Doctor 021

PHARMACOLOGY

Sheet no. 8

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EFFICACY

Efficacy is the maximum effect of a drug, Emax, and does depend on the number of drug-receptor complexes formed, and also on the efficiency of the coupling of receptor activation to cellular responses.

An important parameter that defines efficacy which is **Emax.**

Usually, affinity in the human being measured as a response (ex; it`s effect of relieving pain).

Aspirin and morphine produce the same pharmacologic effect (analgesia) but have very different levels of efficacy.

We compared two drugs that don`t use the same receptor, because we`re looking for the maximum effect a particular drug can produce.

If a drug can stimulate a receptor to produce a biological response it is said to have efficacy or intrinsic activity.

Efficacy refers to the capacity of a drug to produce an effect or the overall magnitude of the maximum response, synonymous with intrinsic activity.

-It is dependent on intrinsic activity. (Actually, it`s not synonymous, we can replace synonymous with dependent).

(Intrinsic activity: the ability of drug to activate cellular responses of the cell).

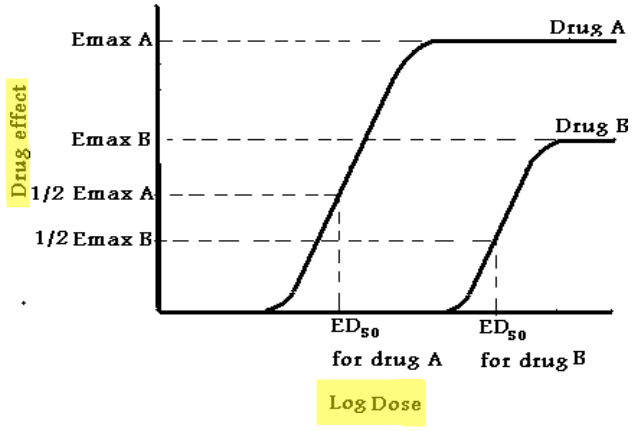
-It`s also dependent on num. of receptors that can be occupied & activated.

If a drug stimulates a full response, it might to said to be a full agonist and to be very efficacious.

-Log dose response curve:

» The smaller the EC50, the greater the potency.

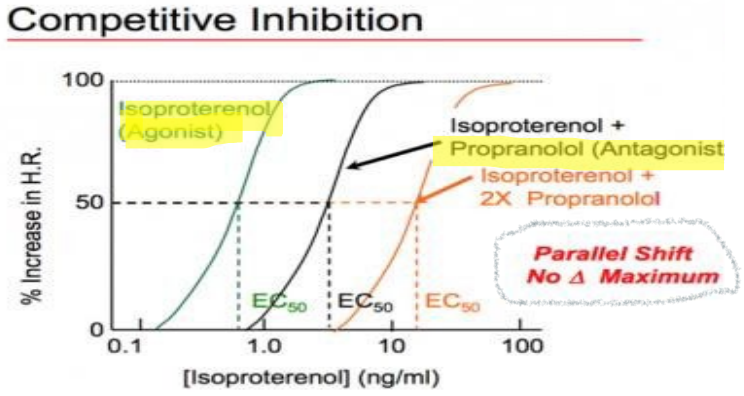
» Efficacy is indicated by the height of the log dose response

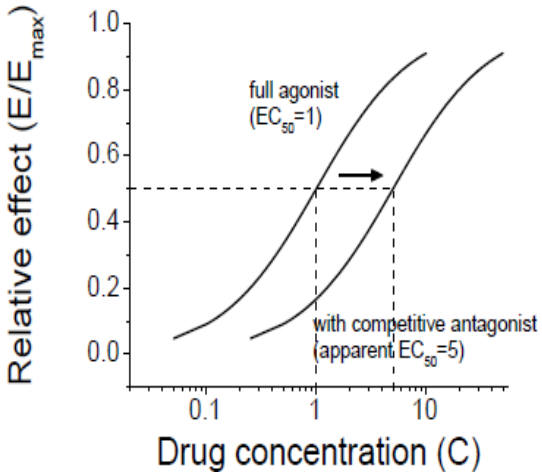


ANTAGONISM BETWEEN DRUGS

A- Pharmacologic antagonism: occurs when an antagonist prevents an agonist from interacting with its receptors to produce an effect, and it can be either competitive or noncompetitive.

B- Competitive antagonists: compete with agonists reversibly in the receptors. The log dose-response curve is shifted to the right, indicating that a higher concentration of agonist is necessary to achieve the response. "Neutral" antagonists. Do not shift the equilibrium towards active or inactive conformation.





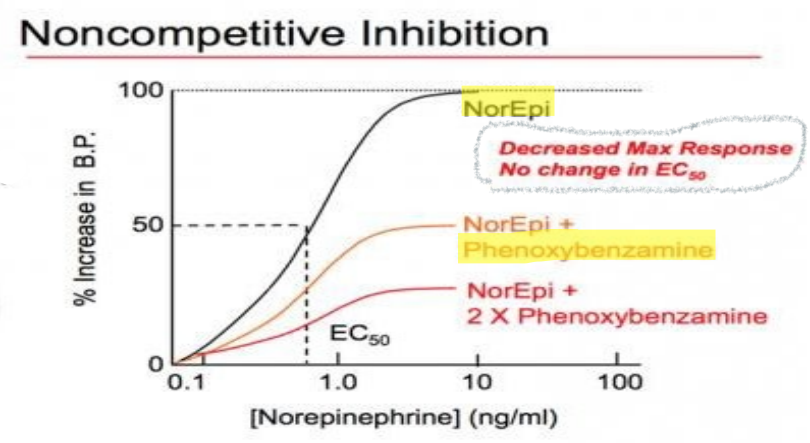
Isoproterenol: agonist of the adrenergic system - Propranolol: Beta-blocker.

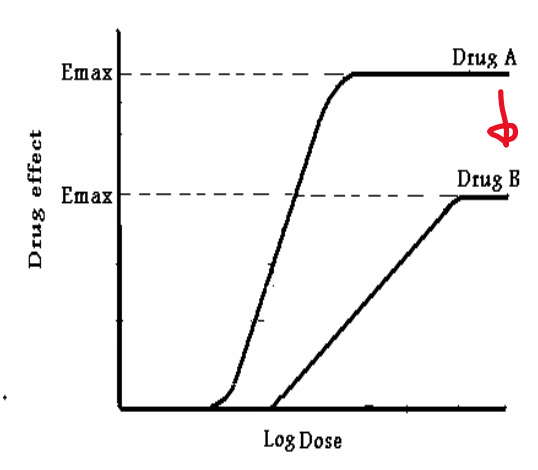
-Propranolol competes with isoproterenol on same binding site(s) of the same receptor(s)

-(because of competition) I will need more conc. of the drug to get the same response I was getting before. Thus, increasing **EC_{50}** -> Parallel shift.

-**E_{max} didn`t change, why?** Because it depends on # of receptors and it`s similar for both drugs.

C- Noncompetitive antagonist: binds irreversibly to the receptor site or to another side that inhibits the response to the agonist. And no matter how much agonist is given, the action of the antagonist cannot be overcome. The shift in the log response curve in this case is nonparallel.





-Nor-epinephrine: agonist (binds @1 adrenergic receptor).

-Phenoxybenzamine: non-competitive antagonist.

- phenoxybenzamine binds covalently (irreversibly) to @1 receptors. The **Emax** of the agonist decreased because the number of receptors decreased.

QUANTAL DOSE-EFFECT CURVES

» Involves all or non responses.

» Obeys Normal Frequency Distribution. (The shape of the curve)

» When transformed into cumulative, will result in a sigmoid curve.

» Straight line for most of the line.

» Can calculate Therapeutic Index= LD50/ED50

Why do we use these curves?

For example, we have paracetamol and I want to see how much pain reduction is doing.

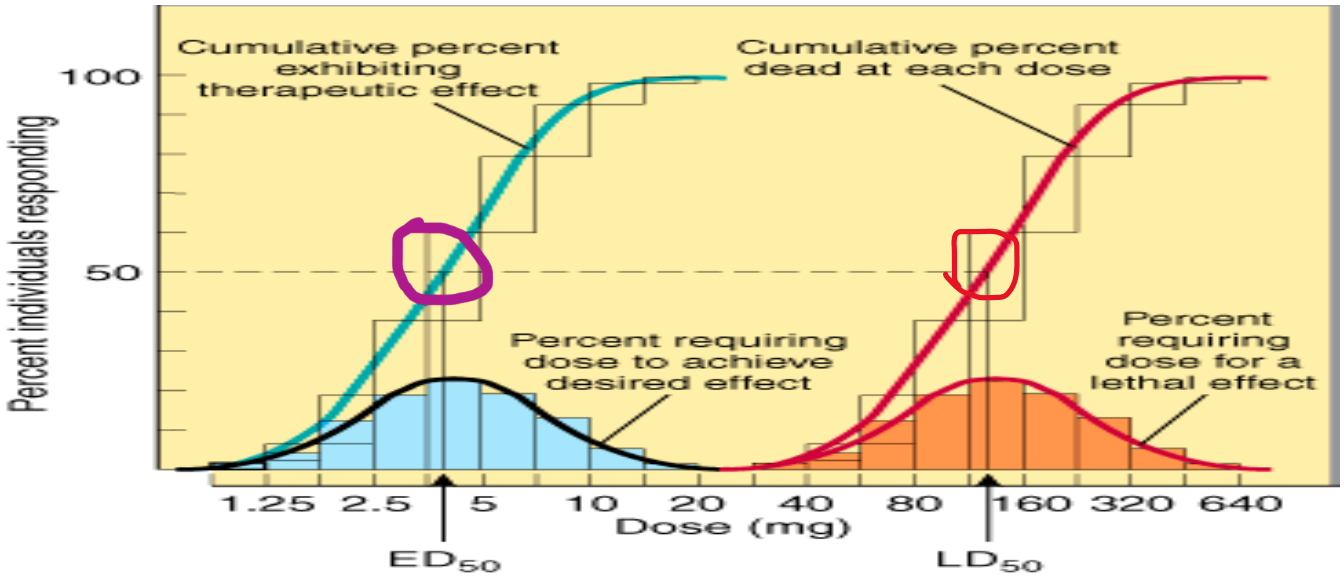
let's say that we have some individuals to test on them: Let`s say Pavard has a 7/10 degree of pain, Mane` has 5/10, and Boateng has 6/10.

When we give them paracetamol, they give responses. for Pavard it goes from 7 to 5/10, for Mane` from 5 to 0/10 . but Boateng has no response (didn`t change).

You noticed that it didn`t give how much reduction. it gave us who responds to the drug and who is not.

So the reason is: to know how many people responded to the drug and how many people still have pain.

It is a graded (graduated) curve (عدفعات بيجي).



Let`s say that we have 100 people that had been given a 100 mg dose

So (by moving with the curve) we see that: 10 (10%) responded at dose 1.25, 10 (10%) at dose 2.5, …..

we **use** another curve which is the **Cumulative curve that gives us the sum of people (the percent) who responded to medication**.

Ex: at 1.25 (10%), at 2.5 (10%), at 5 (20%) -> the cumulative= 50%

The cumulative curve is important for the therapeutic index of the drug.

The therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals. (TI= LD_{50}/ED_{50})

Effective Dose (ED50): the dose at which 50% of individuals exhibit the specified quantal effect. (The minimum dose that is effective for 50% of the population).

The blue circle (the blue curve): the therapeutic effect – pain relief.

We have the red curve: the side effect – toxicity.

Ex; Using Ibuprofen has a side effect of irritation. we increase the conc to see how many people are having this side effect (we do it on animals).

The purpose is to know the right dose to give to the patient in a way to stay behind the toxic effect.

That`s what we call the **therapeutic window.** Can be calculated mimetically by the term <u>therapeutic index</u>.

therapeutic window: The dose range of a drug that provides safe and effective therapy with minimal adverse effects

Lethal Dose (LD50): is the dose required to produce death in 50% of the animals. (the minimum dose that is lethal or toxic for 50% of the population).

the lower the TI the more dangerous because of low LD50 it will reach toxicity faster.

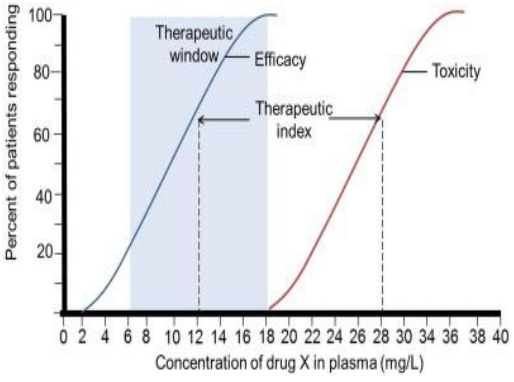
so, we prefer a bigger LD50 and bigger TI (Therapeutic window).

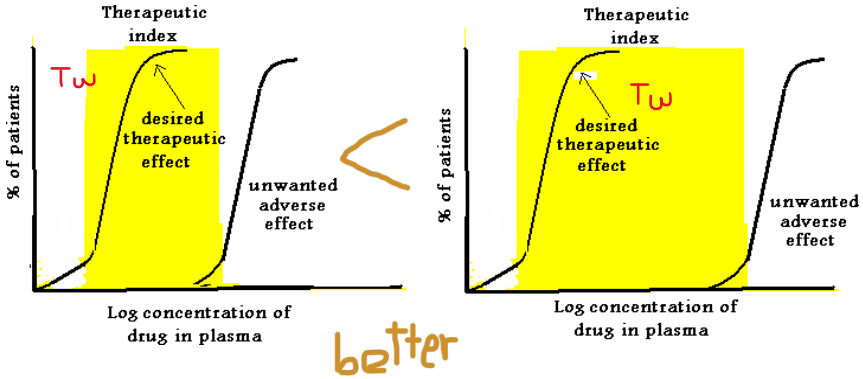
(The bigger the blue curve the better).

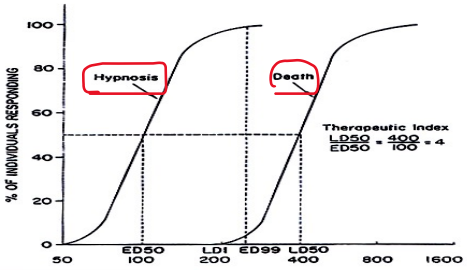
Ideally, the TD50 Should be a much higher dose than the ED50 so that the therapeutic index would be large.

Note: TI and T window are not one thing.

(it has the same meaning but is calculated differently with different answers).







These pictures are important.

ENHANCEMENT OF DRUG EFFECTS

we have a lot of Pain - one Kind of painkiller can`t be used because the amount I`m taking from that painkiller is not sufficient to block the pain fully. If increase it, it will become toxic.

We use 2nd drug (with) that works by different mechanisms to have different side effects and will also relieve the pain.

A. Additive drug effect occurs if two drugs with the same effect, when given together produce an effect that is equal in magnitude to the sum of the effect.

EAB = EA + EB **1 + 1 = 2**

Ex: paracetamol 30% , Ibuprofen 50% → 80%

B. Synergic drug effect occurs if two drugs with the same effect, when given together, produce an effect that is greater in magnitude than the sum of effects when the drugs are given individually.

EAB > EA + EB **1 + 1 > 2**

Ex: 1: 30%, 2: 50% → 100% …. Work on the same pathway.

One of them is upstream of the other so blocking the first part of the pathway will enhance the blocking of the second part. so it will give another block when giving the second drug.

C. Potentiation drug effect occurs if a drug lacking an effect of its increase the effect of a second active drug.

EAB > EA + EB **0 + 1 > 1**

Similar to synergic. Amoclan is an antibiotic that consists of clavulanic acid which has a negligible ability to kill bacteria and amoxicillin (penicillin) which has a high ability (ex 70%).

Together it is 100%. so clavulanic acid makes bacteria sensitive to penicillin

So it can kill.

RECEPTOR REGULATION

-Sensitization or Up-regulation (occurs when):

1- Prolonged/continuous use of receptor blockers.

2- Inhibition of synthesis or release of hormone/neurotransmitter – Denervation.

Lowering the signal → increases # of receptors.

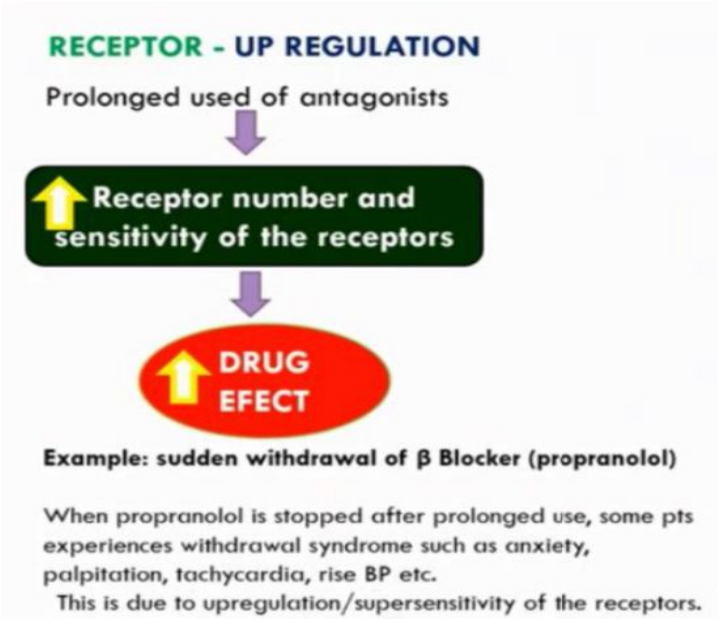
There`s a problem when the blocker is not used anymore, the high # of receptors takes more stimulation putting him/herself at risk

The patient must not cut down onthe drug دغري. it is graduated.

-Desensitization (Tolerance) or Down-regulation (occurs when):

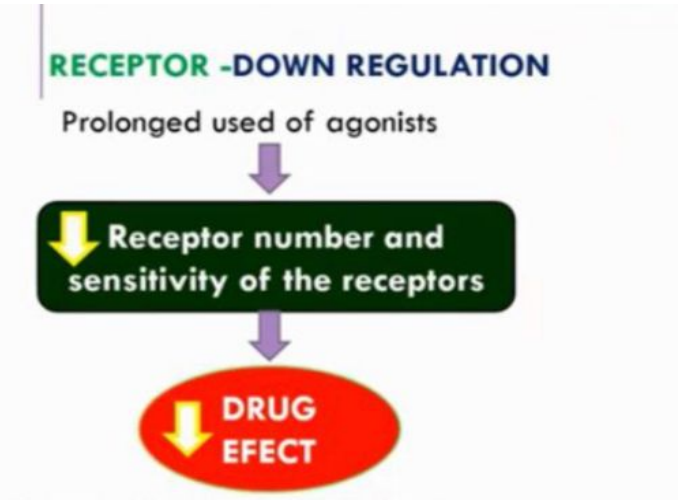
.1Prolonged/continuous use of agonist.

.2Inhibition of degradation or uptake of agonist.



Example: sudden withdrawal of β Blocker (propranolol)

When propranolol is stopped after prolonged use, some pts experiences withdrawal syndrome such as anxiety, palpitation, tachycardia, rise BP etc.
This is due to upregulation/supersensitivity of the receptors.



Example: Chronic use of salbutamol

Repeated admn. – adrenergic agonists(salbutamol;) in asthma----→down regulate β-receptors
(responsible for decreased effect of salbutamol in asthmatics)

TWO-STATE MODEL OF DRUG-RECEPTOR INTERACTION

The receptor is postulated to exist in the inactive, nonfunctional form (Ri) and the activated form (Ra.)

Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity.

Agonists have a much higher affinity for the Ra configuration and stabilize it so that a large percentage of the total pool resides in the Ra–D fraction and a large effect is produced.

Full agonists shift equilibrium "fully" towards the active conformation

Partial agonists shift equilibrium "partially" towards the active conformation

Sub-maximal effect with receptors completely occupied.

(مثال الدكتورة : وظيفتي شرح المحاضرات و كتابتها عن طريق اللابتوب , فلو بدي اكتب عاللابتوب عالواقف فلازم اثني ظهري فهو مش مريح ف كل شوي حكتب و ارد ارفع ظهري عشان اريح . فوجود كرسي بريحني , لكن هاض الكرسي نص نص يعني الشغل و نا على اعصابي فلو كرسي قيمنج مرتب فخم كان الشغل عالمرتاح و مافي تعب يادوب و الشغل بكون افضل اشي)

Receptor Function in an inactive state but is not Stable while working So the response will be low.

If a partial antigen binds to it the Response would be partial.

But when it is Full antigen it is full response And the energy used to work is low.

The effect of receptors, occurring in the absence of agonists, is termed <u>constitutive activity.</u>

(inactive conformation present at the basal level)

The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.

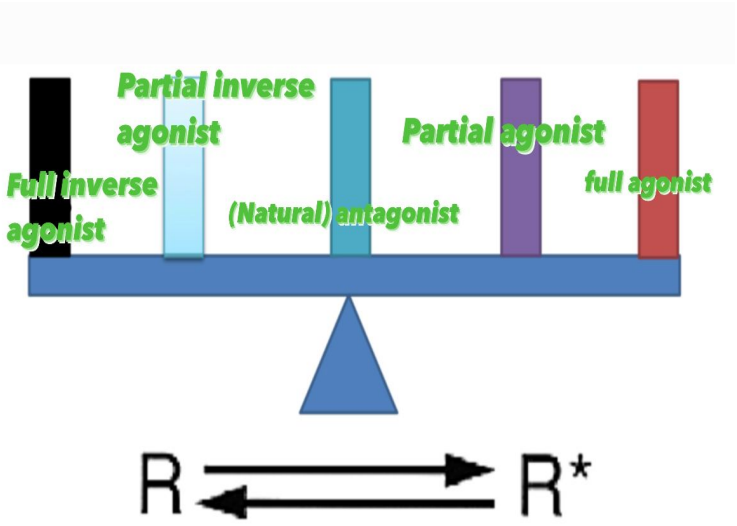
<u>Inverse agonists:</u> While antagonists are traditionally thought to have no functional effect in the absence of an agonist, some antagonists exhibit "inverse agonist" activity because they also reduce receptor activity below basal levels observed in the absence of any agonist at all.

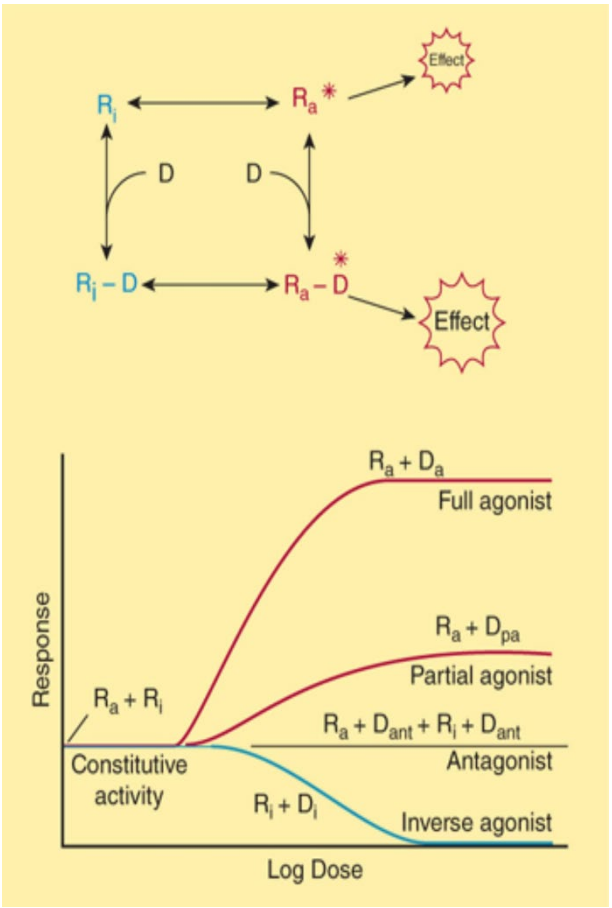
some drugs bound to these receptors and shift towards the inactive conformation it's function is inhibition (antagonist)

But because of the equilibrium between Ri and Ra, Any drug that changes that equilibrium is called an agonist(partial or full)

If the drug is already in Ra and a drug converted (change the state) to Ri

We call it the **reverse agonist** Because it did something, unlike the antagonist.





Ex: Gaba receptors (in 3rd year not now ☺).

COMPETITIVE & IRREVERSIBLE ANTAGONISTS

Receptor antagonists bind to receptors but do not activate them

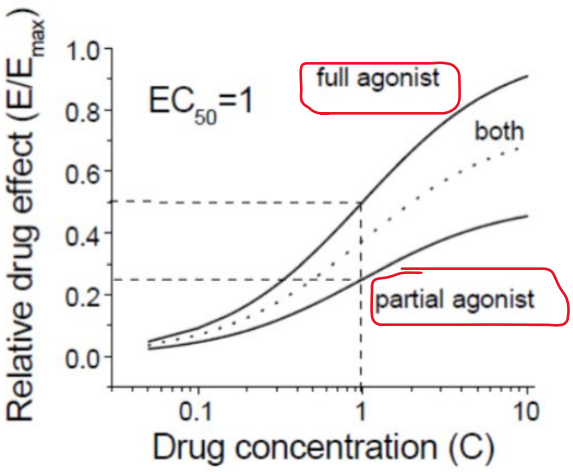
The primary action of antagonists is to reduce the effects of agonists (other

drugs or endogenous regulatory molecules) that normally activate receptors.

Inverse agonists shift the equilibrium towards the inactive conformation

Effect obviously *if* much constitutive activity

in this case, the total is less than the full agonist, with no summation.



why → competition on the binding site.

Application → Varenicline (Santex).

For smoking cessation.

HOW?

Nicotine is an agonist for nicotine receptors (full agonist) … Santex is also an agonist (partial agonist).

Accustom the patient to lower response for gradually quitting smoking.

(when the patient smoke the sensation for nicotine is high, when I give him santex there will be competition, nicotine sensation decreased, and it goes from the full response into smaller and smaller (decreased over time).

THIS SHEET IS LONGER THAN MANUTD IN UCL THIS SEASON

ـ فمّا حاجة , فمّا حاجة , فمّا حاجة ـ