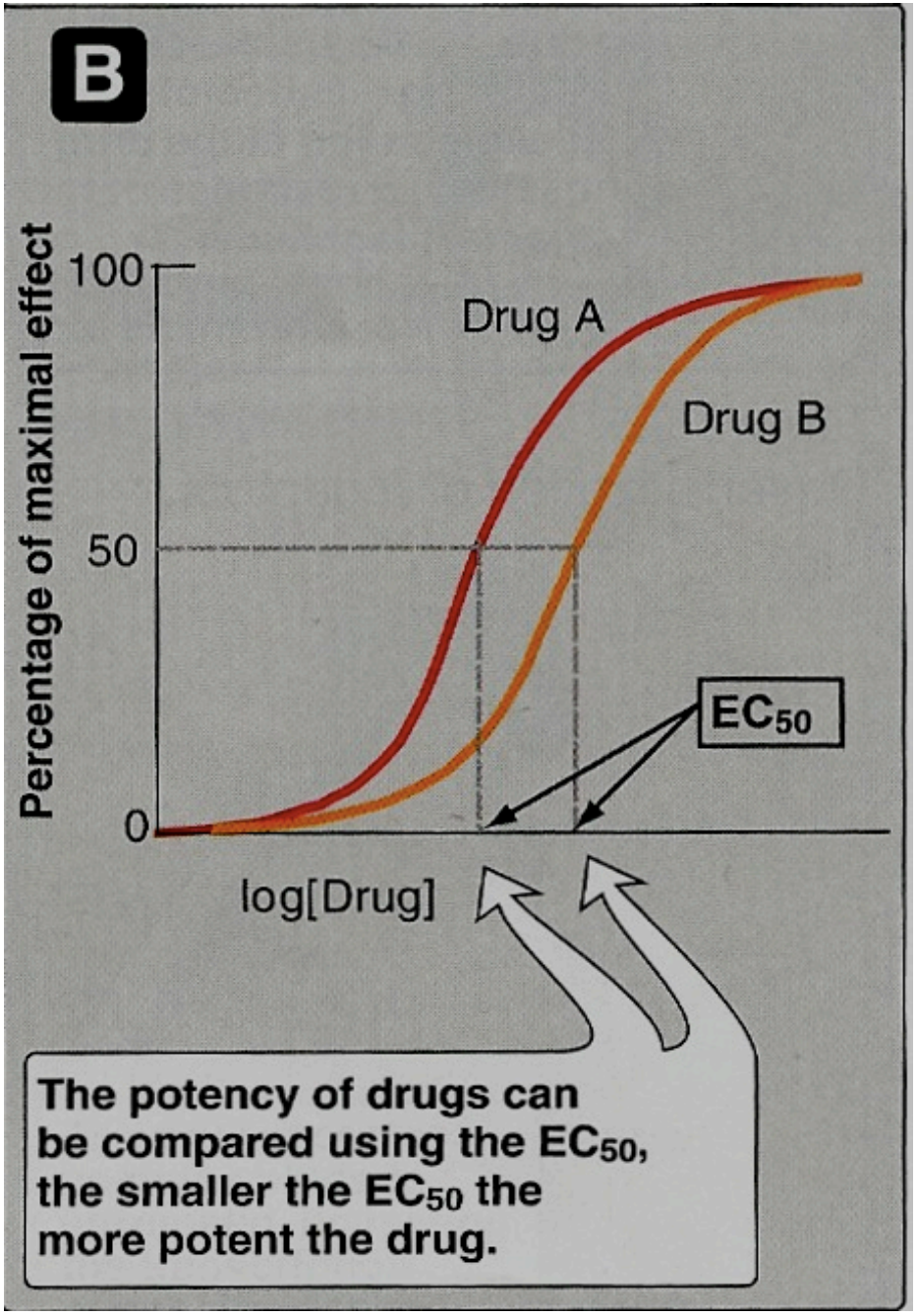
Potency: the concentration of drug required to produce a specified response (**50% of the maximal response = EC_{50}**).

Potency of drugs can be compared using EC_{50},
The smaller the EC_{50}, the more potent the drug.

Potency is inversely proportional to EC_{50}


100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug B


A
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
[Drug]
The EC50 is the concentration of the drug that produces a response equal to fifty percent of the maximal response.


B
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
log[Drug]
The potency of drugs can be compared using the EC50, the smaller the EC50 the more potent the drug.

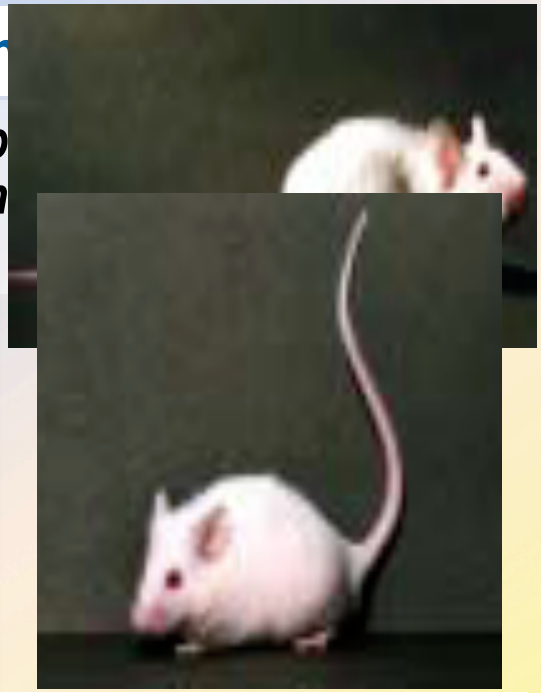
Quantal Dose-response Curve

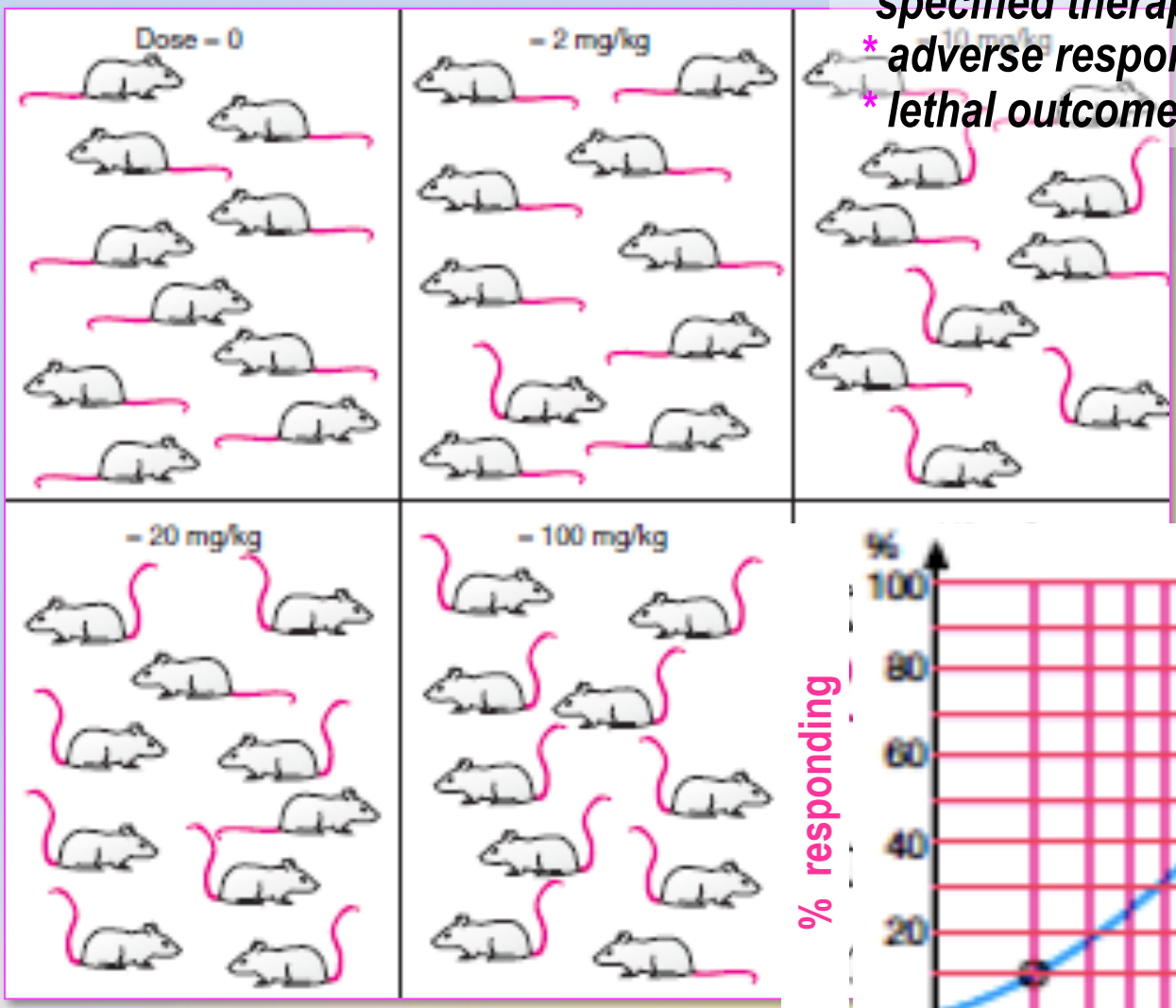
- Relate drug concentration to % percentage of patients responding.
- **all or none response**.
- The response may be **therapeutic response, adverse effect or lethal effect.**
- e.g. prevention of convulsion, arrhythmias or death.
- **Used to determine**
  - ED_{50}
  - TD_{50} & LD_{50}
  - Therapeutic index.

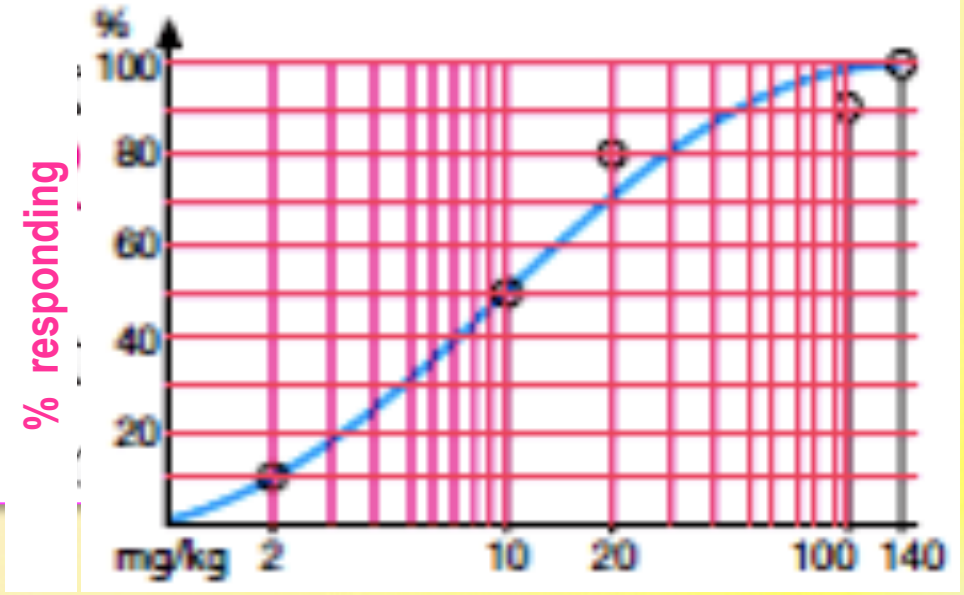
QANTAL DOSE RESPONSE CURVE

All-non respon

* *specified therap*
* *adverse respon*
* *lethal outcome*







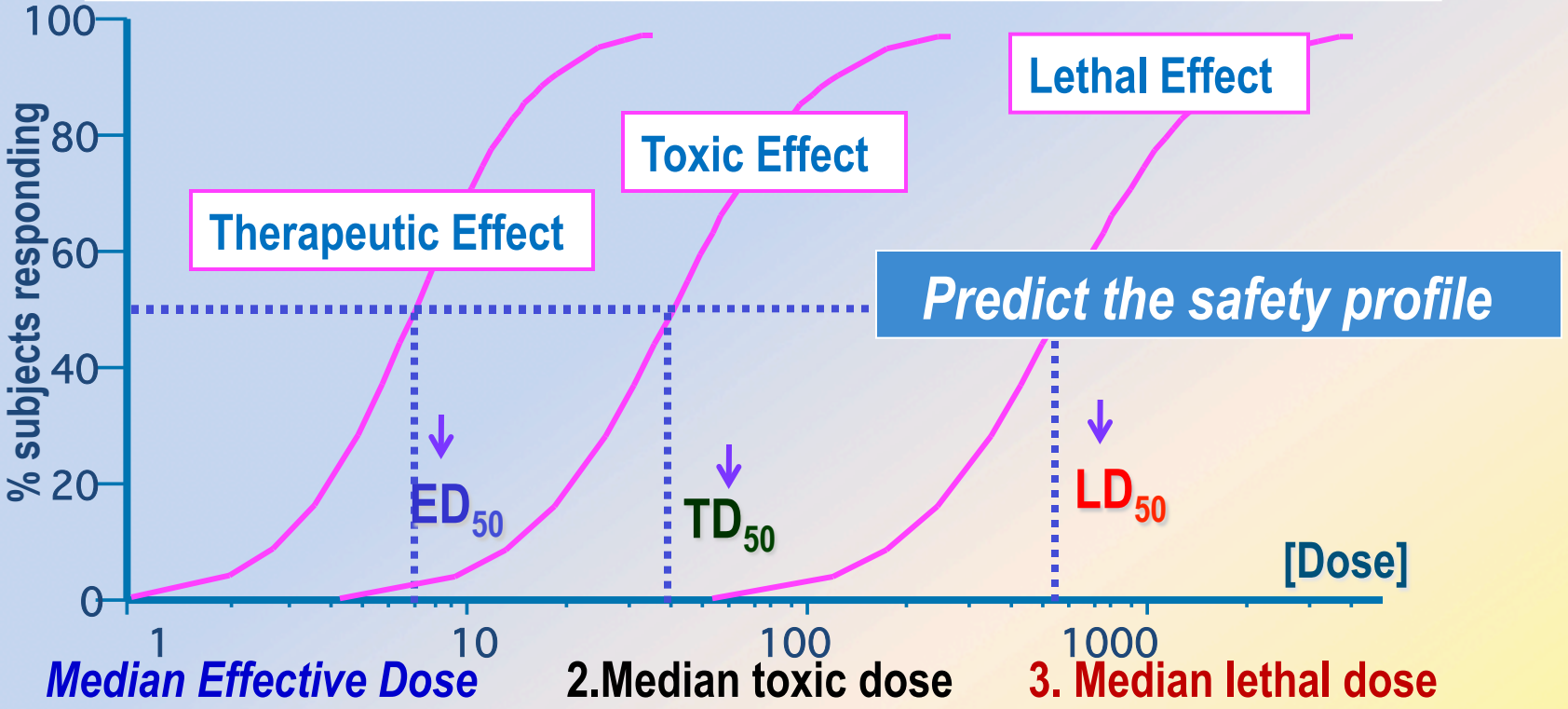
Dose-frequency relationship

Median Effective Dose (ED_{50}): is a dose of the drug required to produce a therapeutic effect in 50% of individuals.

Median Toxic Dose (TD_{50}):
is the dose of a drug required to produce toxic effects in 50 % of individuals.

Median Lethal Dose (LD_{50}): is the dose of a drug required to produce death in 50 % of individuals.

QANTAL DOSE RESPONSE CURVE: *used to determine*



ED_{50} = 50% of individuals exhibit the specified therapeutic response

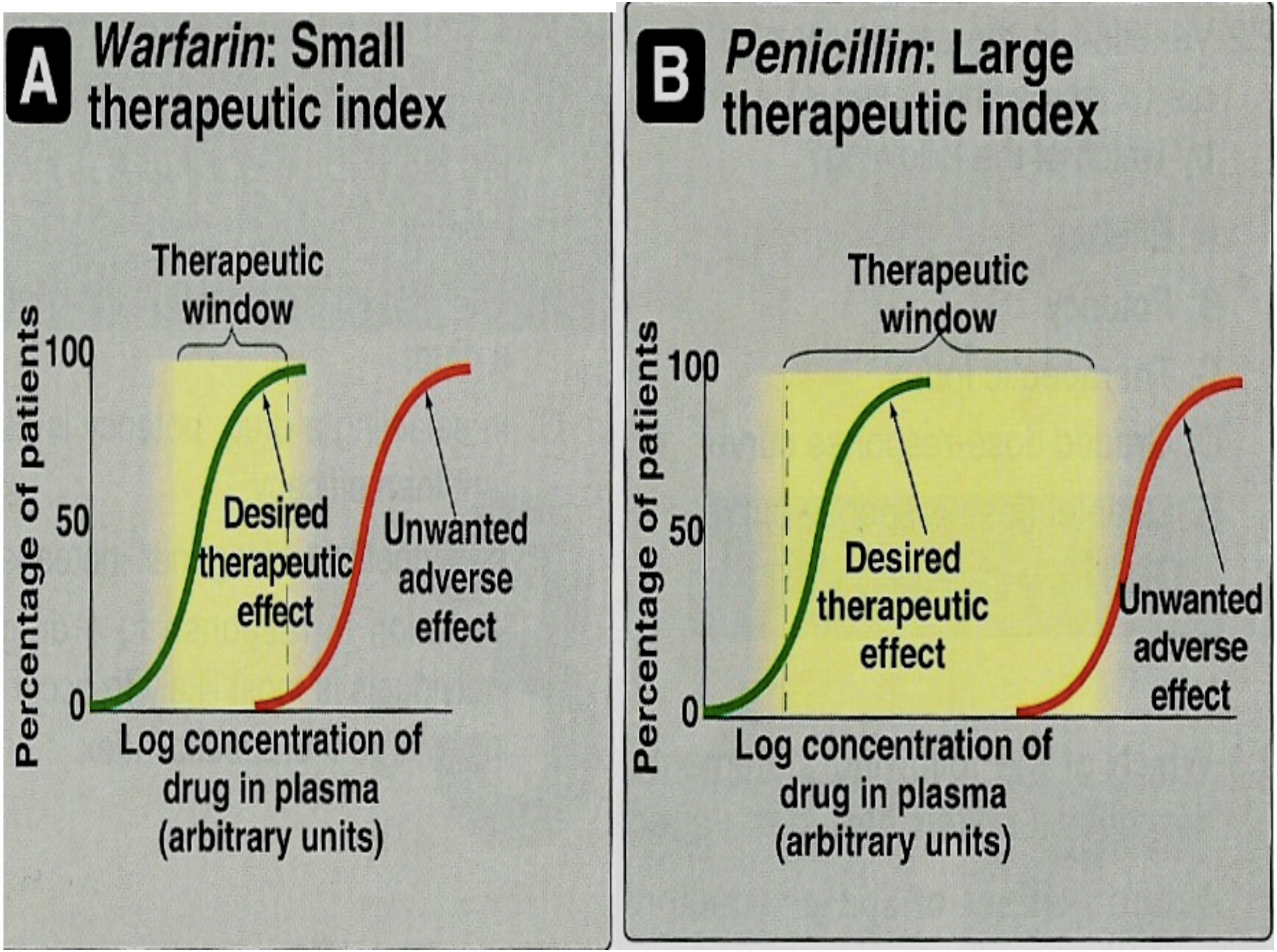
TD_{50} = 50% of individuals exhibit toxic effects

LD_{50} = 50% of individuals exhibit death

Therapeutic Index (TI)

- **Therapeutic index =** $\frac{LD_{50}}{ED_{50}}$
- **Is a measure of safety profile**
- **Large TI means drug has wide margin of safety**

  e.g diazepam, penicillin
- **Small TI = a narrow margin of safety e.g. digoxin, warfarin**


A
Warfarin: Small therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)
B
Penicillin: Large therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)

ANTAGONISM

It is the diminution or the complete abolishment of the effect of one drug in the presence of another.

Types

1. Chemical

Two drugs react chemically resulting in loss of activity of active drug.**Dimercaprol** reduces heavy metal toxicity [lead]

2.Physiological

Two drugs possess opposing actions in body, so tend to cancel each other's effect. **Adrenaline** & histamine

3. Pharmacokinetic

The antagonist effectively reduces the concentration of the active drug at the site of action
Phenobarbitone accelerates hepatic metabolism warfarin

4. Pharmacodynamic (*Competitive*)

- ***Reversible***
- ***Irreversible***

5. Pharmacodynamic (Non-Competitive)

Antagonism

It is the decrease or the complete loss of the effect of one drug by the combination with another drug.

Types of Antagonism

- ✓ **Chemical antagonism.**
- ✓ **Physiological antagonism.**
- ✓ **Pharmacokinetic antagonism**
- ✓ **Pharmacodynamic antagonism**
  - **Competitive**
    - **Reversible**
    - **Irreversible**
  - **Non-competitive**

Antagonist

Types

- Physiological antagonist.
- Chemical antagonist.
- Pharmacokinetic antagonist.
- Pharmacodynamic antagonist.

Chemical Antagonism

- Simple chemical reaction between two drugs resulting into loss of activity.
- No receptors are involved.
- e.g. Dimercaprol used as antidote to reduce heavy metal toxicity (lead toxicity).

Pharmacokinetic Antagonism

- The antagonist effectively reduces the concentration of the active drug at the site of action.
- e.g. Phenobarbitone accelerates hepatic metabolism of warfarin

Physiological Antagonism

- **Two drugs act on different receptors to produce opposite physiological effects.**
- **e.g. Adrenaline is used in anaphylactic shock**

Histamine →

vasodilatation (↓BP) & bronchoconstriction

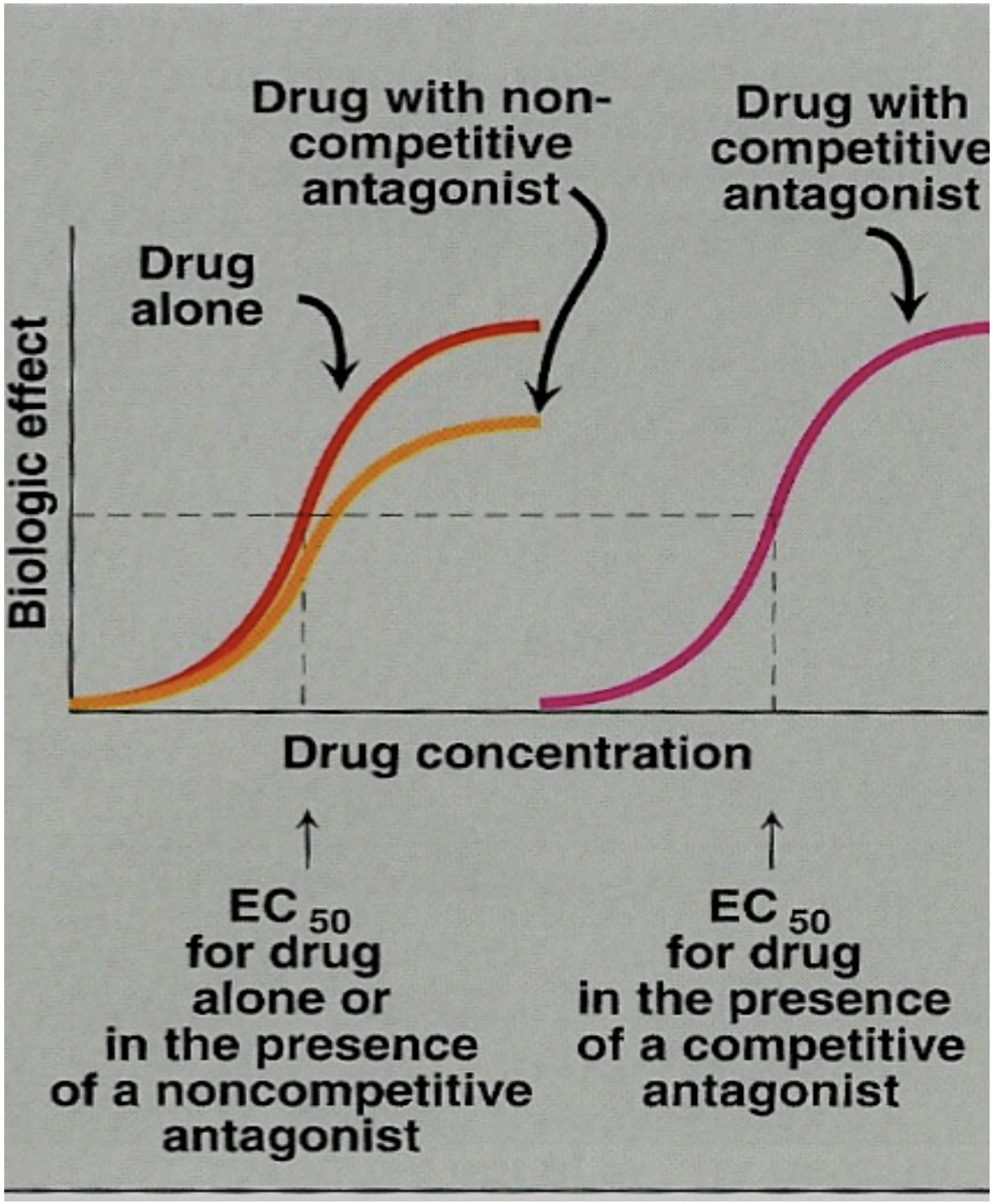
Adrenaline →

Vasoconstriction (↑ BP) & bronchodilation.

Pharmacodynamic antagonism

Competitive (reversible)

- Two drugs compete for the same receptor (only one is bound).
- The antagonist partially or completely prevents the pharmacological effect of agonist.
- Antagonist dissociate rapidly from receptor.
- Antagonism can be overcome by increasing the concentration of the agonist.
- Parallel shift of the D-R curve to the right, without any change in slope or maximum.
- e.g. acetylcholine and atropine.


Drug with non-competitive antagonist
Drug with competitive antagonist
Drug alone
Biologic effect
Drug concentration
EC 50 for drug alone or in the presence of a noncompetitive antagonist
EC 50 for drug in the presence of a competitive antagonist

Pharmacodynamic antagonism

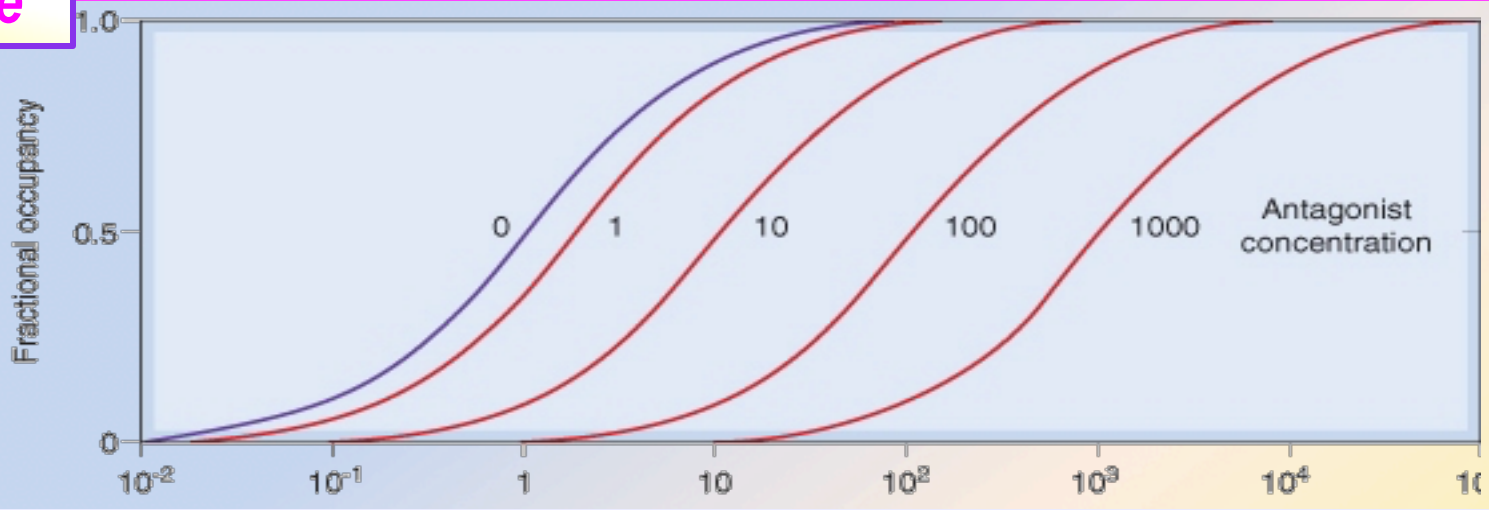
Competitive (irreversible)

- **Two drugs compete for the same receptor.**
- **Antagonist forms stable, permanent chemical bond with receptor.**
- **The original response can not be overcome even by increasing the dose of the agonist.**
- **No parallel shift of D-R curve**
- **a decrease in slope and a reduced maximal response are obtained.**

e.g. phenoxybenzamine and noradrenaline.

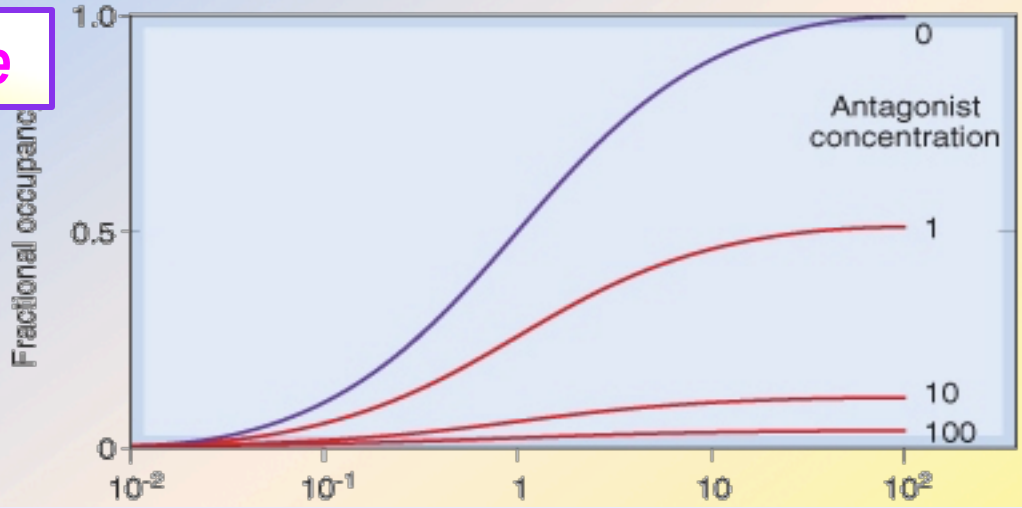
Competitive Antagonism

Reversible



Parallel shift to the right, without any change in slope or maximum

Irreversible



No parallel shift

But both a decrease in slope and a reduced maximum are obtained.

Competitive (reversible)

- Two drugs compete for the same receptor.
- Antagonist dissociate rapidly from receptor.
- The original response can be obtained by increasing the concentration of the agonist.
- Parallel shift to the right
- No change in slope
- No change in maximum effect

e.g. acetylcholine and atropine.

Competitive (irreversible)

- Two drugs compete for the same receptor.
- Antagonist forms stable, permanent chemical bond with receptor.
- The original response can not be obtained even by increasing the dose of the agonist.
- No parallel shift
- A decrease in slope
- Decrease in maximum effect

e.g. phenoxybenzamine and noradrenaline.

COMPETATIVE ANTAGONISM

Reversible

Antagonist readily dissociate from binding site of agonist to the receptor

Antagonism can be overcome by increasing concentration of agonist

Atropine vs Ach

Irreversible

Antagonist form stable, permanent / near permanent chemical bond with receptor.

Inactivation lasts for duration of receptor turnover or its de-novo synthesis → explains its longevity of action

Phenoxybenzamine & Noradrenaline

Pharmacodynamic antagonism

Non-competitive

- Agonist and Antagonist can bound simultaneously.
- **Antagonist block at some point the chain of events that stimulate the response of agonist.**
- Antagonism cannot be overcome by increasing concentration of agonist .

e.g. verapamil and noradrenaline.

ANTAGONISM

Non-Competitive

Agonist and Antagonist can be bound simultaneously

the response of agonist

nist to the

= competes with

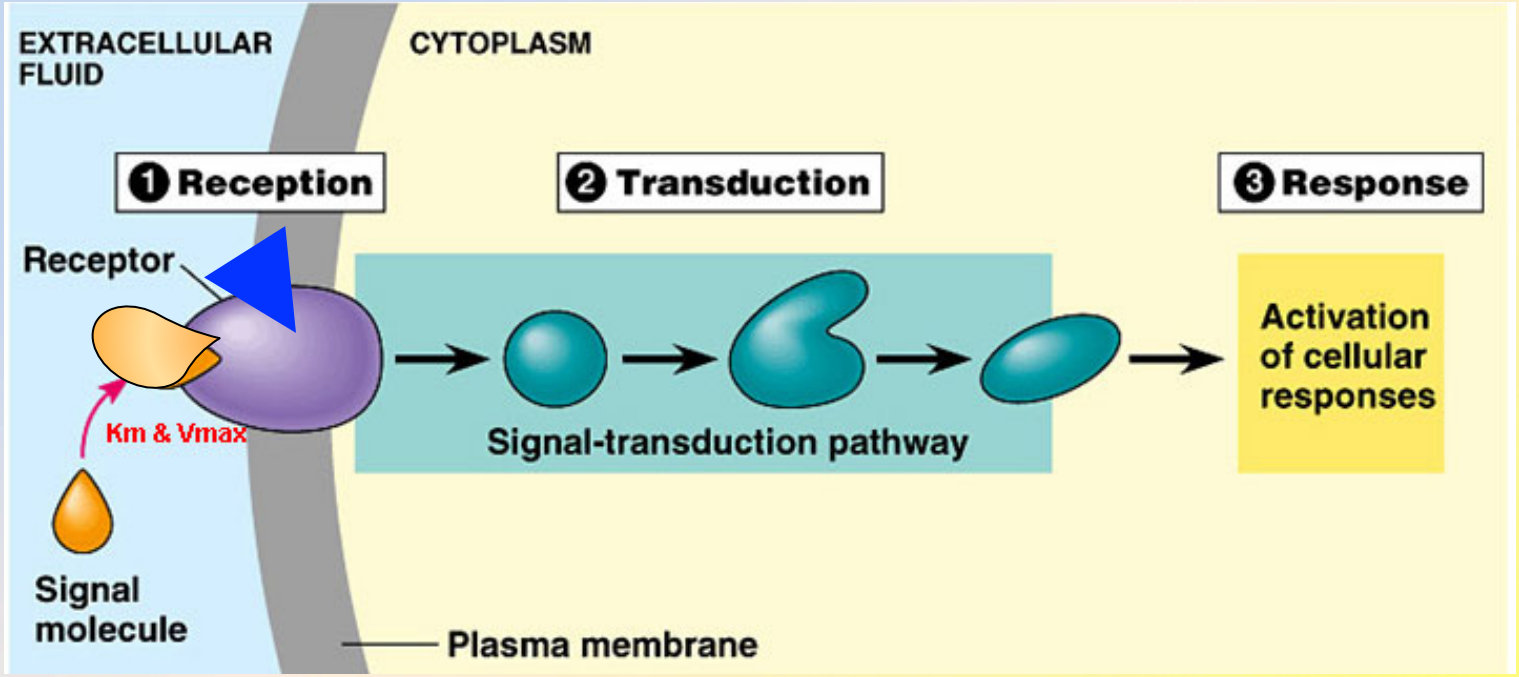
Receptor Blockade Competitive

Reversible

Agonist and Antagonist compete

und)

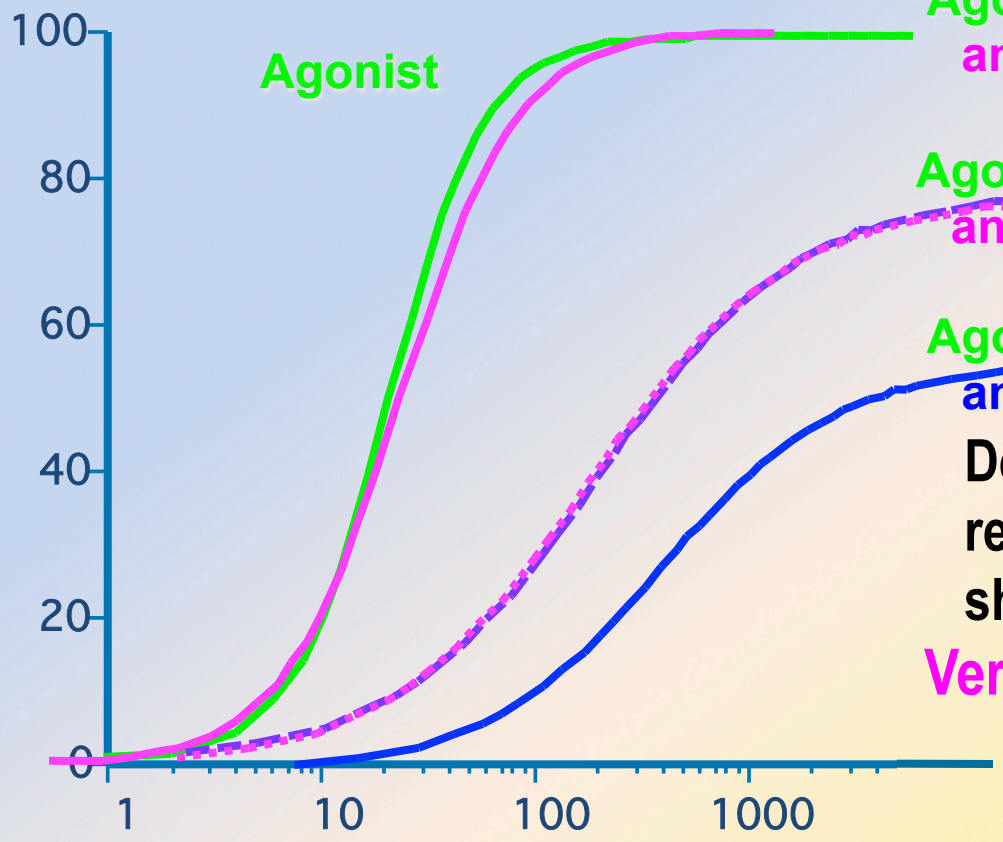
Irreversible



Competitive vs Noncompetative Antagonism

Antagonism can be overcomed by increasing concentration of agonist =

SURMOUNTABLE



Depression of maximal response +/- rightward shifts ***(if some R are spare)***

Verapamil vs noradrenaline

Antagonism cannot be overcome by increasing concentration of agonist = **NON-SURMOUNTABLE**

ANTAGONISM

Non-Competitive

Antagonist block at some point the chain of events that ignite the response of **agonist**

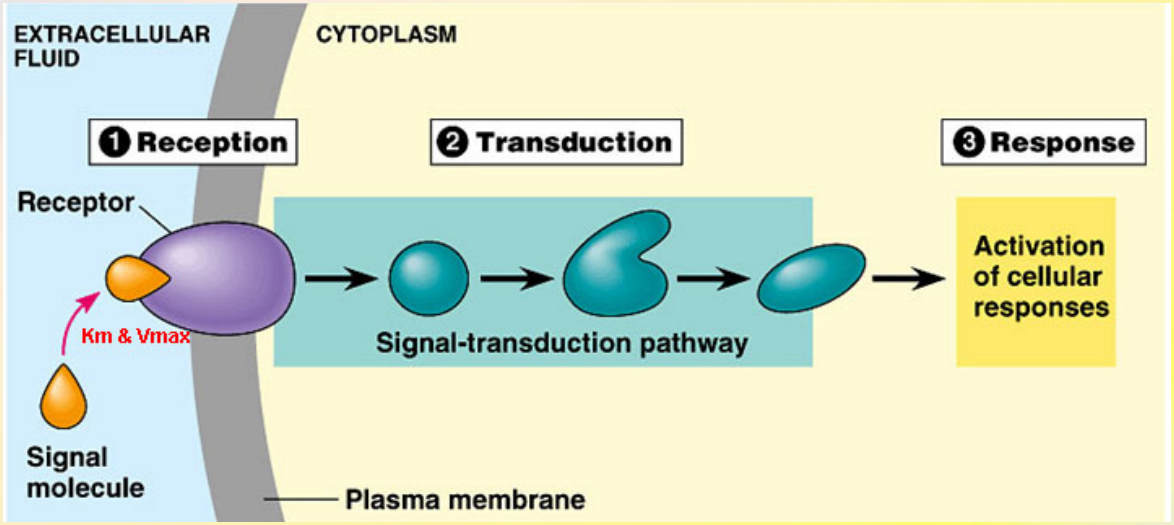
Agonist and **Antagonist** can be bound simultaneously

Receptor Blockade *(Competitive)*

Antagonist prevents binding of **agonist** to the receptor at the same binding site (= competes with it at same receptor)

Agonist and **Antagonist** compete (only one is bound)

- *Reversible*
- *Irreversible*



GLUCOOK

PHARMACOLOGY