PHARMACOLOGY

Modified no.

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Types of drug-receptor interactions:

1. Drug agonism:

NOTE: SLIDES ARE ENOUGH

- Agonist (full agonist):

A drug that interacts with a specific receptor and produces maximum response

(strong agonist produces Vmax with low R (receptor) occupancy; weak agonist has low efficacy but reaches Vmax with high R occupancy)

- Partial agonist

A drug that has reduced efficacy but maximum potency and high affinity

- Agonist-antagonistic agonists

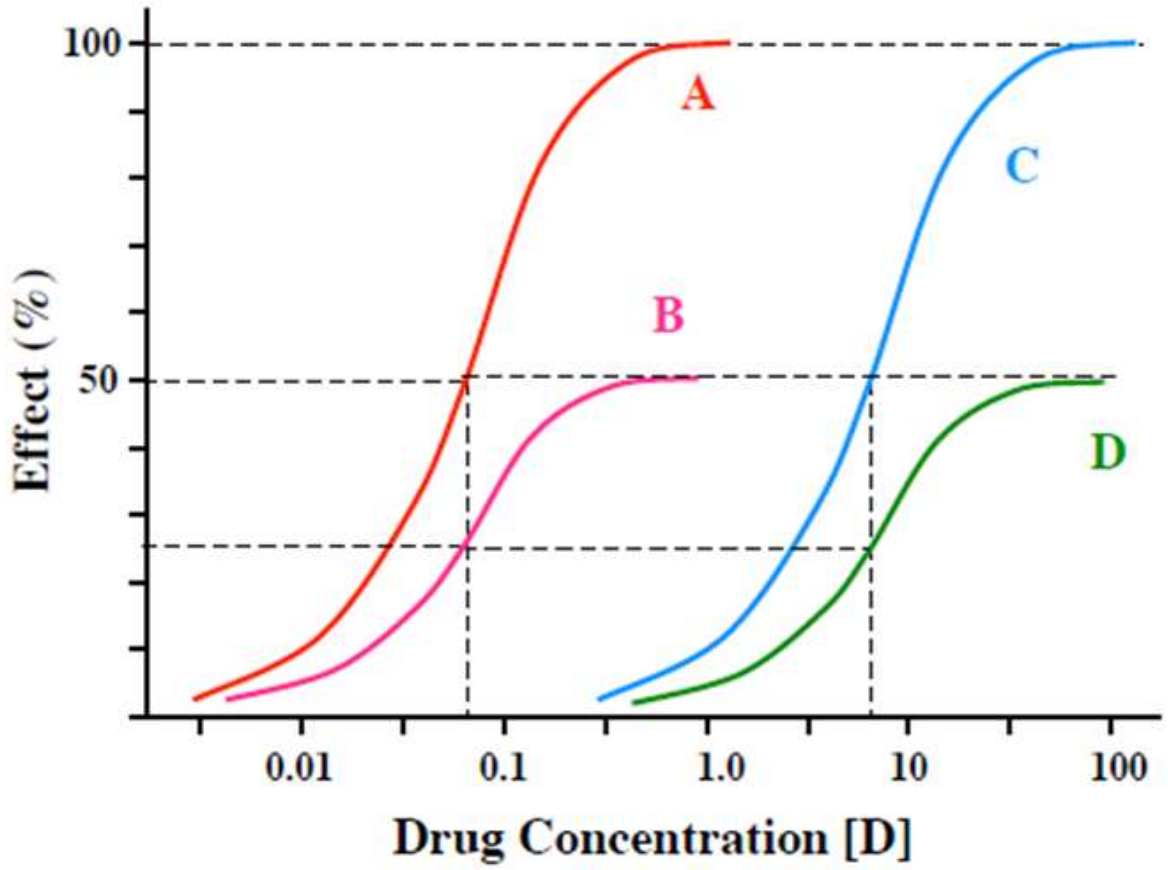
A drug which has both agonistic and antagonistic activities

- Inverse agonist

A drug that produces an effect opposite to agonist

NOTE: produces negative efficacy

Agonist Types: Its All Relative



A: **full agonist**
maximum potency,
maximum efficacy

B: **partial agonist**
maximum potency,
reduced efficacy

C: **full agonist**
reduced potency,
maximum efficacy

D: **partial agonist**
reduced potency,
reduced efficacy

A receptor which is capable of producing its biological response in the absence of a bound ligand is said to display "constitutive activity".

The constitutive activity of receptors may be blocked by inverse agonist binding.

Mutations in receptors that result in increased constitutive activity underlie some inherited diseases, such as precocious puberty (due to mutations in LH receptors) and hyperthyroidism (due to mutations in TSH receptors)

- **NOTE: precocious puberty**
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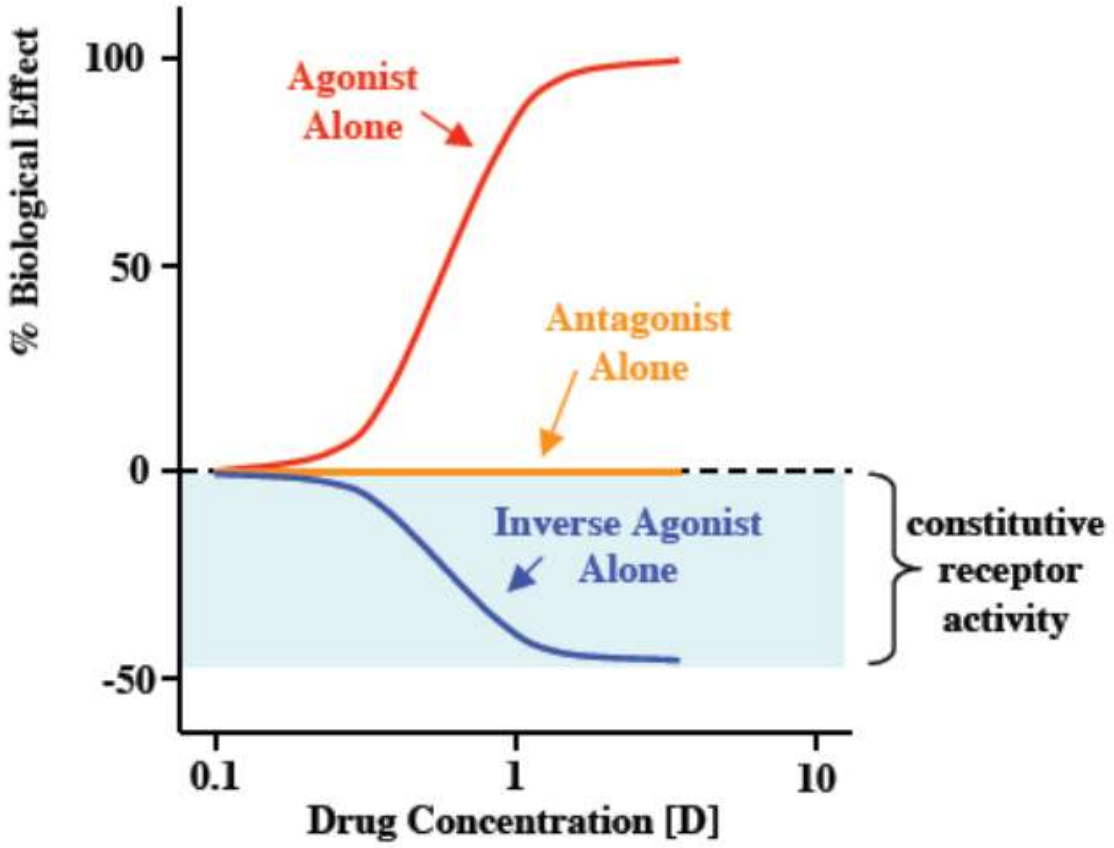
- **NOTE: may lead to immune diseases**

Inverse Agonists Reveal Constitutive Receptor Activity



Agonist

- has an independent impact upon receptor activity

Antagonist

- impacts receptor activity only in the presence of agonist

Inverse Agonist

- has an independent impact upon receptor activity
- produces an effect opposite to agonist

Addition: Applies whenever two drugs producing similar response given together result in a final response equals to the sum of the response of each drug (1+1=2)

Synergism: Applies whenever two drugs producing similar response given together result in a final response greater than the sum of the response of individual drugs (1+1=3 or 5…)

Potentiation: Applies when one drug producing no response given with another producing a specific response results in an increase in the final response of the second drug (0+1=2 or 5…)

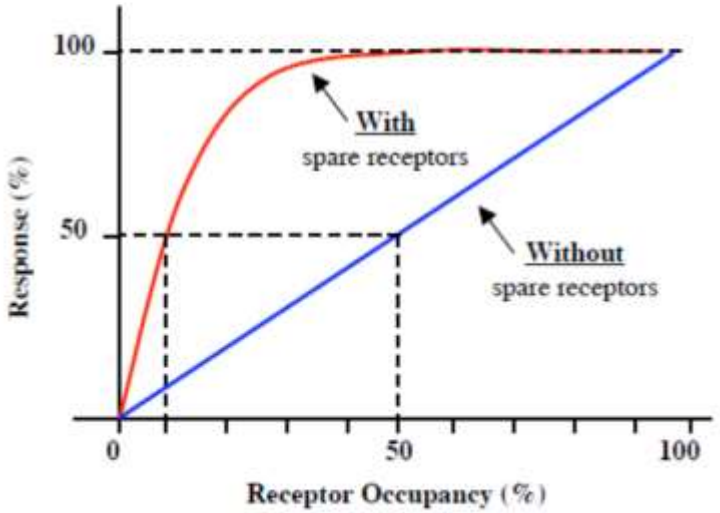
- NOTE: beta blockers applies addition or Synergism

- NOTE: Probenecid & Penicillin is an example of potentiation (Slide 82 in previous slides)

Spare Receptors

- In some systems, full agonists are capable of eliciting 50% response with less than 50% of the receptors bound (receptor occupancy)
- Pool of available receptors exceeds the number required for a full response
- Common for receptors that bind hormones and neurotransmitters

Receptor Occupancy *versus* Physiological Response



***Without** spare receptors:*

- *50% response = 50% occupancy*
- *Biological effect is proportional to [DR] at all drug concentrations*

***With** spare receptors:*

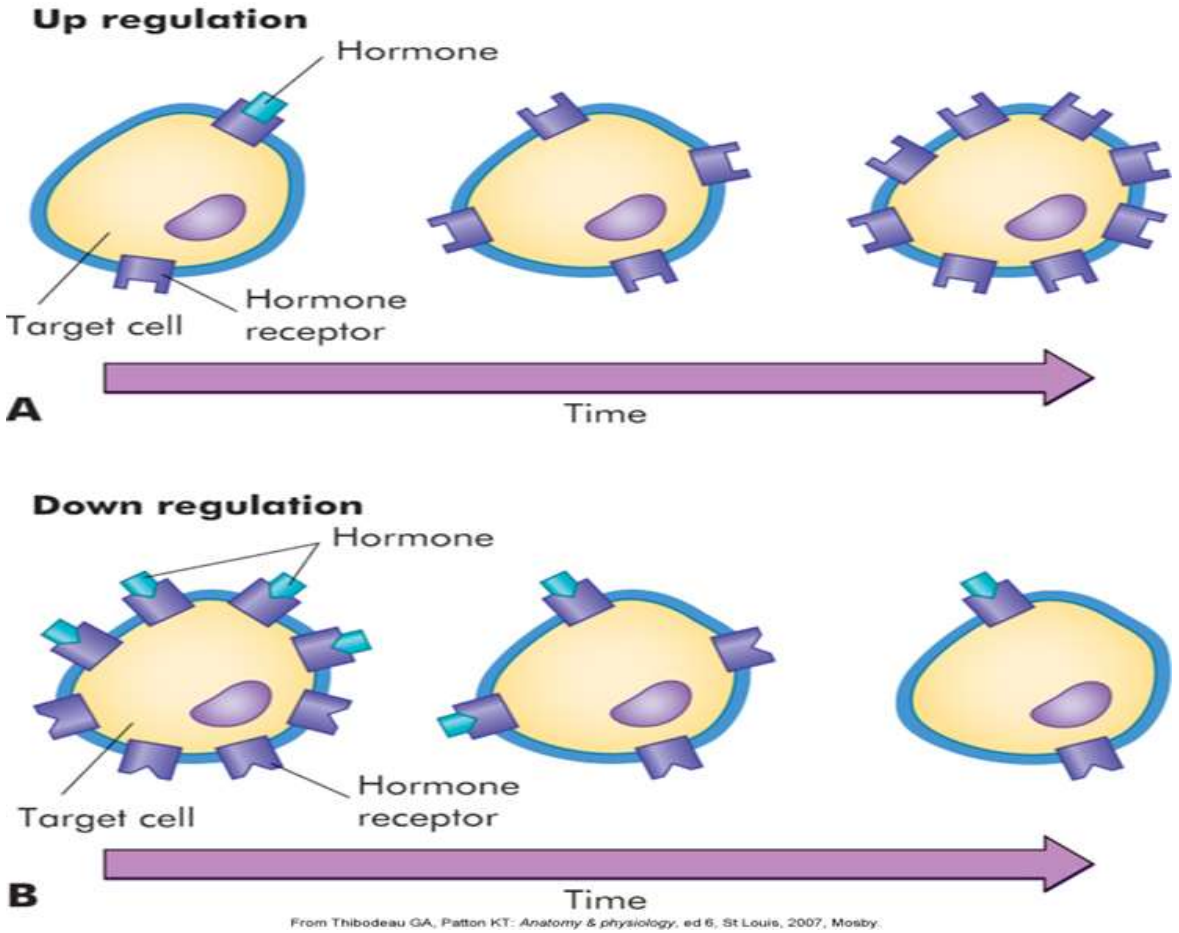
- *50% response = 10% occupancy*
- *Biological effect is proportional to [DR] only at low drug concentrations*

Spare receptors:

Some agonists may lead to 50% of response with less than 50% of the receptors bound (receptor occupancy)
The pool of available receptors exceeds the no. required for a full response
e.g. hormones (insulin); neurotransmitters (E; NE)

- **NOTE:** There is no need to occupy all the receptors to reach Vmax, e.g, insulin to lower blood glucose level, they occupy only 10% of the receptors in target tissues (rest 90% is free), but when these receptors are used for long period of time, they get damaged and spare receptors take place or comes in charge.

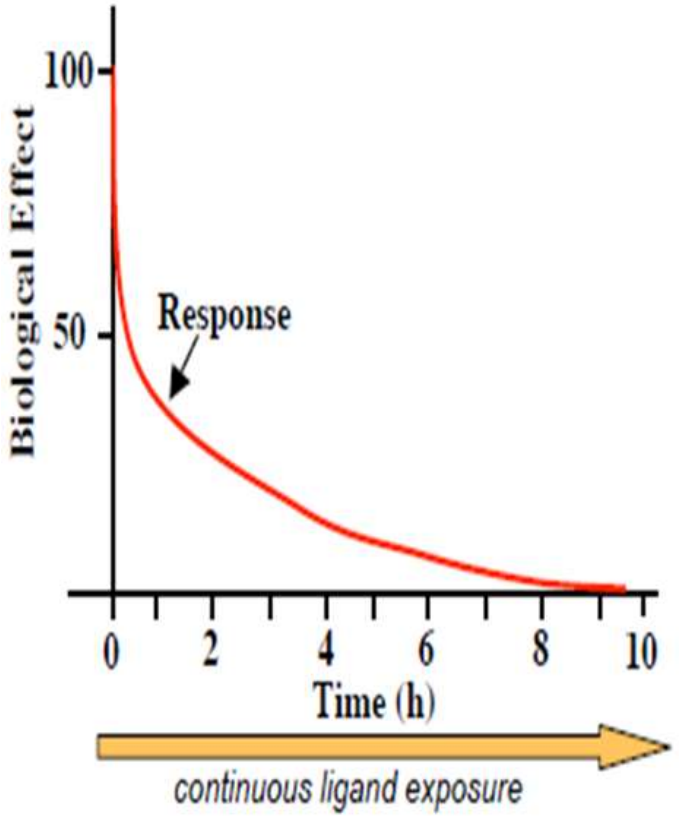
Receptors are subject to either upregulation or downregulation



- **NOTE:** sensitization (increase of receptors with time)

- **NOTE:** desensitization (decrease of receptors with time)

Drug Desensitization



- effect of a drug often diminishes when given continuously or repeatedly
- *desensitization, tachyphylaxis, refractoriness, resistance, tolerance*
- receptor-mediated and non-receptor-mediated mechanisms

- **NOTE:** type 2 diabetes they have high insulin level in blood high, they have hyperglycemia,, they have insulin resistance, the major mechanism is downregulation.
- Now we have downregulation, how can we solve it ? By using antagonist or invert agonist

2. Drug antagonism:

A pure antagonist is a drug which binds a specific receptor producing no effect or response , but if given with an agonist it reverses the effect of the agonist

Antagonism may take many forms:

a. Physiologic antagonism:

Sympathetic vs parasympathetic

b. Antagonism by neutralization:

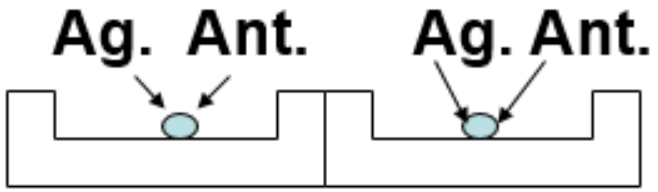
Applies whenever two drugs given together form an inactive complex

NOTE: you need to know that sympathetic is mostly the opposite of parasympathetic in mechanism. Eg: heart rate is ↑ increased in sympathetic while decreased ↓ in parasympathetic

Addition info: the use of antitoxins to neutralize the effects of toxins in the body

c. Pharmacologic antagonism: 2 major types

1. Surmountable antagonism (competitive; equilibrium; reversible)

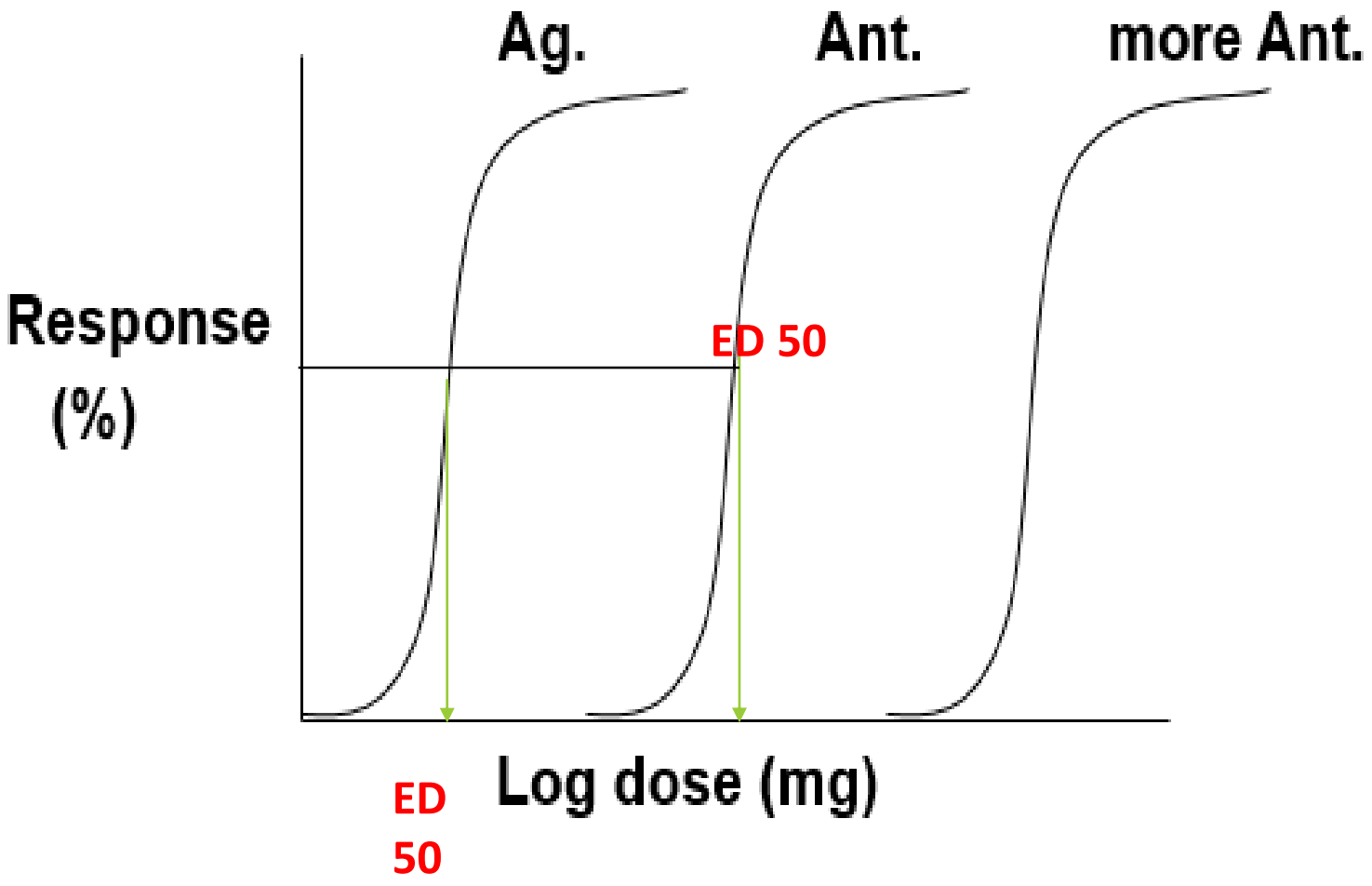


Characteristics of competitive antagonism:

- Both Agonist and antagonist compete directly for the same receptor or even site
- It is reversible
- ED50 of agonist ↑ in presence of antagonist
(affinity ↓ and potency=relative affinity ↓)
- No change in total # of receptors
- No change in Vmax
- Dose-response curves are shifted to the right

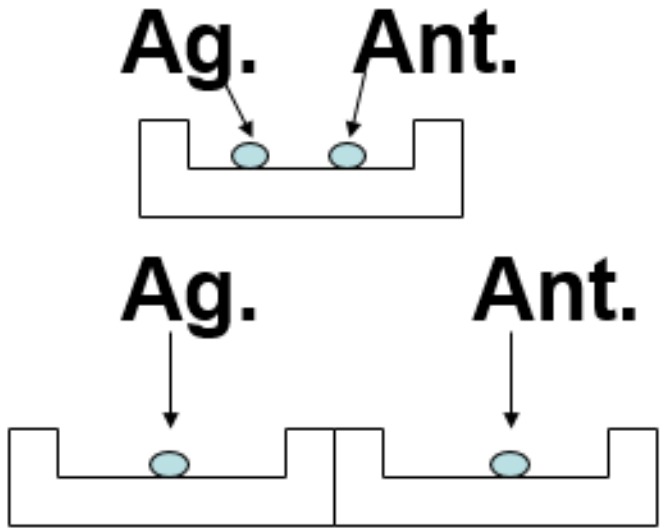
NOTE: reversible means that increasing the agonist dose (concentration) lead to displace the antagonist and vice versa

- **NOTE:** → ED 50 increased (presence of antagonist)
- Shifted to right
- Vmax & efficacy didn't change



2. Unsurmountable antagonism: 2 types

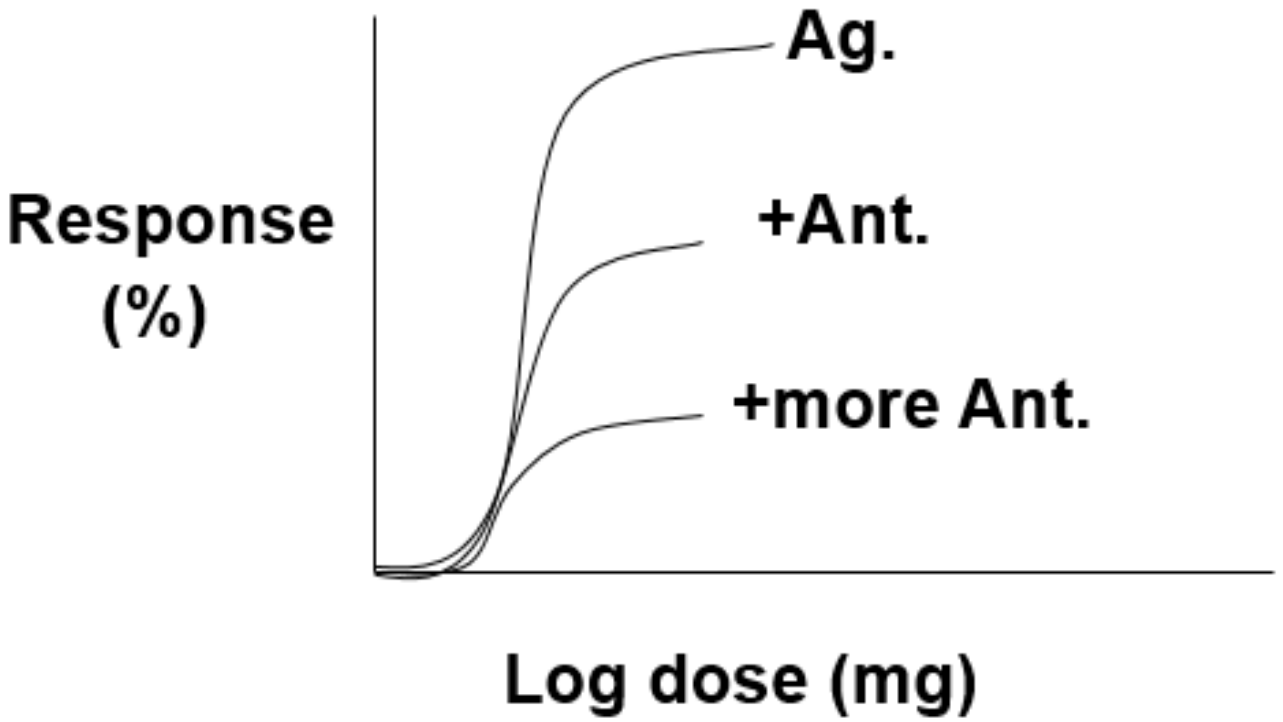
-Noncompetitive=uncompetitive=irreversible.



Characteristics of noncompetitive antagonism:

- Both Agonist and antagonist act on different sites of a given receptor or even different receptors
- It is irreversible; ↑ dose of agonist produces no pharmacological response
- Vmax ↓ with increasing dose of antagonist
- Results in no change in the ED_{50} of agonist (no change in affinity or potency) but results in ↓ in Vmax
- Total # of receptors ↓
- Results in downward shift in the Dose-response curves

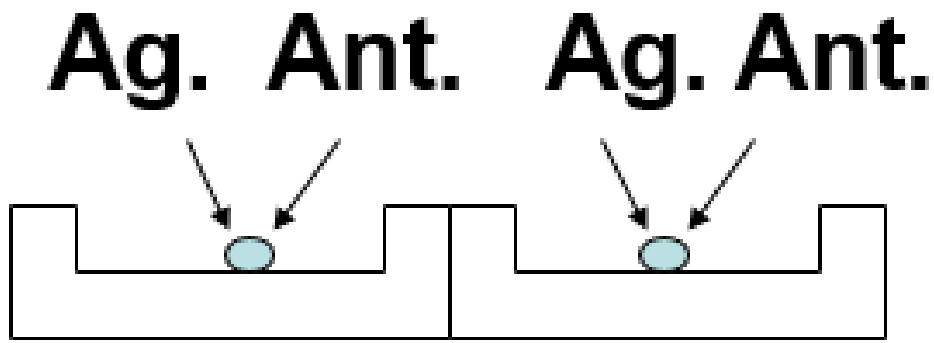
NOTE: irreversible means that I can't displace the antagonist despite the dose (concentration) of the agonist, until the antagonist fulfills its job, by then the agonist will work.



- **NOTE:** Vmax has decreased with antagonist
- The potency didn't change

- Competitive nonequilibrium irreversible

Both the agonist and the antagonist bind at the same receptor site. However, the antagonist binds irreversibly (forms a covalent bond) with the receptor and can't displace the agonist



NOTE from the Doctor: Differences between Blockers vs antidote vs antagonists

BLOCKERS	ANTAGONIST	ANTIDOTE
Definition: drug that reverses the action of another drug used normally in your body.	A pure antagonist is a drug which binds a specific receptor producing no effect or response.	Definition: drug binds to another drug inactivating it helping its excretion by a non-receptor mechanism.
Example: epinephrine and norepinephrine produce certain actions of the sympathetic system, Beta blockers will reverse the actions by receptor mediated mechanism.	Example: atropine to treat bradycardia(slow heart rate)- additional information-.	Example: chelation (as we took previously).

- NOTES: epinephrine and norepinephrine are ENDOGENOUSLY produced substances.
- antagonist must be receptor mediated.
- Beta blockers are considered antagonists.(receptor mediated)
- They are named blockers because in addition of blocking exogenous substances, they block endogenous substances.
- ALL Beta blockers are antagonists, but not all antagonists are beta blockers.