جامعة الملك سعود
King Saud University

•نشكر تيم فارماكولوجي 433 لإتاحتهم الفرصة لنا للاستفادة من عملهم

Pharmacology 434

LECTURE 6

Pharmacodynamics II ; Quantitative Aspects of Drug Action

OBJECTIVES:

- ✓Determine quantitative aspects of drug receptor binding
- ✓Recognize different dose response curves.
- ✓ Distinguish the therapeutic utility of each of these curves.
- ✓ Classify different types of antagonism.

Abbreviations :

BP “blood pressure”, HR “heart rate”, FBG “fasting blood glucose”
Ach “acetylcholine” , C “concentration” , D “Drug” .

QUANTIFY ASPECTS OF DRUG ACTION

Concentration-Binding Curve

This curve Used to determine **drug affinity**.
(the ability of binding between the drug and the receptor)

Dose Response Curve

This curve used to determine **drug efficacy**
(the ability to produce a response)

K_1 : **Association rate constant**

Drug ⇌ **Receptor**

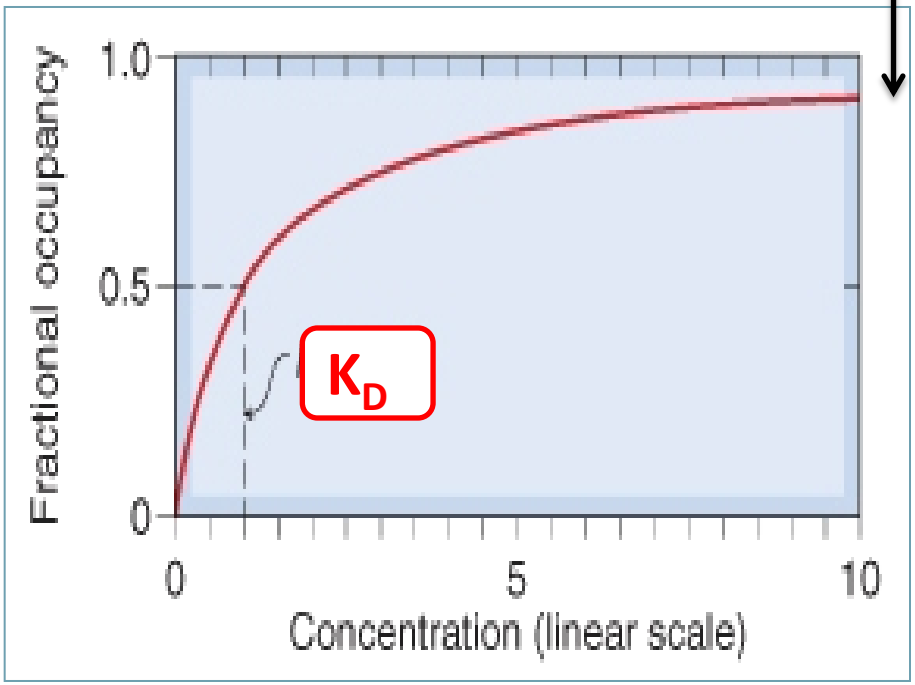
K_2 : **Dissociation rate constant**

At equilibrium the equilibrium dissociation constant (K_D) is presented by ratio (k_2/k_1)

K_D: The concentration Of drug regarding to bind 50% of receptor.

Concentration-Binding Curve

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



The relationship between drug binding & drug concentration is expressed mathematically by the following equation:-

$$B = \frac{B_{max} \times C}{C + K_D}$$

If we increase C The binding will increase.

K_D :The concentration of drug regarding to bind 50% of receptor.

Concentration-Binding curves are used to determine:

1-The binding capacity (Bmax) → total density of receptors in the tissues.

2-The affinity of D for receptor

The higher the affinity of D for receptor the lower is the KD i.e. inverse relation

So (↑KD ↓affinity) and (↓KD ↑affinity)

DOSE RESPONSE CURVE

could be either :

Graded Curve

Continuous response

e.g. ↓BP, HR, FBG, Cholesterol

It can take any value like (continuous value): BP, HR, FBG and cholesterol level.

Quantal Curve

Frequency response (An all-or-non response)

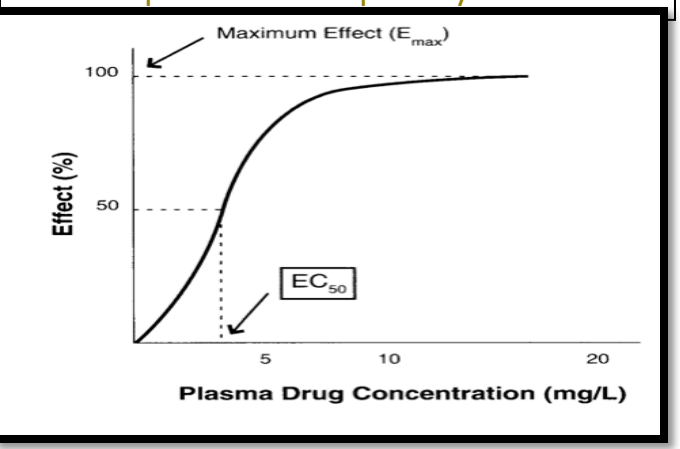
e.g. epilepsy (الصرع), arrhythmias or death.

Relate C to % of patients eliciting the :

*Specified therapeutic response.
*Adverse response.
*Lethal outcome.

Graded Curve Response

Maximum effect (E_{max}) : Effect when all the receptors are occupied by D



$$E = \frac{E_{max} \times C}{C + EC_{50}}$$

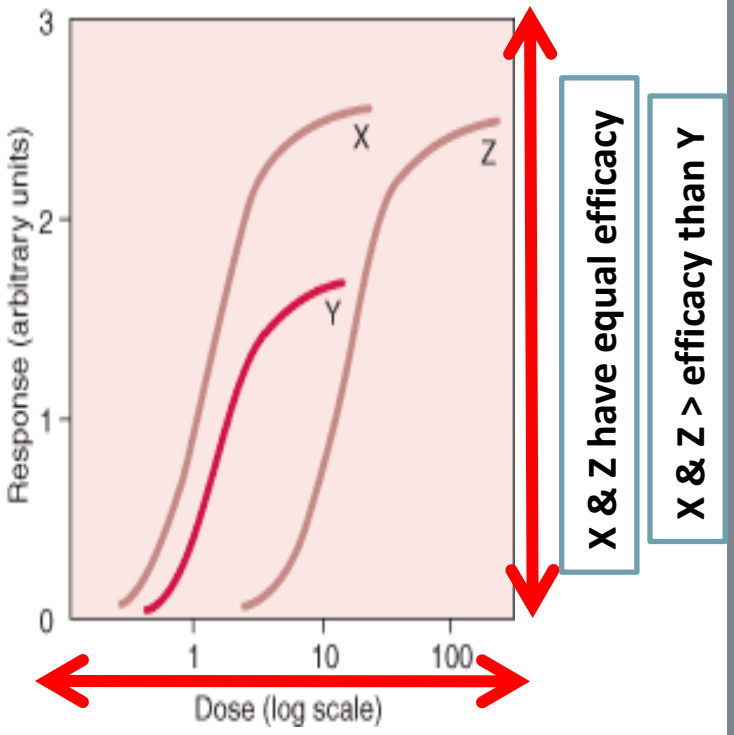
EC50 : C of D that produce 50% response .

Graded dose-response curves are used to determine:

1-The max efficacy (E_{max}) → **highest** limit of dose-response relationship on response axis.

2-The potency = The concentration of drug required to produce a specified response, the smaller the EC_{50} , the greater the potency of the agonist, i.e. the lower C needed to elicit the max biological response.

3. Compare the relative potency and efficacy of drugs that produce the same effect.



YouTube

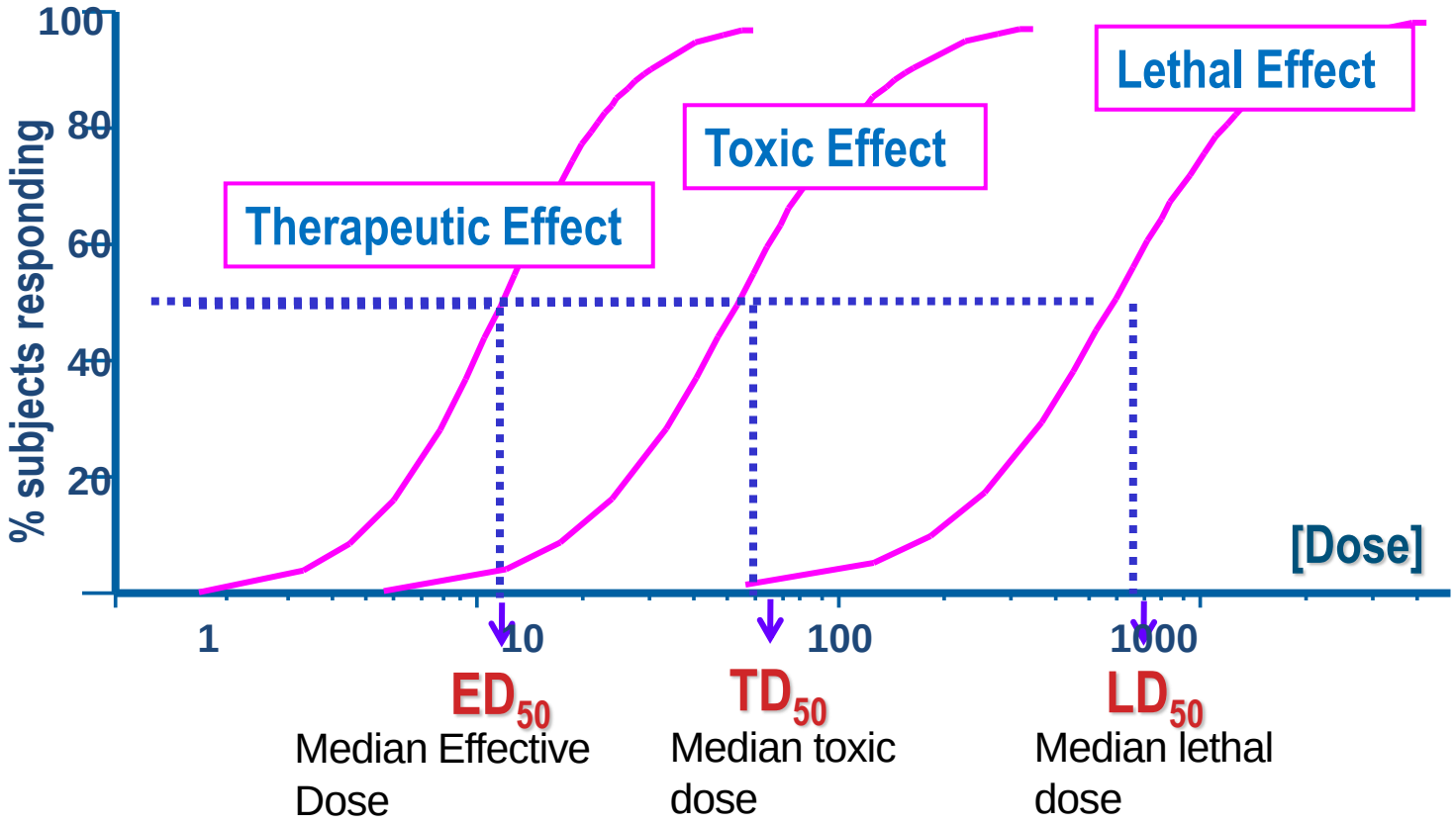
X > potent than Y & Z

Y> potent than Z

Y > potent Z

Y< efficacious Z

Quantal Curve Response



ED_{50} : It is a dose of drug that produces response in 50% of the individuals.

TD50 : It is a dose of drug that produces toxic effects in 50% of the individuals.

LD_{50} : It is a dose of drug that kills 50% of the individuals.

Therapeutic Index

$$\frac{TD_{50}}{ED_{50}}$$

The relation between dose to induce a desired effect versus that producing the unwanted effect.

YouTube

When high ⟶ the drug has a safe profile diazepam

When low ⟶ the drug has a narrow margin of safety digoxin

Antagonism

The process of diminution or the complete abolishment of the effect of one drug in the presence of another, and includes:

chemical

- Two drugs react chemically resulting in loss of activity of active drug.
- Treatment by : Dimercaprol reduces heavy metal toxicity [lead]
- kidney damage, Brain toxicity

physiological

- Two drugs possess opposing actions in the body, so tend to cancel each other's effect
- Omeprozole & histamine

pharmokinetic

- The antagonist effectively reduces the concentration of the active drug at the site of action
- Phenobarbitone induces an accelerated hepatic metabolism warfarin

Receptor blockade (competitive)

- Antagonist prevents binding of agonist to the receptor at the same binding site (= competes with it at same occupancy site)
- Agonist and Antagonist compete (only one is bound)
- Reversible and irreversible
- Connects with the active site of an enzyme

Non-competitive

- Antagonist block at some point the chain of events that ignite the response of agonist
- Agonist and Antagonist can be bound simultaneously
- Connects with the allosteric site of an enzyme

The difference between competitive and non competitive antagonism: http://youtu.be/99Xlu3pTQ0s

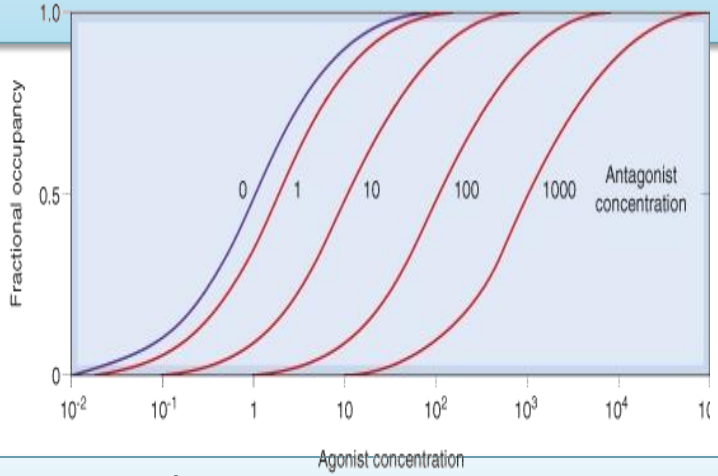
Competitive antagonism

Reversible

- **Antagonist** readily dissociate from binding site of **agonist** to the receptor
- Antagonism can be overcome by increasing concentration of agonist = **Surmountable**
- **Atropine** vs Ach

surmountable means that it is possible to exceed it.

Note that when the antagonist concentration is increased, a bigger concentration of the agonist is required to maintain the same fractional occupancy*.

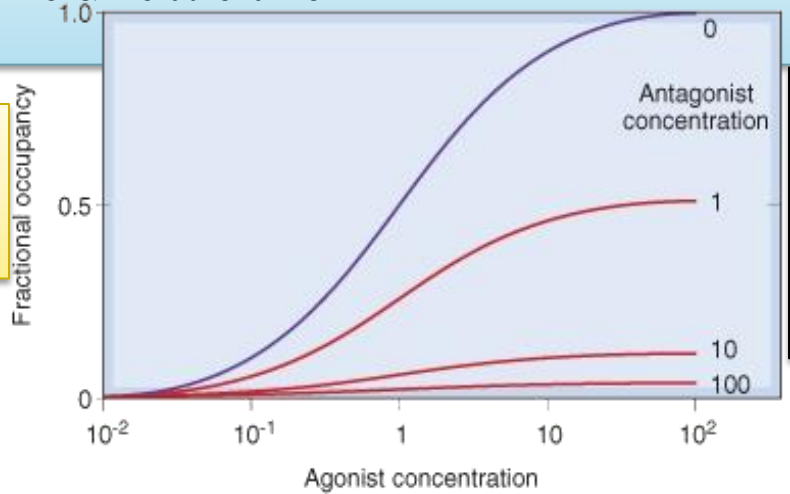


Parallel shift to the right, without any change in slope or maximum

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

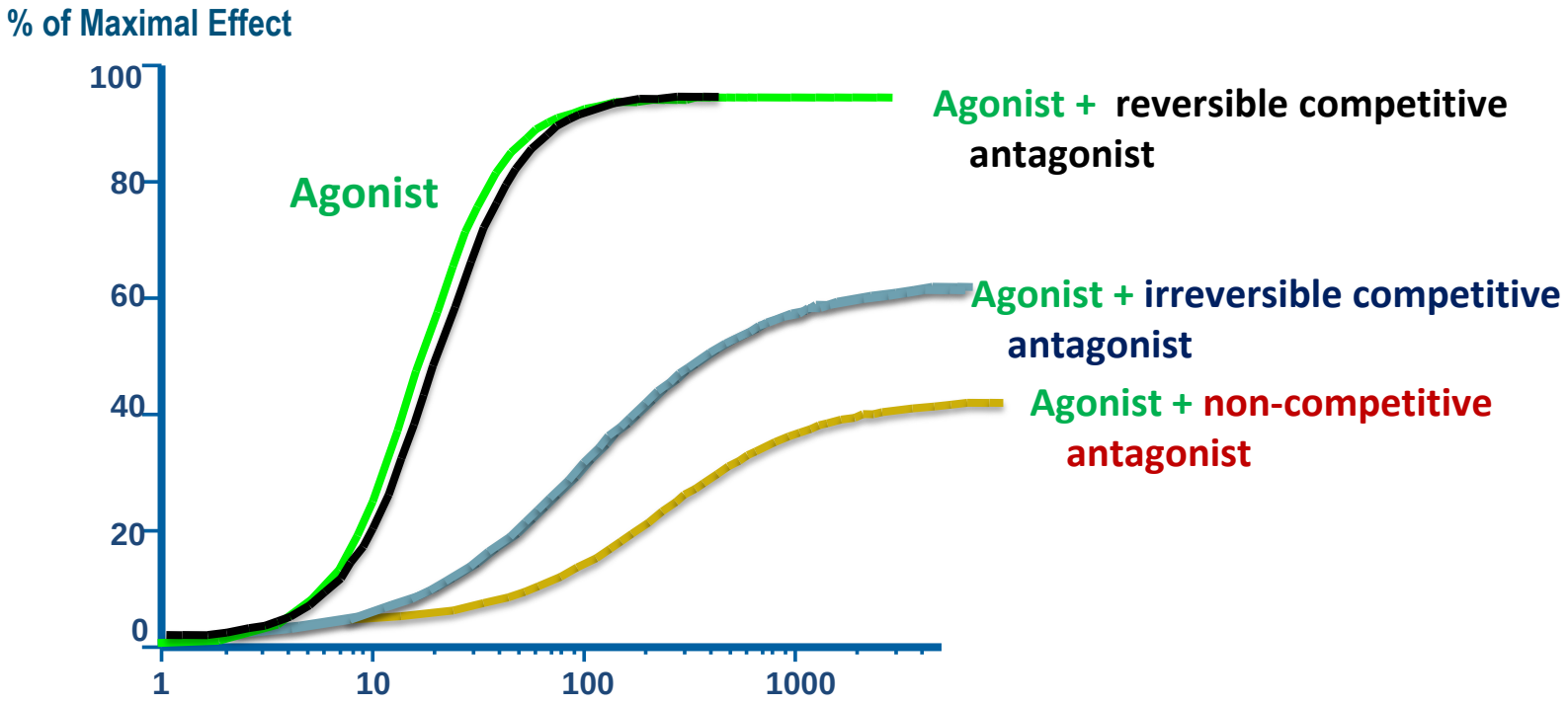
Note that when the antagonist concentration increases the fractional occupancy* decreases with no regard to the agonist concentration.



No parallel shift but both a decrease in slope and a reduced maximum are obtained.

*fractional occupancy: the fraction of all receptors that are bound to a ligand.

Competitive vs. Noncompetitive Antagonism



*Agonist + reversible competitive antagonist ➔ antagonism can be overcome by increasing concentration of agonist : SURMOUNTABLE

*Agonist + irreversible competitive antagonist or agonist + non-competitive antagonist ➔ antagonism can not be overcome by increasing concentration of agonist: NON-SURMOUNTABLE

*Agonist + non-competitive antagonist : Depression of maximal response +/- rightward shifts (if some R are spare)e.g. : Verapamil vs noradrenaline

SUMMARY

We have two response curves ✓

1- Graded dose response curves which is monitoring something continuous in our bodies as heart rate or blood pressure.

2- Quantal dose response curve which is monitoring dose frequency relationship, how much dose and how many patients responded to it or how many patient got side effect of it or how many patients died because of it .

The Quantal dose response curve ✓

Is important because it helps us predict the safety profile and know the Therapeutic Index which is so important in medicine.

The Graded dose response curve ✓

Is important because we get the Maximum efficacy and then we can have the potency. Therefore, we can determine the dose needed to have a response

We have 5 types of antagonism ✓

Chemical
Physiological,
Pharmacokinetic,
Receptor Blockade "Competitive" (two subtypes Reversible and Irreversible)
,
Non-Competitive antagonism .

MCQS

1. Graded dose-response curves are used to determine all of the following except:
A-Median effective dose
B-Median toxic dose
C-Both A&B
D-The potency

2. Two drugs possess opposing actions in the body, so tend to cancel each other's effect ,is the:
A-Chemical Antagonism
B-Physiological antagonism
C-Receptor blockade antagonism
D-None of the above

3. Example of irreversible competitive antagonism is:
A-Phenoxybenzamine and Noradrenaline
B-Atropine and Acetylcholine
C-Omeprazole and Histamine
D-Phenobarbitone and warfarin

4. The curve of the reversible competitive antagonism has:
A-Parallel shift to the right and decrease in efficacy
B-No parallel shift
C- Parallel shift to the right
D- None of the above

5. The smaller the EC50 :
A-The greater the potency of the drug
B-The smaller the potency of the drug
C-The greater the efficacy of the drug
D-None of the above

6. Reversible and irreversible antagonism are types of :
A-Chemical antagonism
B-Non-Competitive antagonism
C-Pharmacokinetic antagonism
D-Competitive antagonism

1-C , 2-B , 3-A , 4-C , 5-A , 6-D

MCQS

7. Drug A gives response at 2mg and adverse effect at 10mg,while drug B gives response at 3mg and adverse effect at 50mg.Which drug is safer:

A-Drug A
B-Drug B
C-Both are equally safe
D-None of the above

8. Omeprazole and Histamine is an example of :

A-Non-competitive antagonism
B-Pharmacokinetic antagonism
C-chemical antagonism
D-Physiological antagonism

9. When the antagonism can be overcomed by increasing the concentration of agonist it is called :

A-Surmountable
B-Physiological
C-Non-surmountable
D-None of the above

10. Example of non-competitive antagonism :

A-Dimercaprol and heavy metal toxicity (lead)
B-Atropine and Acetylcholine
C-Verapamil and Noradrenaline
D-None of the above

7-B , 8-D , 9-A , 10-C

Good luck

Done by pharmacology team 434

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