Pharmacodynamics-2

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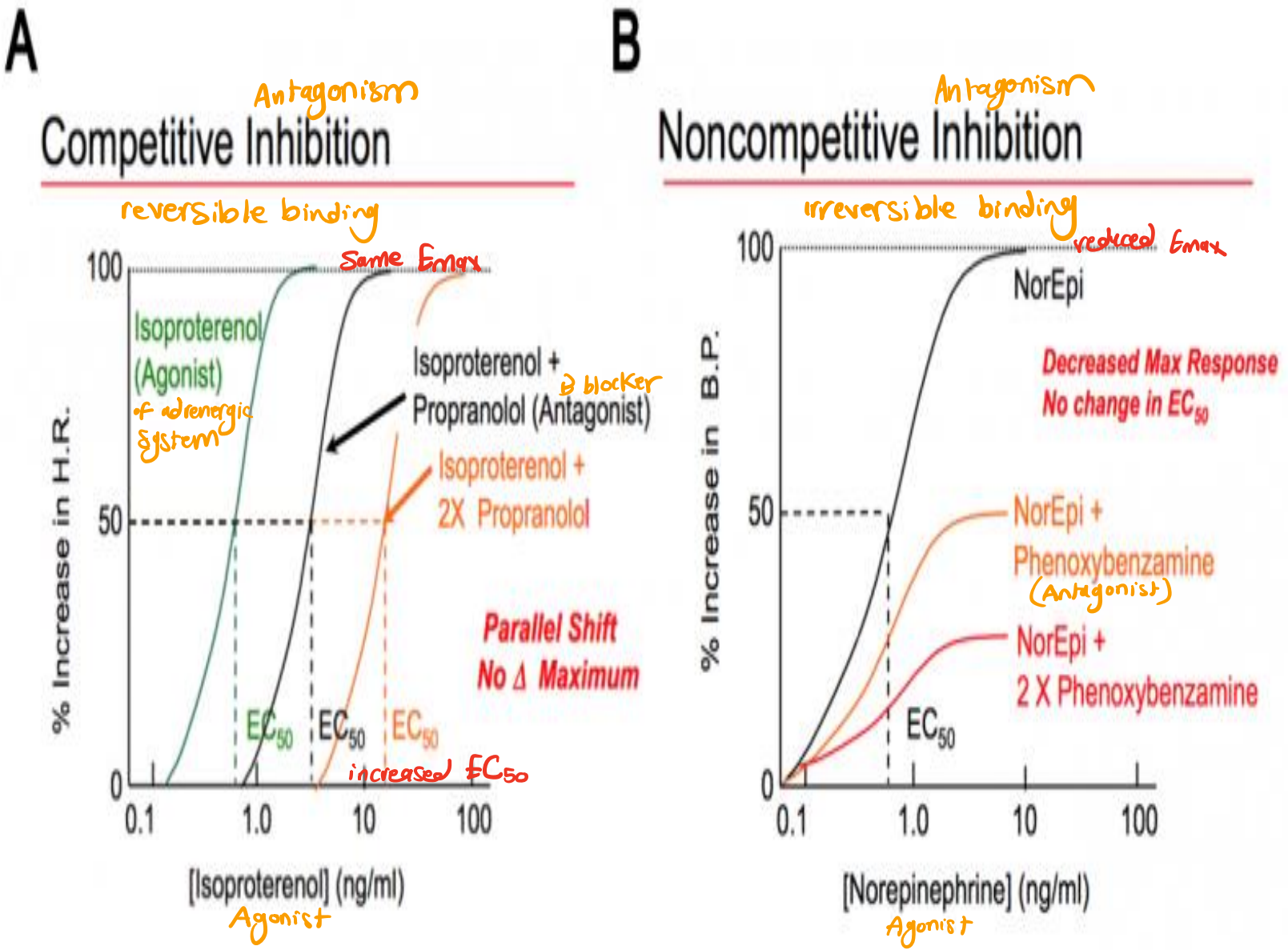
between the drug and endogenous ligand ← → between two different drugs

Antagonism between drugs

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

Competitive antagonist compete with agonist in a reversible fashion 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.

Noncompetitive antagonist binds Covalently irreversibly to the receptors site or to another side that inhibit the response to the agonist. And no matter how much agonist is given, the action of the antagonist can not overcome. The shift in the log response curve in this case is a nonparallel shift. In this case, the agonist won't ever be able to bind its receptors as long as the anatgonist is present, so it's as if the number of receptors is reduced, reducing E_{max}. (increasing the agonist concentration won't help)


A
Antagonism
Competitive Inhibition
reversible binding
Same Emax
100
50
0
% Increase in H.R.
Isoproterenol
(Agonist)
of adrenergic
system
Isoproterenol +
Propranolol (Antagonist)
β blocker
Isoproterenol +
2X Propranolol
Parallel Shift
No Δ Maximum
EC50
EC50
EC50
increased EC50
0.1
1.0
10
100
[Isoproterenol] (ng/ml)
Agonist
B
Antagonism
Noncompetitive Inhibition
irreversible binding
reduced Emax
100
50
0
% Increase in B.P.
NorEpi
Decreased Max Response
No change in EC50
NorEpi +
Phenoxybenzamine
(Antagonist)
NorEpi +
2 X Phenoxybenzamine
EC50
0.1
1.0
10
100
[Norepinephrine] (ng/ml)
Agonist

Here we're talking about antagonism between drugs

Which is an interaction between two drugs that exert two opposite effects.

So at the end, drug antagonism may block or reduce the effectiveness of one of the drugs.

Antagonsim can be either competitive or noncompetitive

- competitive inhibition (antagonism): In the case of reversible binding, two drugs with equal access to a certain receptor can compete for the same binding site. Competition is governed by the concentration of these drugs, the one with higher concentration would overcome the other.

Looking at the left picture in the previous slide, we will notice 3 different curves with the same Emax but with different EC_{50} values.

- The left curve: agonist drug only, here we will have the lowest EC_{50} of the drug because there's no other disturbing factors, so it binds the adrenergic receptor increasing its effect (heart rate)

- The middle curve: adding an antagonist drug with the same concentration of the agonist, causes an increase (parallel shift) in the EC_{50} value (meaning that the concentration needed to exert the same response we were getting before the antagonist, is increased)

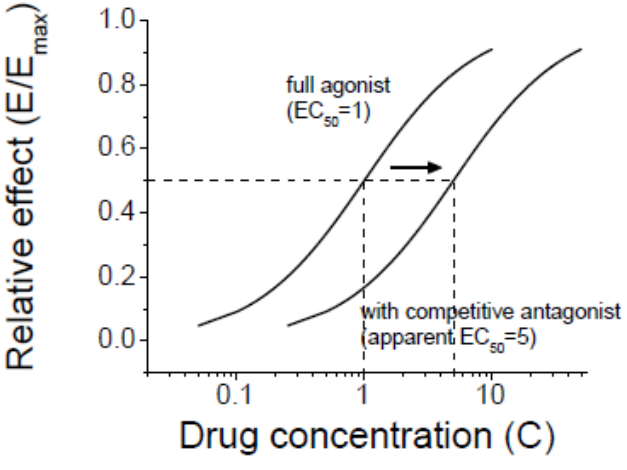
- The right curve: adding even more concentration of the antagonist increases EC_{50} more (we have to increase the agonist concentration to to bind its receptor and reach the same Emax)

- Emax won't change because it depends on receptors num that is not affected, because the agonist is still able to binds its receptor with higher concentration.

- The most important thing to know: competitive inhibition causes parallel right shift to the dose-response curve (increases EC_{50})

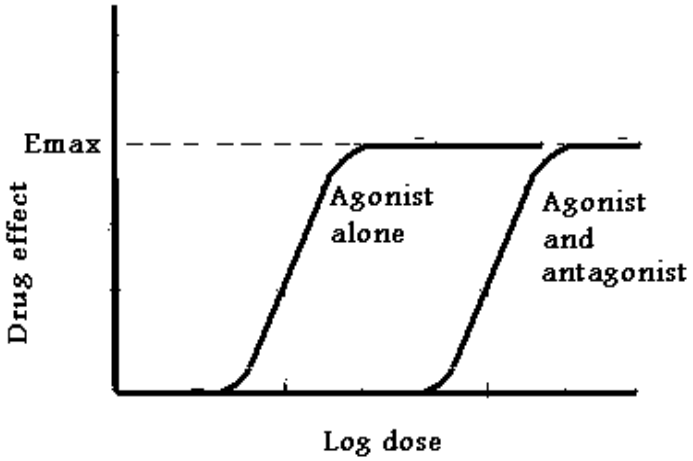
Competitive antagonists

- Bind agonist site
- Do not shift equilibrium towards active or inactive conformation
- “Neutral” antagonists

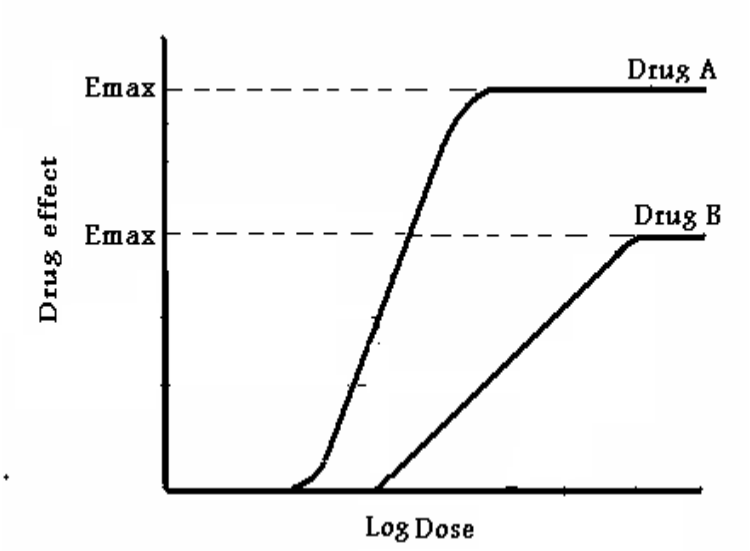


Shift in the log-dose response

Competitive antagonist



Noncompetitive antagonist

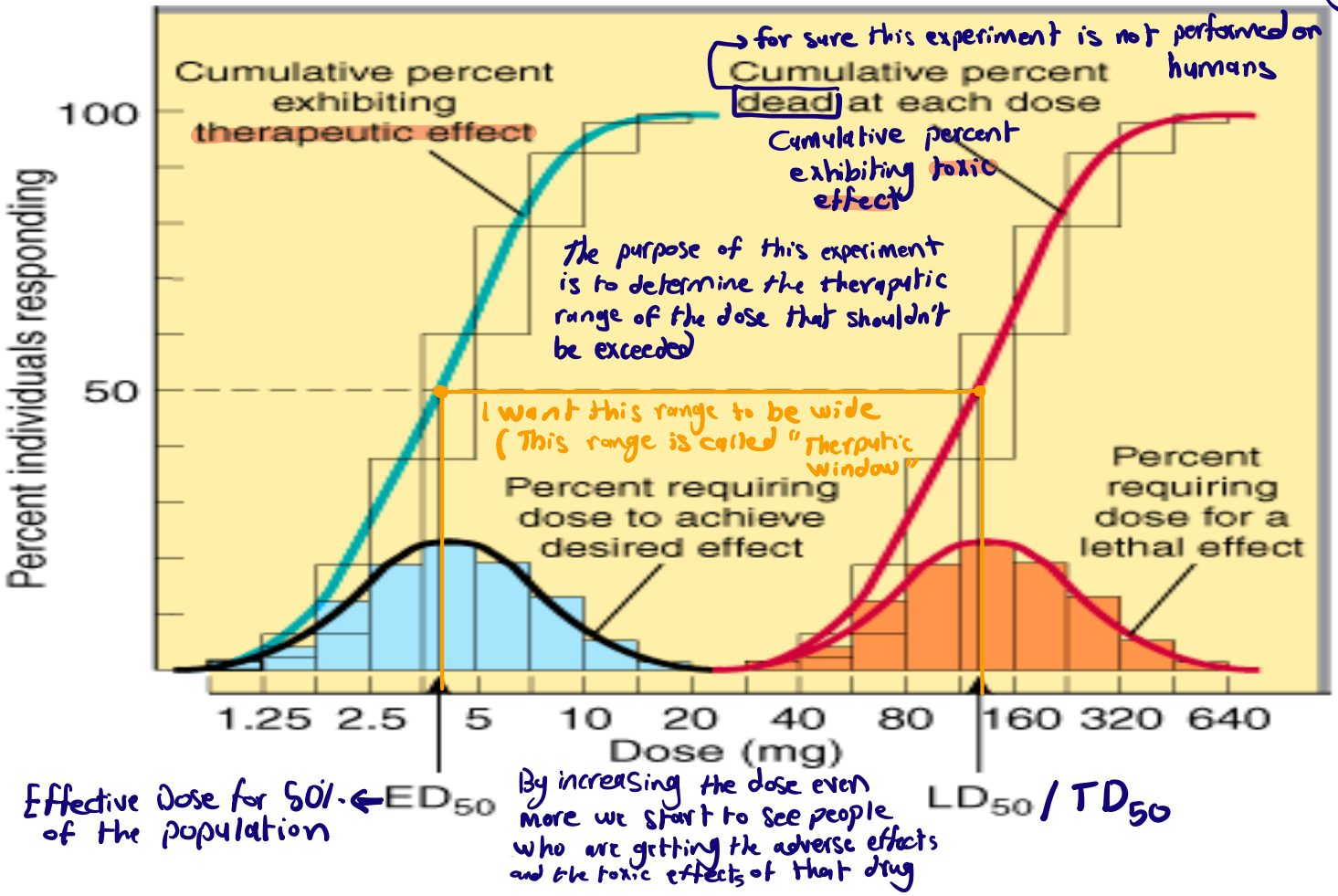


Quantal Dose-Response Curves

graduate
quantal

↳ All or non effect

depends on interindividual variations in response to a particular drug



Features of Quantal Dose-Effect Curves

- Involves all or non responses.
- Obeys Normal Frequency Distribution.
- When transformed into cumulative, will result in a sigmoid curve.
  - Straight line for most of the line .
- Can calculate Therapeutic Index= LD50/ED50

Therapeutic window

Quantal Dose-Effect Curves

According to the curve type you can determine what ED_{50} is

- **Effective Dose (ED50): is the dose at which 50% of individuals exhibit the specified quantal effect.**
  desired effect
- **Toxic Dose (TD50): is the dose required to produce a particular toxic effect in 50% of animals.**
- **Lethal Dose (LD50): is the dose required to produce death in 50% of the of the animals.**

we can't perform toxicity studies on humans ☹

Therapeutic index and margin of safety

Quantal Dose response curve is to determine

(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 individuals:

Therapeutic window

the lower the TI, the more dangerous the drug is

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

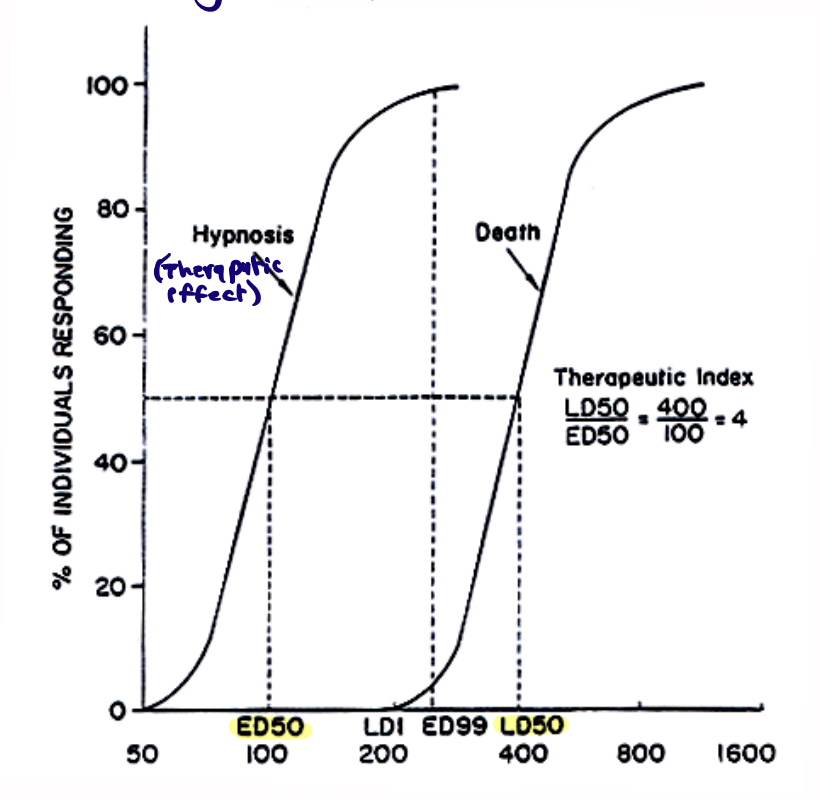
Where TD_{50} is the minimum dose that is lethal or toxic for 50% of the population, and ED_{50} is the minimum dose that is effective for 50% of the population.

if the TI of a drug is small it is easier to be exceeded, for example a drug with TI = 2, if the patient took double the dose he would reach toxicity. While a drug with high TI would still be safe if I accidentally doubled the dose

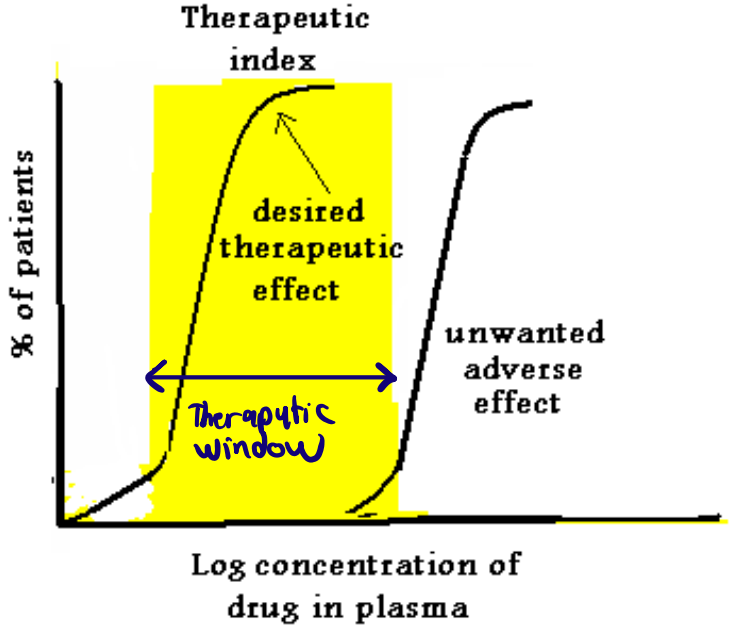
Ideally the TD_{50} Should be a much higher dose than the ED_{50} so that the therapeutic index would be large.

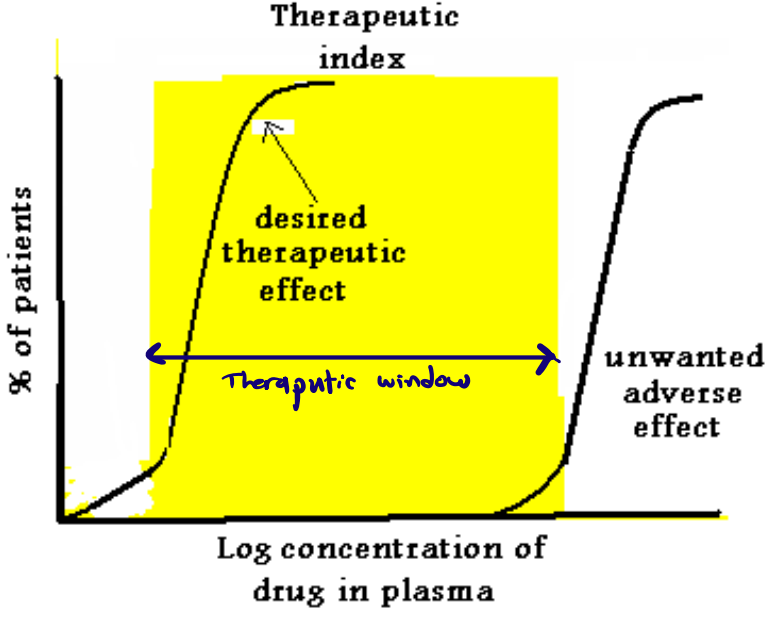
paracetamol for example has a high TI, the maximal dose is about 4 gm (8-10 peices) So it's hard to exceed its TI and reach toxicity

Here is an example where we did an experiment about a drug that causes hypnosis (increased attention and concentration), with a side effect that is lethality (causes suppression of respiratory center)



Therapeutic index and margin of safety





This drug is safer depending on TI value

Enhancement of drug effects

if I need a higher dose of a drug to relieve pain for example, and this required dose would causes toxicity, here I would take another drug with the same effect along with the first one.

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

Mind you that this second drug must work in different mechanism so it would have different side effect

$$E_{AB} = E_A + E_B \qquad 1 + 1 = 2$$

B. Synyrgic 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. meaning that they enhance each other's effect in a way that increases their normal effect

يعني اذا الحالو بعمل ٢٠٪

بس مع دوائاني بغير الحالو بعمل ٥٠٪

$$E_{AB} > E_A + E_B \qquad 1 + 1 > 2$$

C. Potentiation drug effect occurs if a drug lacking an effect of its own increase the effect of a second active drug. (Similar to Synyrgic effect, except that one drug have zero effect when working alone)

$$E_{AB} > E_A + E_B \qquad 0 + 1 > 1$$

• Enhancement of drug effect

- Additive drug: the increase in the effect occurs because of the sum of the two drugs effect

(ex.) The first drug with 30% ability to produce effect

+

The second drug with 40% ability

=

70%

- Synyrgic drug effect: the increase in the effect occurs because of ① the sum of their effects
② they togther increase their effects

(ex.) The first drug with 30% ability → becomes 50% along with the other drug

+

The second drug with 40% ability → becomes 50%

=

100%

- potentiation drug effect: like the synyrgic effect, the effect of the two drugs is more than the sum of them

0% + 40% = 60%

• Those aren't accurate numbers

Receptor Regulation (up, Down)

The receptors can be either down-regulated or up-regulated depending on the kind of drug

- **Sensitization or Up-regulation**
  - .1Prolonged/continuous use of receptor blocker
  - .2Inhibition of synthesis or release of hormone/neurotransmitter - Denervation

- **Desensitization or Down-regulation**
  - .1Prolonged/continuous use of agonist
  - .2Inhibition of degradation or uptake of agonist

- Receptor up-regulation

There are particular number of receptors on an organ, if I used a drug that blocked those receptors, I'm gonna lower the signal that this organ is getting. So this organ adapt itself resulting in needing less signals to exert the same response as before (up-regulate the num of receptors)

That's why we call it (sensitization), because now the receptors are more in number and sensitivity so we need less signals

When is this problematic?

Suddenly stopping the receptor blocker (antagonist) while there's still a lot of receptors (from the up-regulation) causes the agonist to bind many more receptors it usually binds to, resulting in undesirable effect

(ex) β blocker is an antagonist that upregulates the num of receptors, when the patient stops taking the drug suddenly, adrenaline will bind to these receptors leading to extra stimulation and increased heart rate.

So patients should never stop the antagonist suddenly, instead they have to decrease the dose gradually.

- Receptor down-regulation

When I continuously stimulate a particular receptor (too much of a signal) receptors would be down regulated (decreased in number) resulting in loss of response of that agonist drug in something called "Tolerance", "Densesitization".

REGULATION OF RECEPTOR

RECEPTOR -DOWN REGULATION

Prolonged used of agonists

↓ Receptor number and sensitivity of the receptors

↓ DRUG EFECT

Example: Chronic use of salbutamol

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

RECEPTOR - UP REGULATION

Prolonged used of antagonists

↑ Receptor number and sensitivity of the receptors

↑ DRUG EFECT

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.

Two-state model of drug-receptor interaction

- The receptor is postulated to exist in the inactive, nonfunctional form (Ri) and in the activated form (Ra.(
- It keeps changing between these two forms $Ra \rightleftharpoons Ri$
- 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

In the presence of agonists, it's more stable to have most of Receptors in the Ra form

Two-state model of drug-receptor interaction

- 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

Receptors that tend to be in the active form even without being bound to the agonist is said to have "high constitutive activity"

- The effect of receptors, occurring in the absence of agonist, is termed constitutive activity. → effect 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.

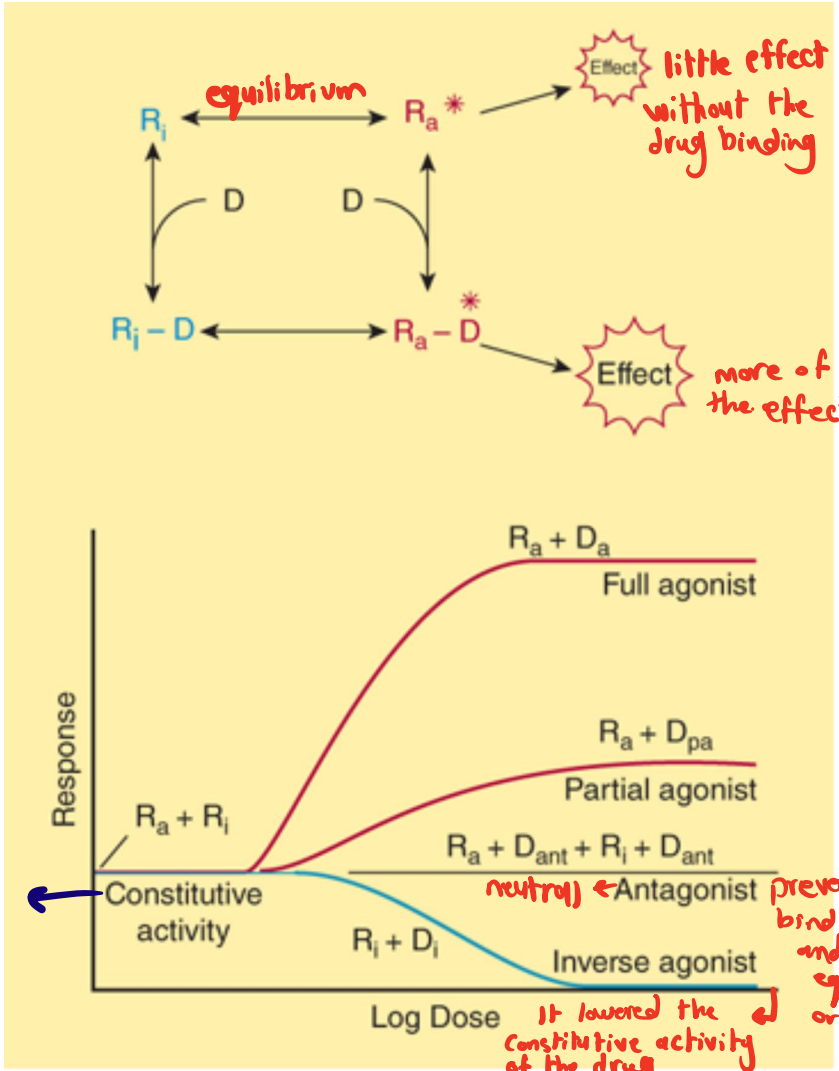
Inverse agonists:

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.

for example B blocker (antagonist) won't decrease the heart rate but an inverse agonist will.

Remember: we have equilibrium between R_a and R_1

- the drug that will shift the equilibrium toward the active form is said to be agonist ← fully / partially
- the drug that will shift the equilibrium toward the inactive form by exerting an opposite effect is said to be inverse agonist

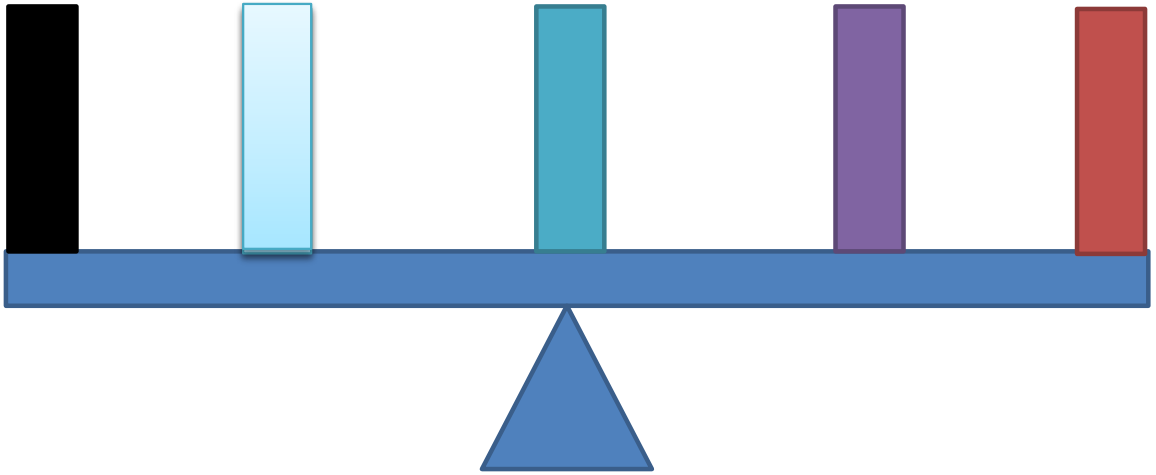


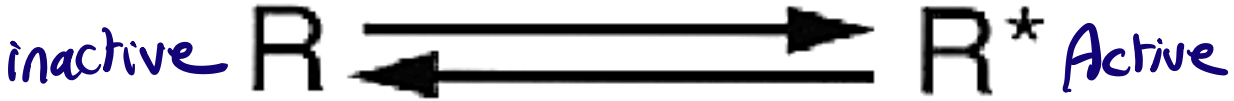
Because the constitutive activity was more than zero we were able to see the effect of inverse agonist

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 equilibrium towards the inactive conformation (are inverse agonists considered antagonists? YES)
- Effect obvious *if* much constitutive activity

But if the receptor itself have no constitutive activity we won't be able to see the effect of the inverse agonist





Full agonist

Partial agonist

Antagonist

Partial inverse agonist

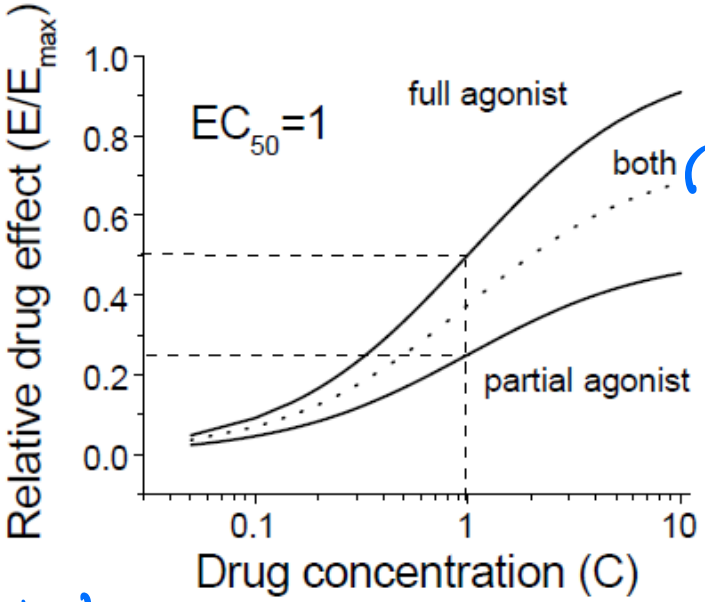
Full inverse agonist

Inverse agonists

- Inverse agonists shift equilibrium towards the inactive conformation
- Effect obvious *if* much constitutive activity

Here we are using two drugs with same effect (partial, full agonist)
So enhancement of the effect is expected as we said before

As shown in the curve no summation of their effects occured, why?
Instead, competition between them happened on the same binding site.
If the partial agonist binds it will have less effect than if the fully agonist binds



(in between their effects
No summation of their effects)

This drug is used for smoking cessation ← Varenicline
Varenicline is a partial agonist competing with the fully agonist (nicotin) to bind the nicotinic receptors. So it causes less response of the nicotin, helping smokers to quit smoking gradually ←