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Advance I

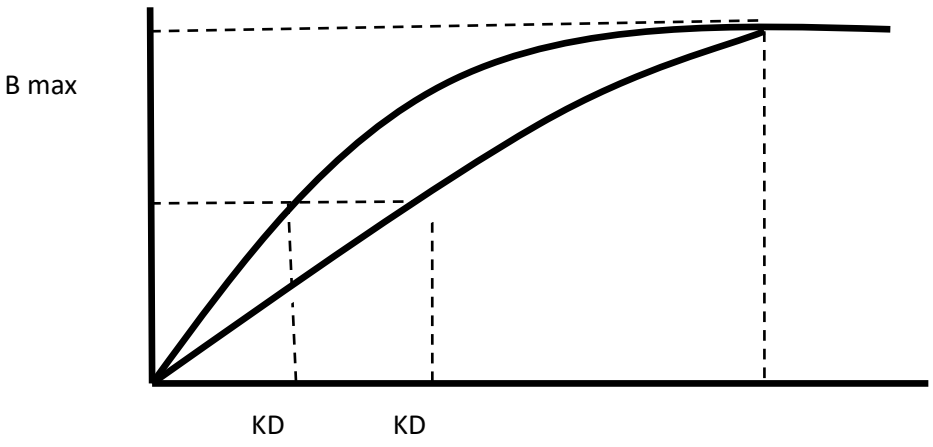
Pharmacodynamic part 2:

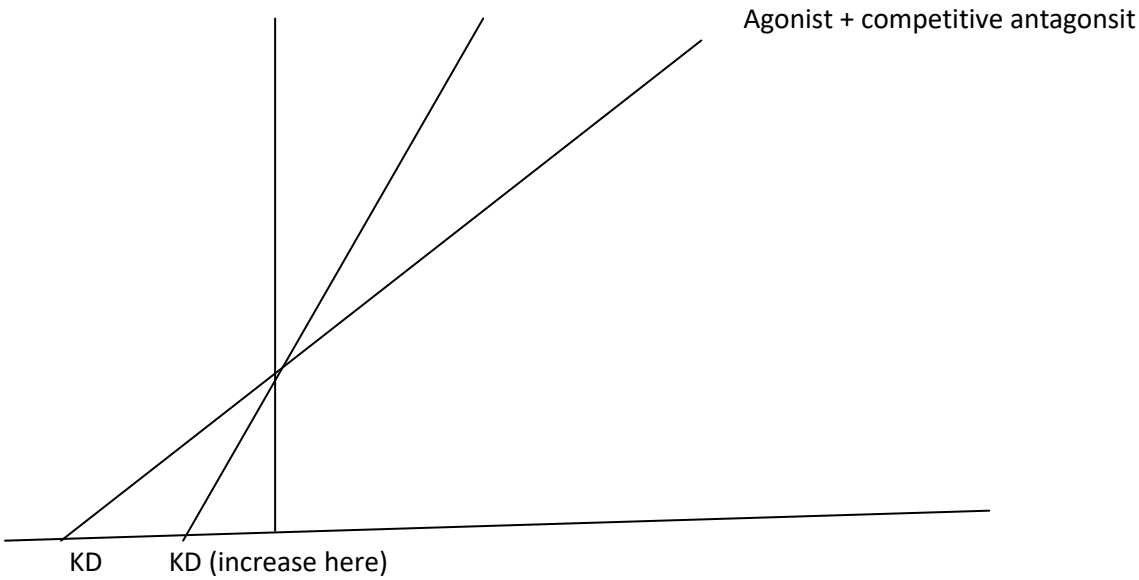
Agonist : drug which stimulate the receptor after binding and give response e.g (Ach, histamine, NE) , hormone neurotransmitter or drugs morphine, phenylephrine , isoproterenol , all act as agonist. Phenylephrine is an agonist α1 adrenoreceptors because it produce effect resemble the action of ligand NE.

Antagonist: drug which block receptor or prevent receptor activation and block action of drug it have not efficacy.

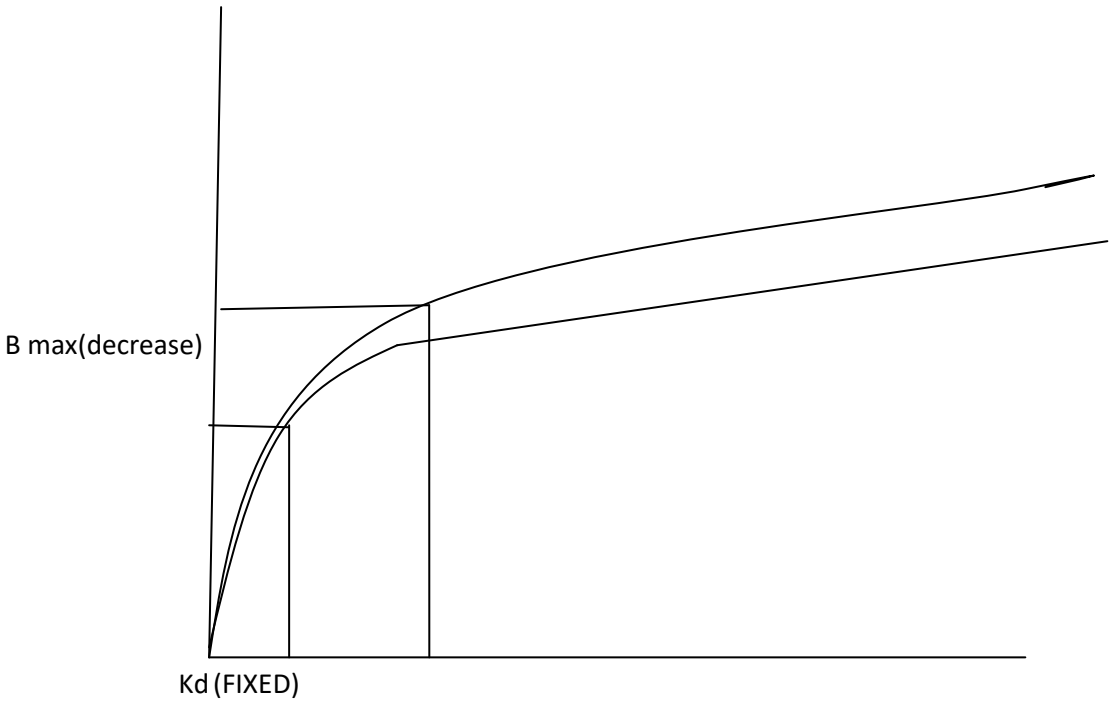
*antagonist it either reversible or irreversible , reversible antagonists readily dissociate from receptor, irreversible antagonists form astable(chemical bond with receptor). **It 2 type:**

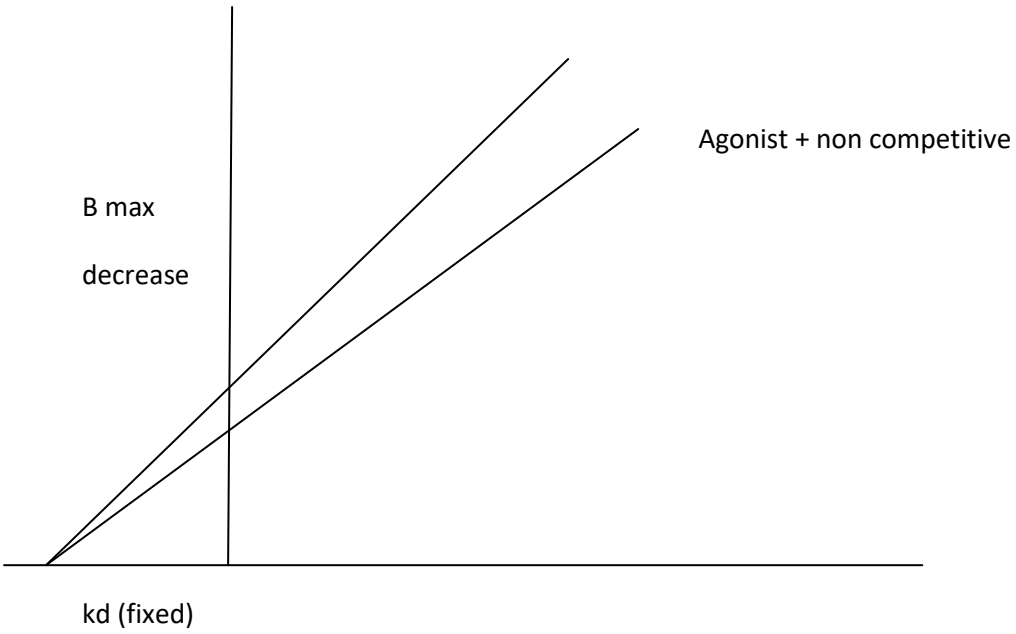
1. **Competitive antagonist :** binding of the antagonist to the receptor prevent binding of the agonist to the receptor and this bind is reversible and can be overcome by addition higher concentration of agonist . e.g. naloxone (an opioid receptor antagonist that is structurally similar to morphine when given shortly before or after morphine block morphine effect.
   - Both antagonist & agonist bind to the same site on the receptor prazocin competes with NE
   - In case competitive KD increase while B max fixed





2. **Non-competitive**: agonist and antagonist can bound simultaneously but antagonist binding reduce or prevent action of agonist.
   - Either bind irreversibly by covalent bonds to the same site as the agonist or bind to different site which reduces the binding of the agonist by allosteric mechanism reduction the maximal effect produce by agonist. E.g. phenoxy benzamin + NE





Eadie scatcharad curve plot:

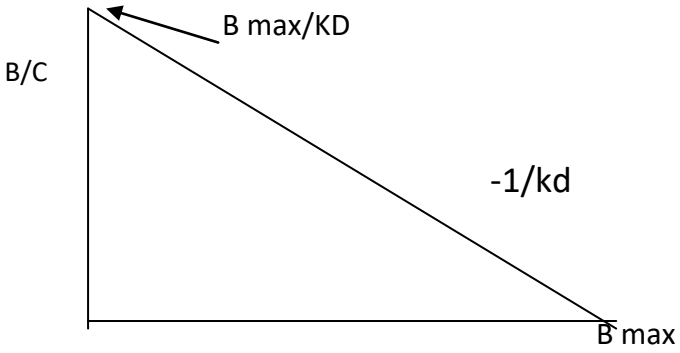
B= Bmax χ C/ KD +C

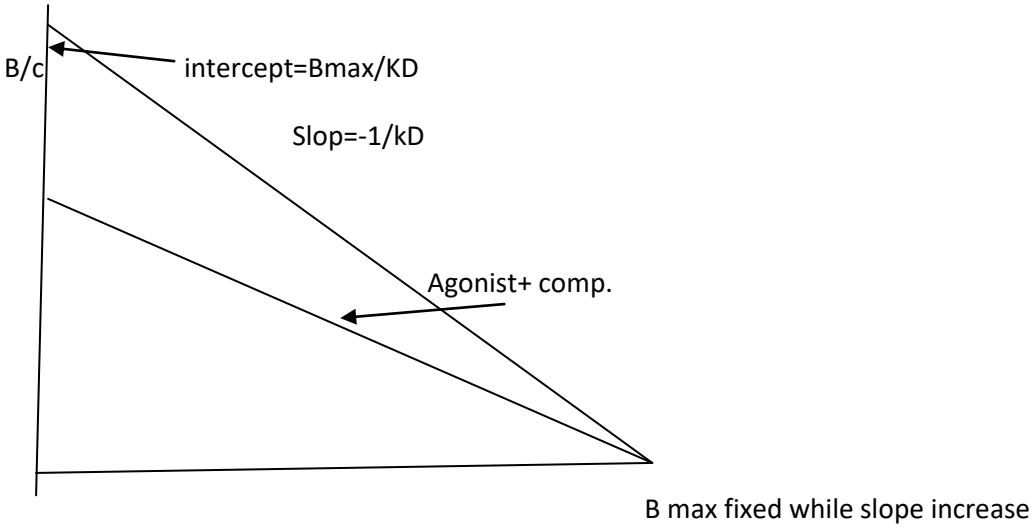
Bmax χ C= B(KD+ C)

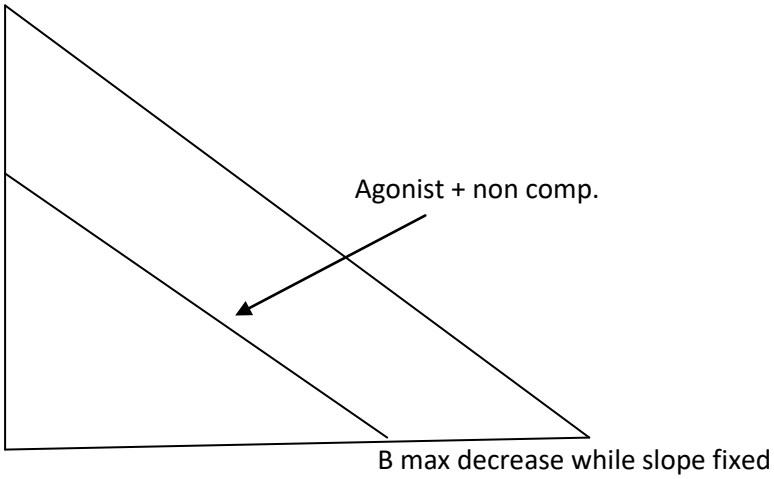
Bmax= B KD+ BC/ C ⟹ B KD / C + B (KD على تقسيم طرفي المعادلة)

B max/KD= B/C + B/KD ⟹ B/C= B max /KD- 1/KD χ B

Y=INTERCEPT – SLOPE χ X





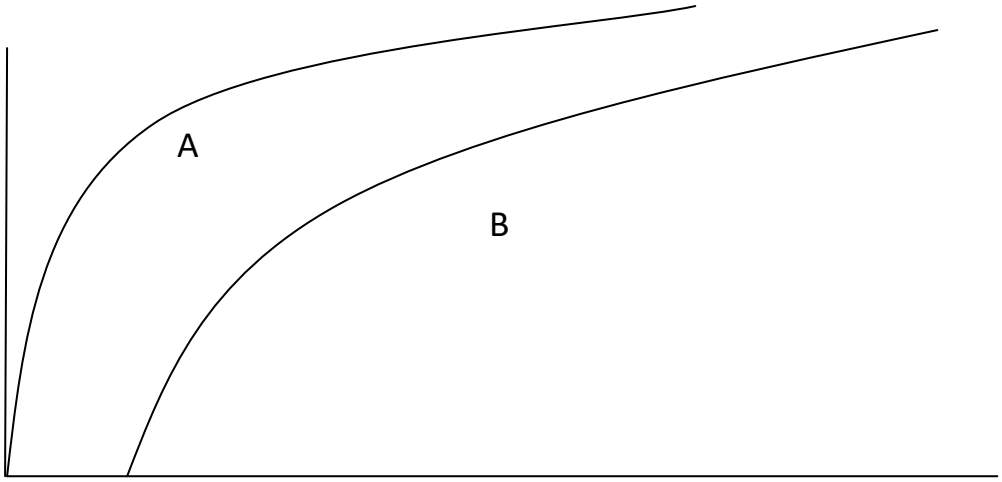


Log- Dose Response Curve LDR:

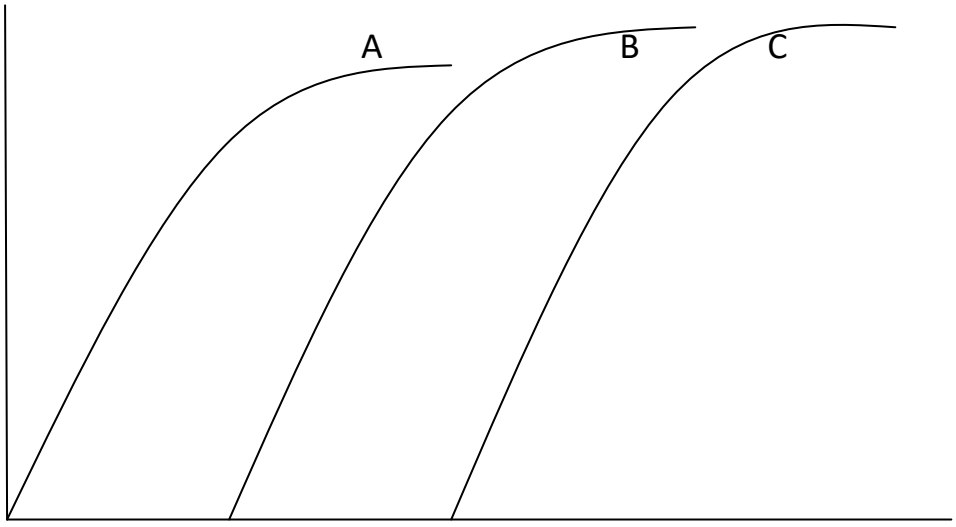
1- Comparison two similar drug , this by:

Potency: range of dose mean produce action in lower dose mean either highly potent , e.g. fentanyl, risperidone, or low potent e.g. codeine .

Efficacy: measurement the ability of drug to bind with receptor and give maximum response of that receptor.



A is more potency while B is more efficacy .



A is more potency than C , and C more efficacy than A,B. while B more efficacy than A.

2- **Calculation of the therapeutic index** measure the LD50 (lethal dose) which killed 50% of tested animal and measure ED50 (effective dose which cure 50% of tested animal).

Therapeutic index : give how save drug, measure safety of drug.

Therapeutic index= LD50/ED50.

e.g. **warfarin** is narrow therapeutic index (the desired response is two fold increase in prothrombin time) so higher doses result hemorrhage. So therapeutic index is low.

penicillin: large therapeutic index it is safe and common to give doses in excess (ten- fold excess) give desired response.

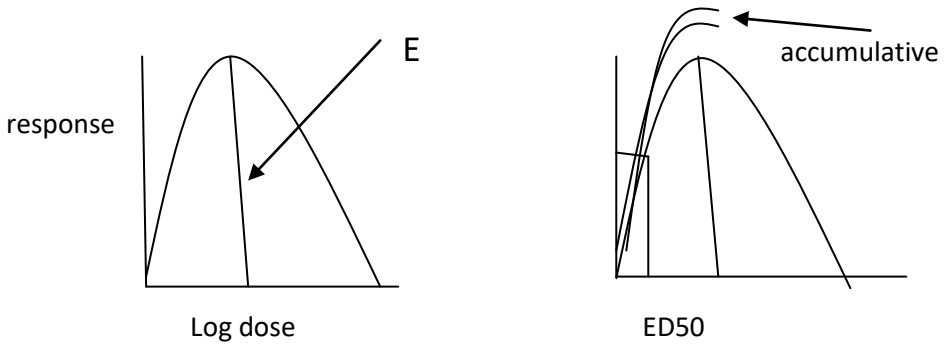
A=1000/10= 100

B= 100/10= 10 A best than B.

Types of response:

1. Graded , when concentration increase the response increase until reach to saturation.
2. All or non response (quantal) either cure or not, kill or not kill.

If 100 animal s taken , the effectiveness will distribution like bell shape.



In quantal should do accumulative % to convert normal curve to LDR.

EC50: the concentration of drug that produce response equal to 50% of maximal response .

Relationship between % of fraction of bound receptor and drug concentration.(quantitative relationship)

[D-R] / [R t] =[D] / KD + [D]

[D-R]: concentration of bound drug.

[R t]: total concentration of receptor.

[D]: conc. Of free drug.

*relation between effect of drug and concentration of drug

[E] / [E max] =[D] / KD + [D]

[E]: effect of drug

[D] : conc. Of drug

[E max] : maximal effect of drug.

Types of antagonism:

1-**non receptor antagonists** (non specific) can be divided into:

a- Non specific chemical: mean inactivates the agonist of interest by modifying or sequestering it, so that the agonist is no longer capable of binding and activity the receptor. E.g.: protamine is a basic protein bind to acidic heparin (class of anticoagulants) and thereby inactivates these agents, because of this chemical antagonism protamine can be used to terminate the effect of heparin rapidly.

b- **Physiological antagonism:** substances that have opposing physiological actions, but act at different receptors.

E.g. histamine lowers arterial pressure through vasodilatation at histamine H1 receptor while adrenaline raises arterial pressure through vasoconstriction mediated by α- adrenergic receptor activation. E.g. treatment hyperthyroidism (tachycardia effect endogenous thyroid hormone), blocking β- adrenergic stimulation can nonetheless relieve tachycardia caused by hyperthyroidism.

2-**specific or pharmacological antagonism:** e.g. atropine antagonist Ach, phenolamin block α receptor, propranolol (inderal) block β-recepyor , simatiden block action of H2 histamine so they are true receptors.

Variation in drug:

There are some variation in drug response:

*__Tolerance:__ gradual decrease in the response to drug due to frequent used.

*__Tachyphylaxis:__ it is the sudden decrease in drug response due to or after usage of drug one or time.

*__Idiosynacracy:__ unusual effect of the drug its occur rarely, its frequently occur with exposure to new drugs (they have not been fully tested).

Reasons of variation of response:

1. **Pharmacokinetic :** concentration of drug is not enough to produce action.
2. **Number of receptor** : drug, aging, genetic mutation and disorders can increase (up regulate) or decrease (down regulate) the number of receptors. E.g. clonidine down regulate α2 receptor thus rapid with drawal clonidine cause hypertensive crisis (decrease in functional number of receptor).

   Chronic therapy with β-blockers up-regulate β-receptor density, thus sever hypertension (increase number of functional receptor) , so when change the hypertension drug must firstly decrease the dose then change the drug.

3- **Concentration of endogenous transmitter** e.g. decrease in propranolol dose not cause hypertension, and increase in propranolol cause hypertension, this depend on conc. Of NT. If the NT. Is strong the antihypertensive is effect although the conc. Is low , while if the NT. Is weak the anti hypertensive is not effect although given high dose.

4- **Compensatory mechanism:** e.g. in case of body loss, take compensatory mech. to regain the body. or take pace (non function) from cardiac and make function then increase C.O.P.

- **The drugs are selective in it action, two selective :**

1- Beneficial effect if it is increase it is good drug

2- Toxic

Drugs have three cases in their selectivity:

1. Beneficial & toxic on the same receptor like insulin.

2. Beneficial in one receptor and toxic in same receptor in different tissue . e.g. digitalis in heart effect on Na-K Atpase cause contract while in eye and intestine have side effect, cortisone has anti-inflammatory effect (beneficial) but cause decrease in protein and blood sugar (Toxic).
3. Beneficial in one type of receptor and toxic in different type e.g. histamine.