DRUG RECEPTOR INTERACTION

Dept. Pharmacology & Therapeutic

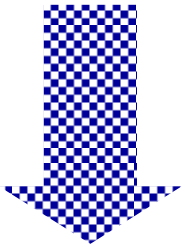
Universitas Sumatera Utara

- ***Defenition***
- ***Receptor***
- ***Effector***
- ***Drug receptor binding***
- ***Dose-Response Relationship***
  - ***Graded Dose Response Relationship***
  - ***Quantal Dose Response Relationship***
- ***Drug Receptor Interaction***
  - ***I. AGONIST***
  - ***II. ANTAGONIST***
    - ***II.1. Competitive receptor antagonists***
    - ***II.2. Non competitive receptor antagonist***
  - ***III. Partial Agonist***
  - ***IV. Inverse Agonist***
  - ***V. Spare Receptor***

The Pharmacodynamic Phase

- Describes the biochemical and physiologic action and effects of drugs in the body.
- This phase occurs when the medication reaches the target cell, tissue, organ and a therapeutic effect occurs.

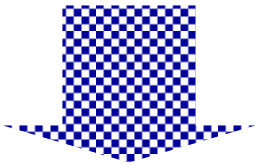
The important principles



1. **Drugs act by affecting biochemical or physiological processes in the body**

2. **Most drugs act at specific receptors either by mimicking the effects of endogenous molecules (*agonist drugs*), or by preventing these effect (*antagonist drugs*)**

The important principles (cont.) :



3. A specific drug acts only at one receptor, but may produce multiple effects due to the location of receptors in various organs
4. Selective drug produces only one effect
5. Drugs that are both specific and selective in their actions are more likely to be clinically useful than drugs that more potent on the basis of dose

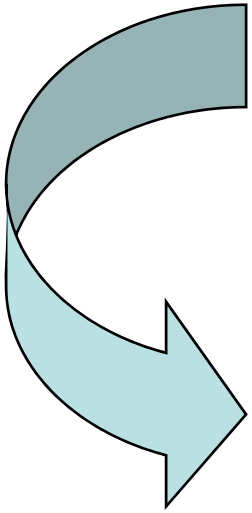
- **affinity**: strength of attraction between drug and receptor

- **Efficacy (intrinsic activity):** the maximum effect (Emax) a drug can bring about, regardless of dose
- **potency**: amount of drug needed to produce an effect

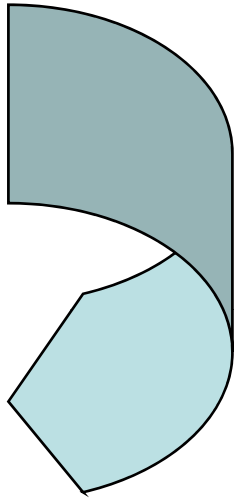
Action vs. Effect

- **action** = how the drug works
  - usually by enhancing or inhibiting cell function
- **effect** = consequence of drug action on body

Drug Receptor Interaction



AGONIST



ANTAGONIST

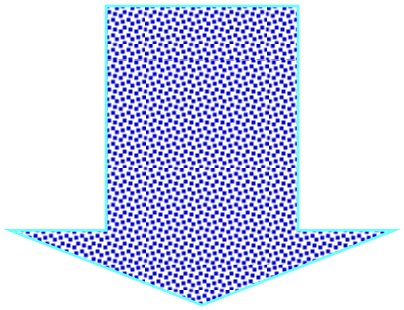
Receptor antagonist

(Competitive/Non Competitive)

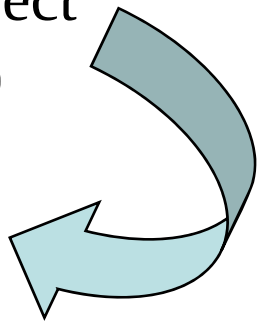
Non Receptor antagonist

(Chemical/ Physiological)

AGONIST

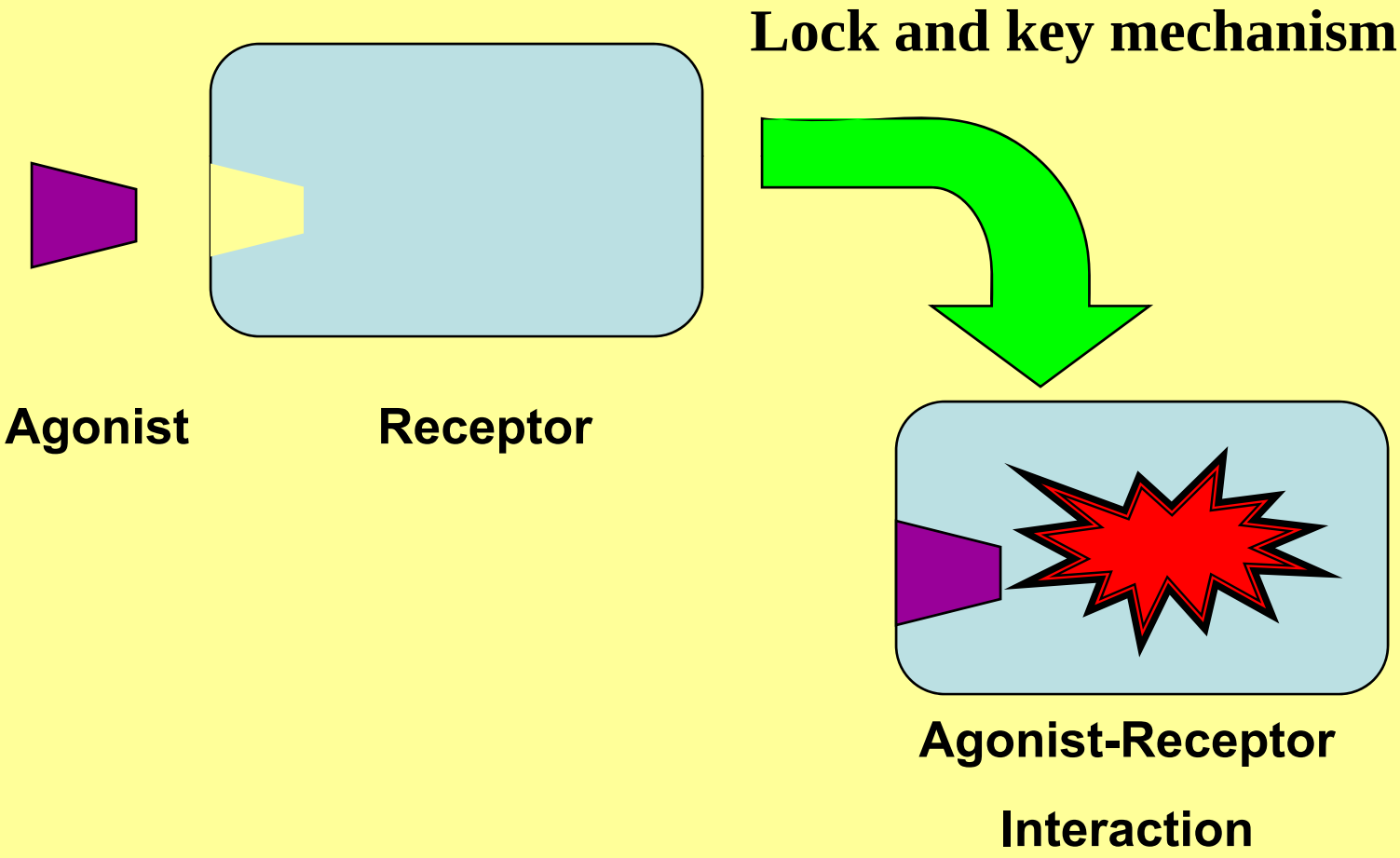


Binds to a receptor and causes the biological effect
(a drug that activates its receptor upon binding)



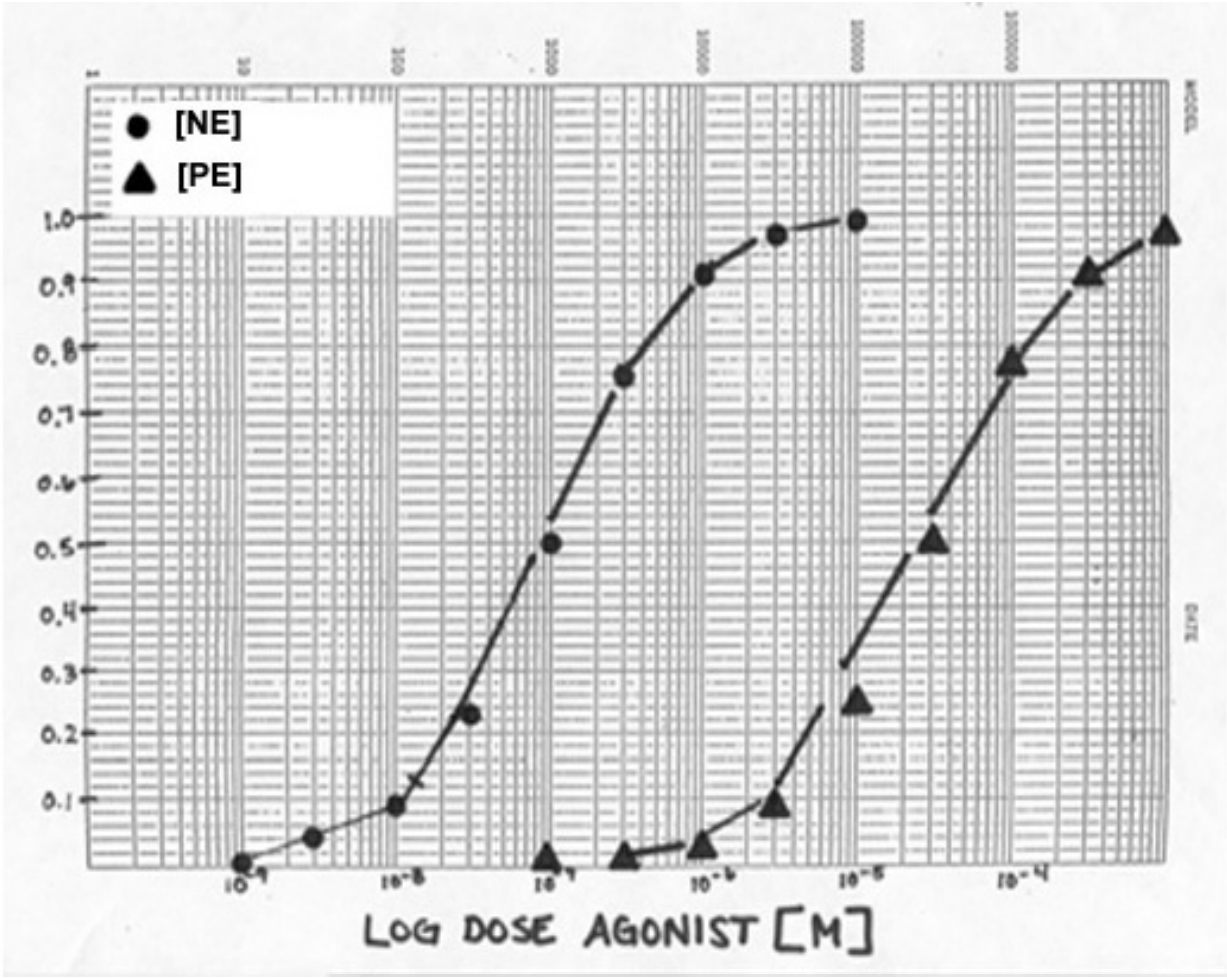
Adrenalin with receptor → adrenergic effect

Receptor Interactions

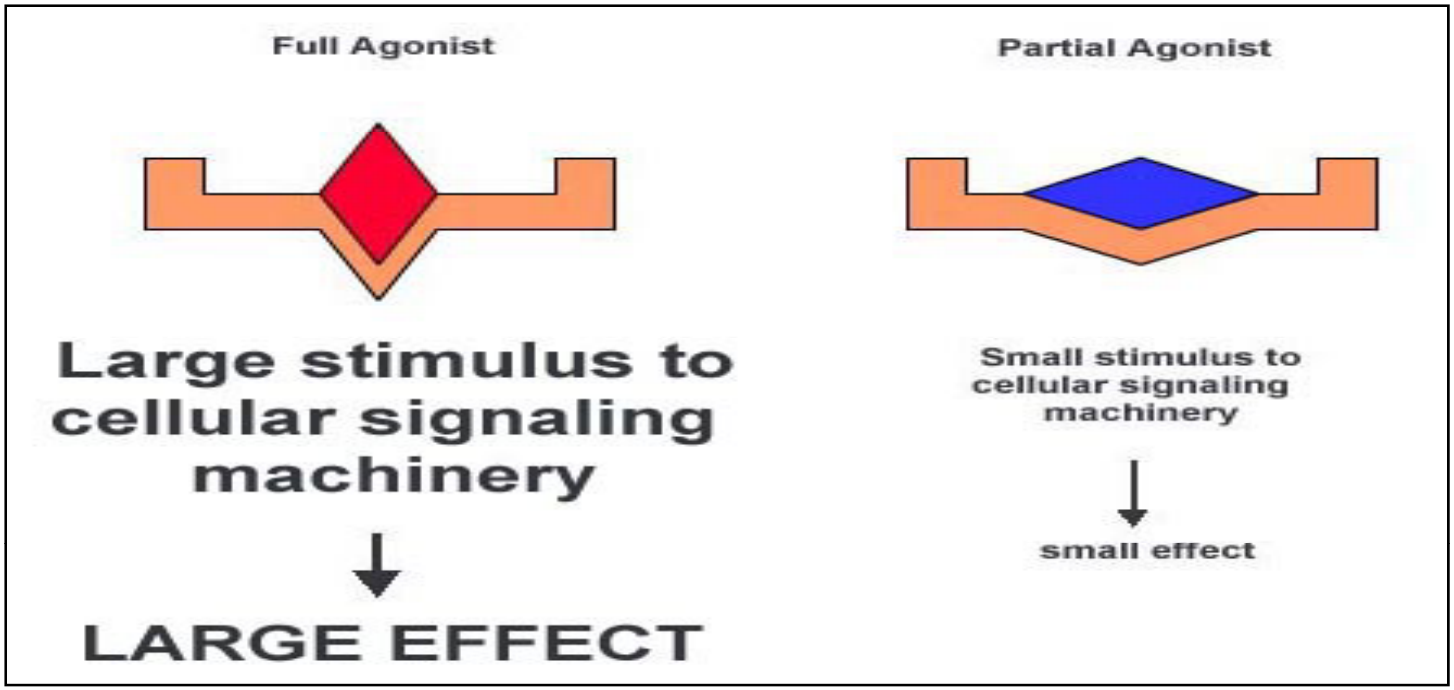


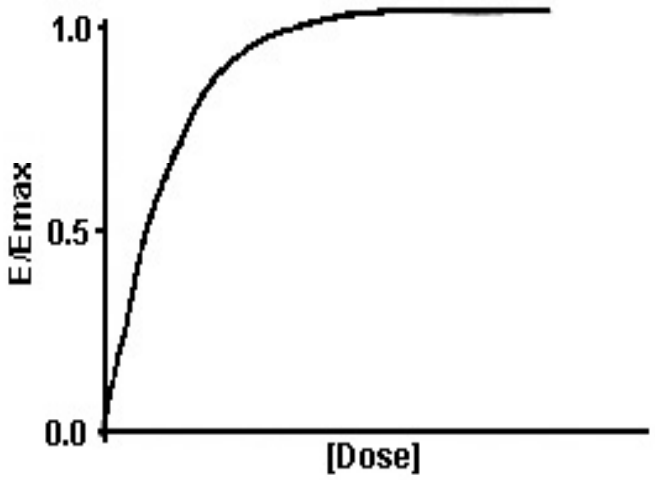
Perangsangan Adrenergik

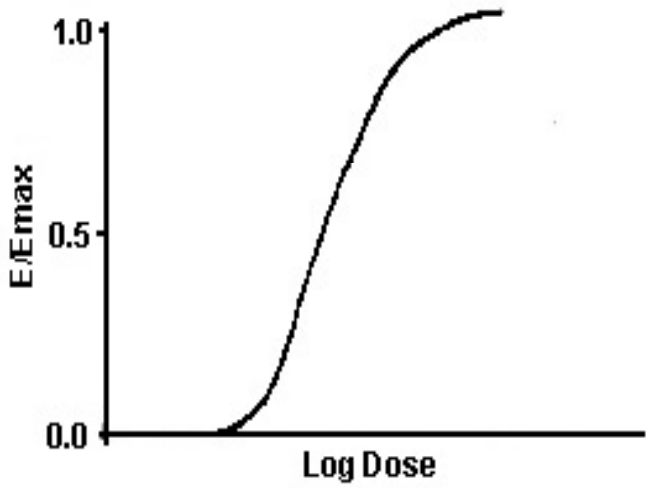
Organ efektor	Reseptor	Respon
Heart	ß1	**Contractilitas ↑**
Vena	Alpha 1	Constriction
	ß 2	Dilatation
Bronchus	ß 2	Relaxation
Uterus	Alpha 1	Constriction
	ß 2	Relaxation

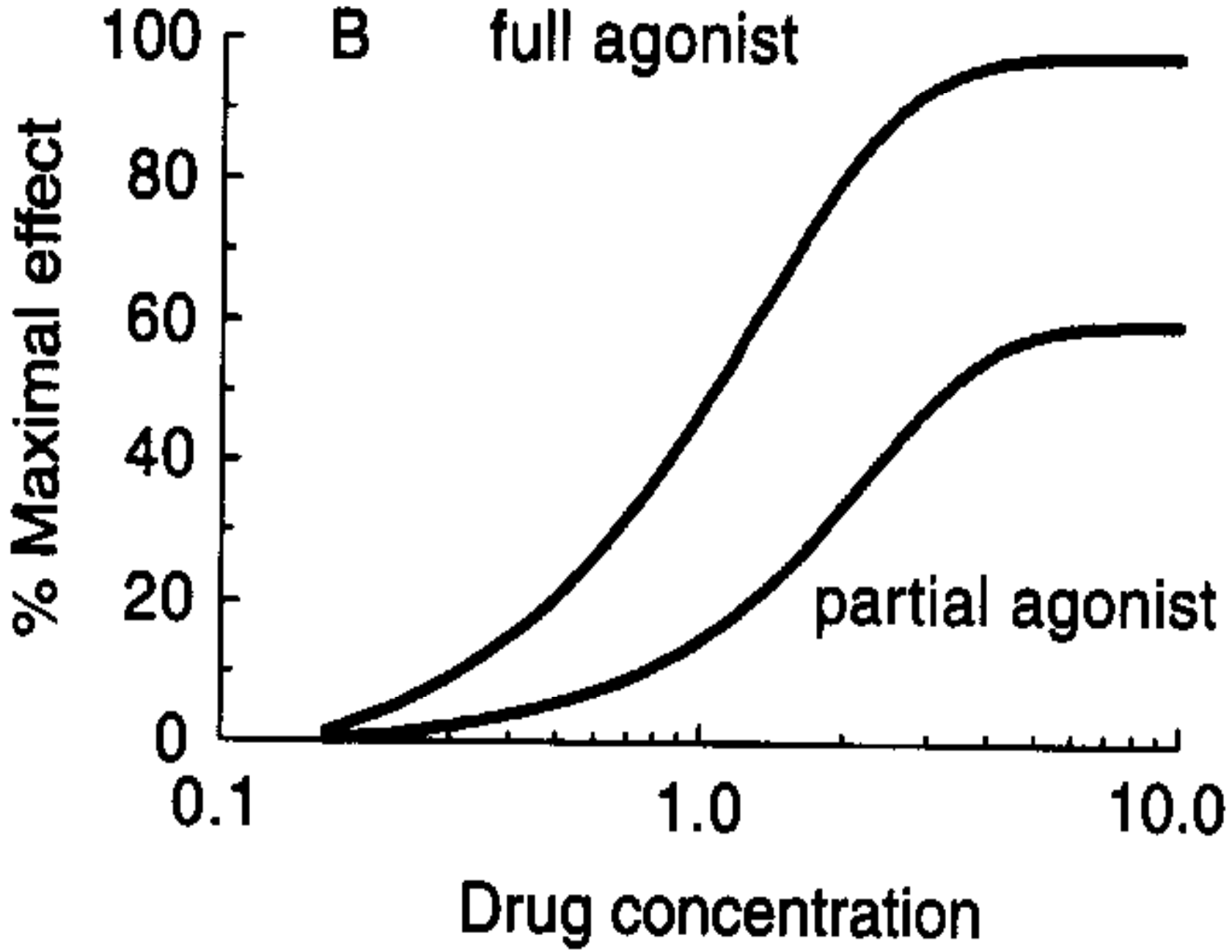


Norepinephrine and phenylephrine are full agonists with intrinsic activity values of 1. However, Norepinephrine has a higher affinity for the receptor. As is illustrated, affinity affects the position of the dose-response curve on the x-axis


Full Agonist
Partial Agonist
Large stimulus to cellular signaling machinery
LARGE EFFECT
Small stimulus to cellular signaling machinery
small effect


1.0
0.5
0.0
E/Emax
[Dose]

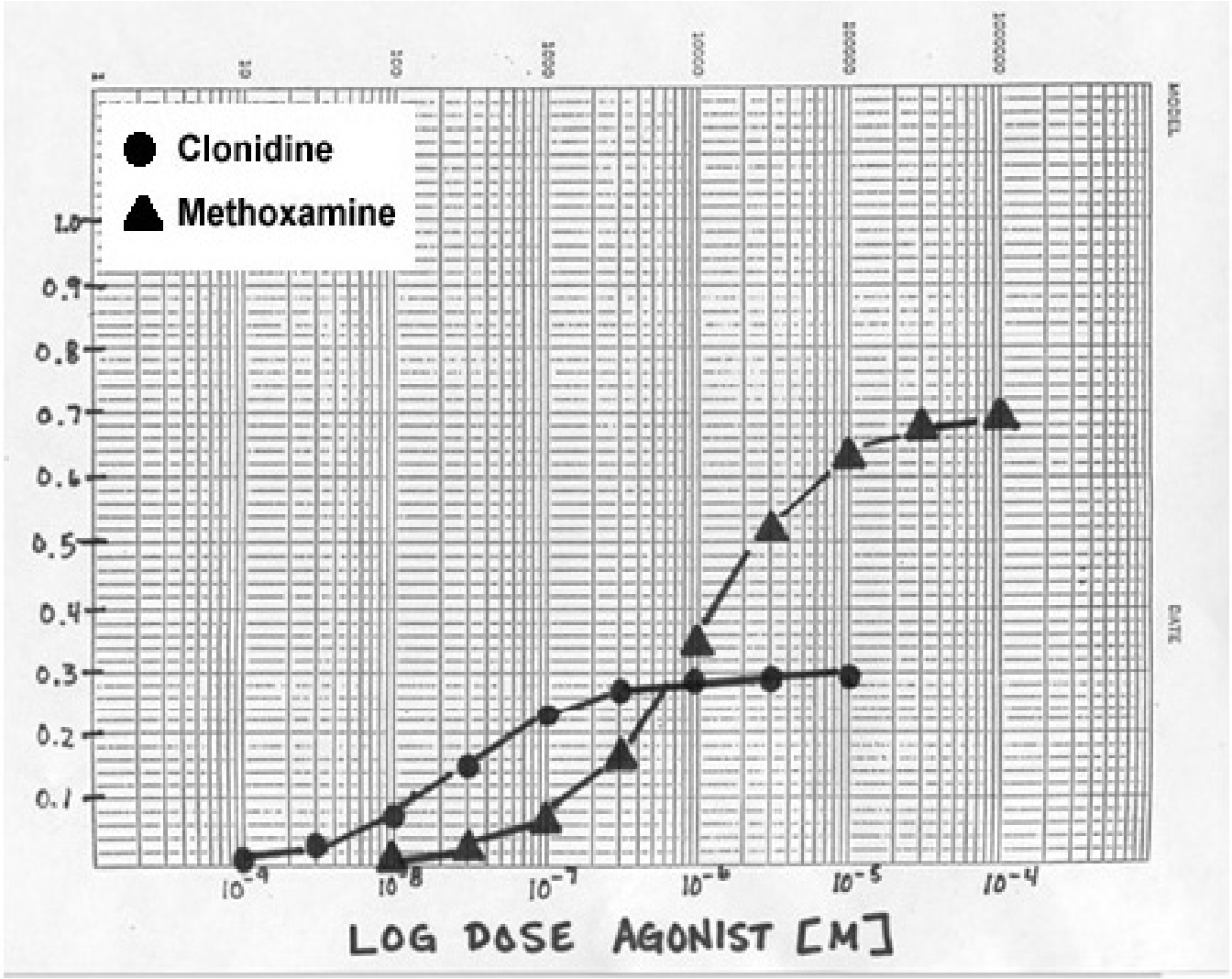

1.0
0.5
0.0
E/Emax
Log Dose


B
full agonist
partial agonist
100
80
60
40
20
0
% Maximal effect
0.1
1.0
10.0
Drug concentration

Partial Agonist

A drug that binds to a receptor at its active site but produces only a partial respon, never reach maximal effect of the real agonist even when all of receptor are occupied (bound) by the partial agonist

Morphine with Buprenorphine

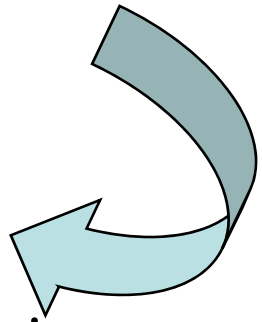


- Clonidine and Methoxamine are partial agonists.
- Clonidine has a higher affinity but a lower intrinsic activity than does Methoxamine.
- Intrinsic activity affects the magnitude of the response

ANTAGONIST

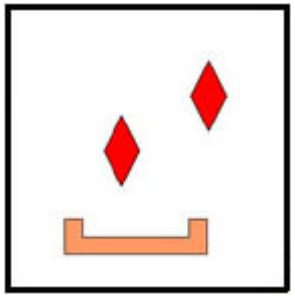
(Anti – Agonist)

Binds to the receptor and blocks or reverses the effect of agonists but has no effect in the absence of the agonist

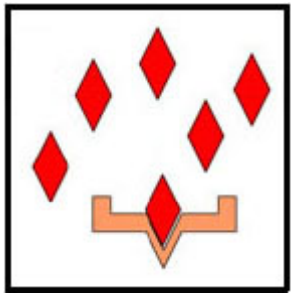


Propranolol, beta adrenergic blocker, binds beta adrenergic receptor and block or inhibit adrenalin from binding to its receptor

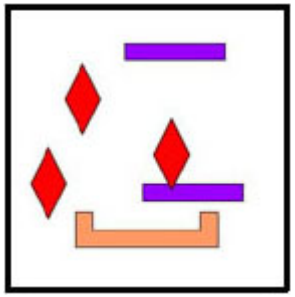
Antagonis yang menggeser kurva ke kanan:



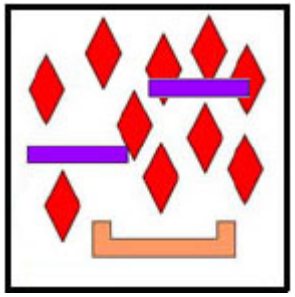
Kondisi pada poin A
Konsentrasi agonis rendah → efek yang dihasilkan kecil



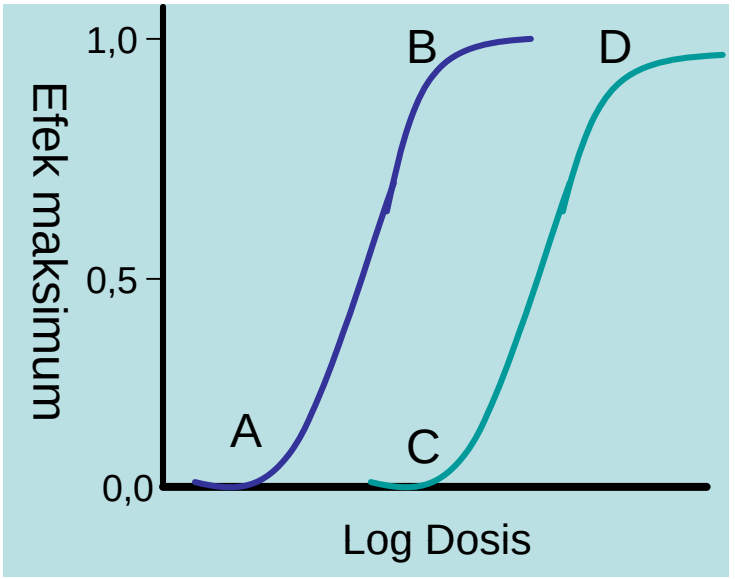
Kondisi pada poin B
Konsentrasi agonis tinggi →efek maksimal



Kondisi pada poin C:
Lebih banyak dibutuhkan agonis untuk mencapai efek yang sama sebab antagonis bersaing menduduki R



Keadaan pada poin D:
Efek maksimal dapat dicapai apabila konsentrasi agonis lebih besar dibanding konsentrasi antagonis



Antagonist

1. Competitive rec'r antagonist

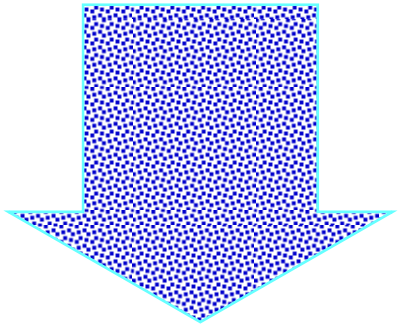
- Acts on the same receptor
- Blocks the binding of the agonist to its receptor
- Can be overcome by greater concentrations of agonist depend on the affinity of each drugs

(eg, adrenergic drugs vs adrenergic blocker $\Rightarrow$ adrenalin vs propranolol)

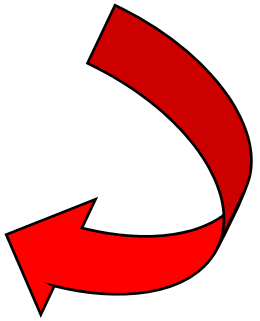
2. Non-competitive rec'r antagonist

- Acts on different receptors
- Produce effect against each other (physiologically or pharmacologically)

Competitive Receptor antagonist



- Acts on the same receptor
- Blocks the binding of the agonist to its receptor, while maintaining the receptor in the inactive conformation
- Reduce agonist potency



Adrenergic drugs vs adrenergic blocker (adrenalin vs propranolol)

Competitive antagonist

- Reversible binding to the receptor.
- The blockade can be overcome by increasing the agonist concentration.
- The maximal response of the agonist is not decreased.
- The agonist dose-response curve in the presence of a competitive antagonist is displaced to the right parallel to the curve in the absence of agonist.

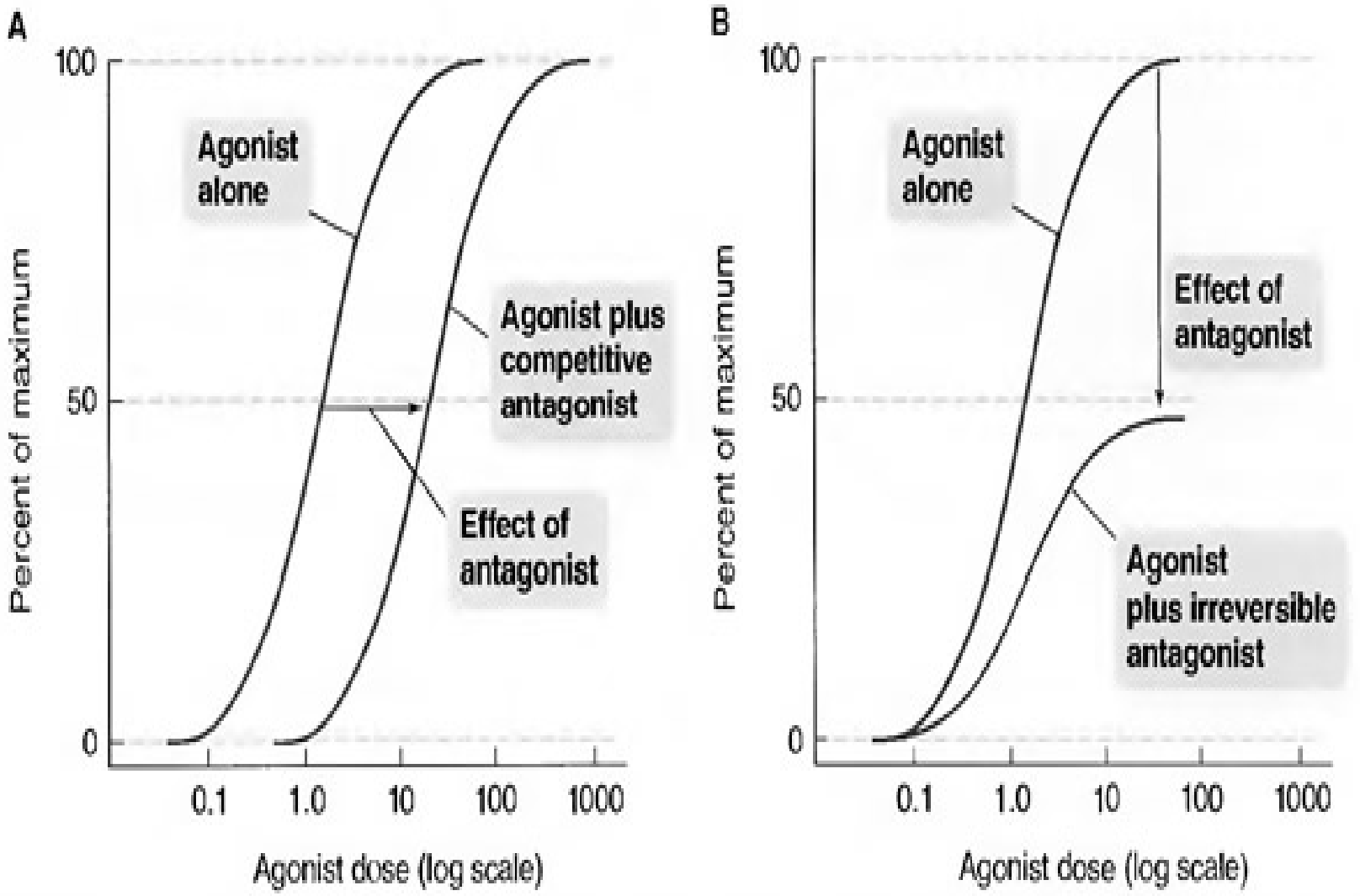
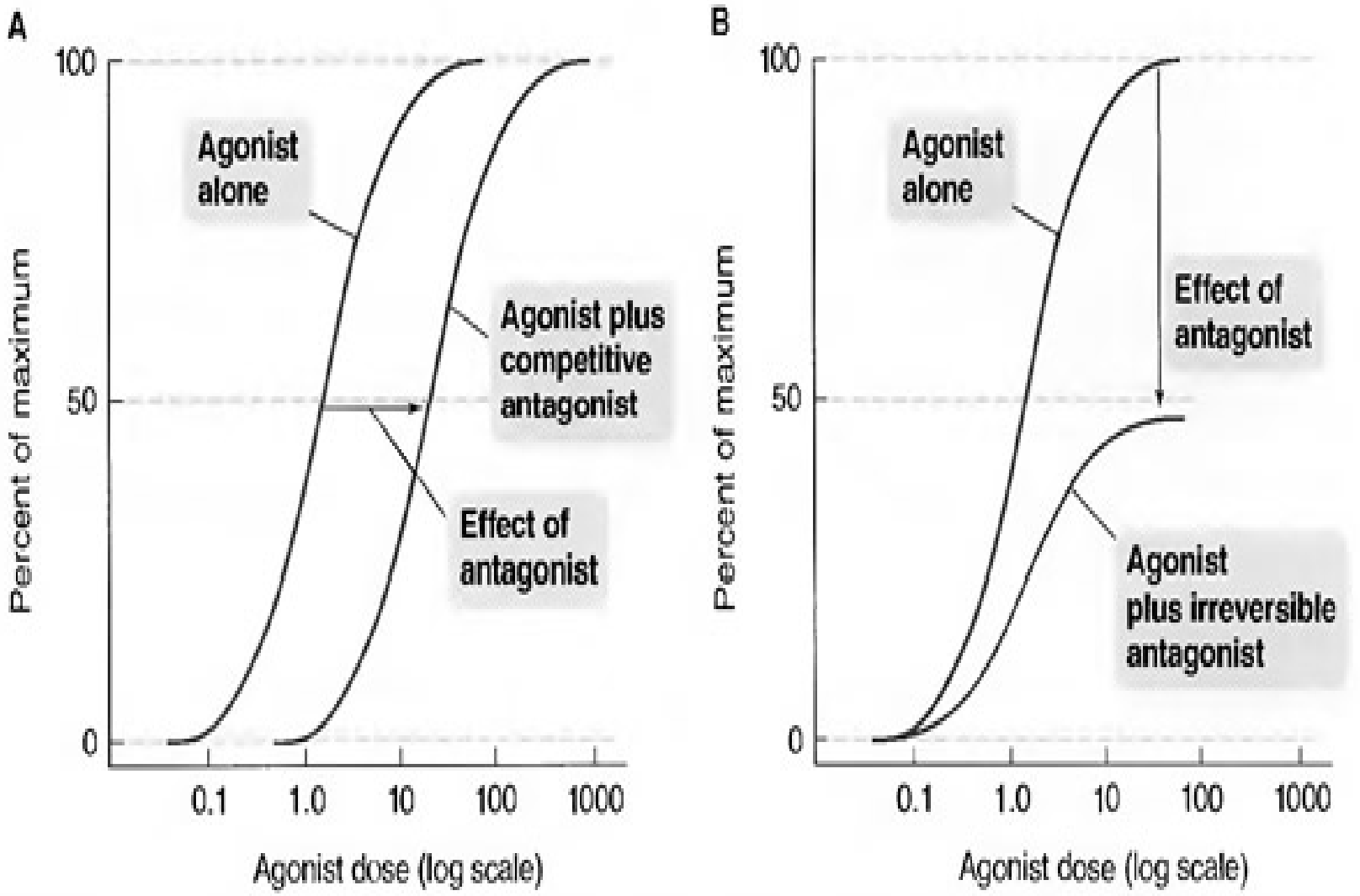


Figure 2–5. Agonist dose-response curves in the presence of competitive and irreversible antagonists. Note the use of a logarithmic scale for drug concentration. ***A.*** A competitive antagonist has an effect illustrated by the shift of the agonist curve to the right. ***B.*** A noncompetitive antagonist shifts the agonist curve downward.

Irreversible receptor antagonist :

- Chemically reactive compound, therefore covalently binds with the receptor
- The receptor is irreversibly inactivated and the blockade can not be overcome with increasing agonist concentration.
- Shifts the agonist dose-response curve to the right and depresses maximal responsiveness



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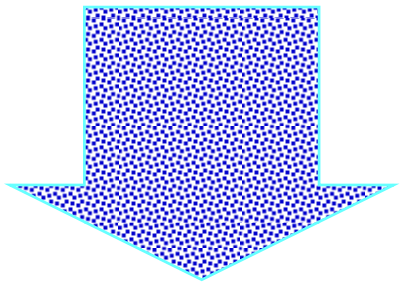
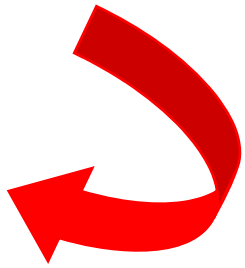
Non Competitive rec'r antagonist

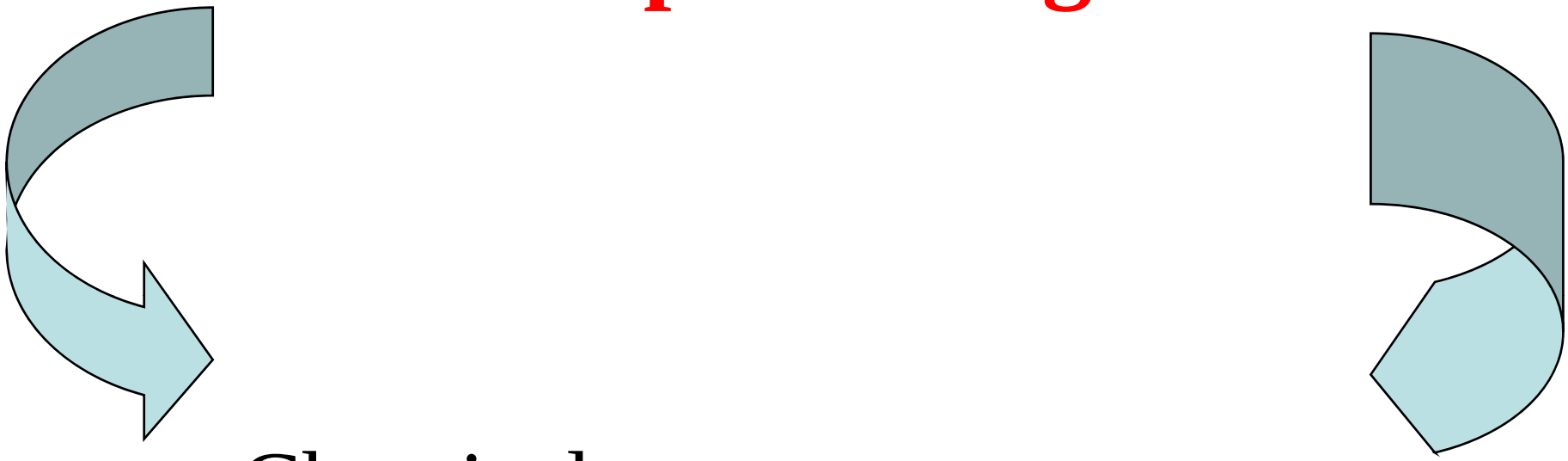


- Acts on the different receptor
- Produce effect against each other
- Reduced agonist efficacy



Phenoxybenzamine (α-adrenoceptor antagonist) to control hypertention caused by cathecolamines released from pheochromocytoma

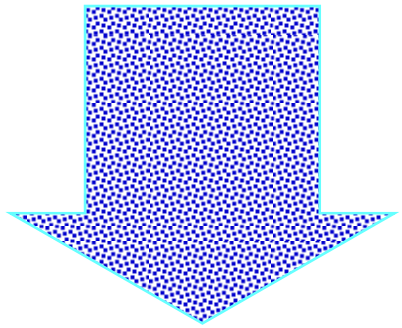
Non receptor antagonist



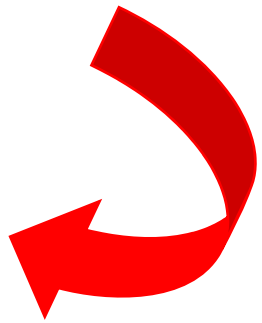
Chemical

Physiological

Chemical antagonist

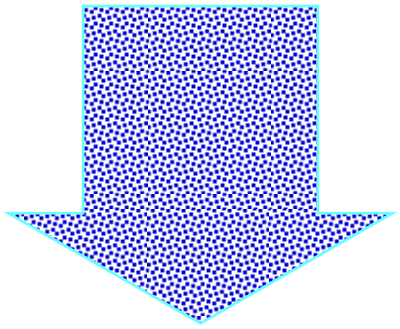


Inactivates the agonist of interest by modifying or sequestering it, so that the agonist is no longer capable of binding to and activating the receptor

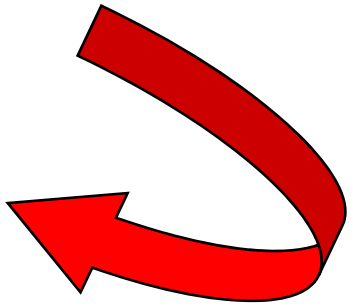


Protamin with Heparin
(protamin can be used to terminate the effect of heparin rapidly)

Physiological antagonist



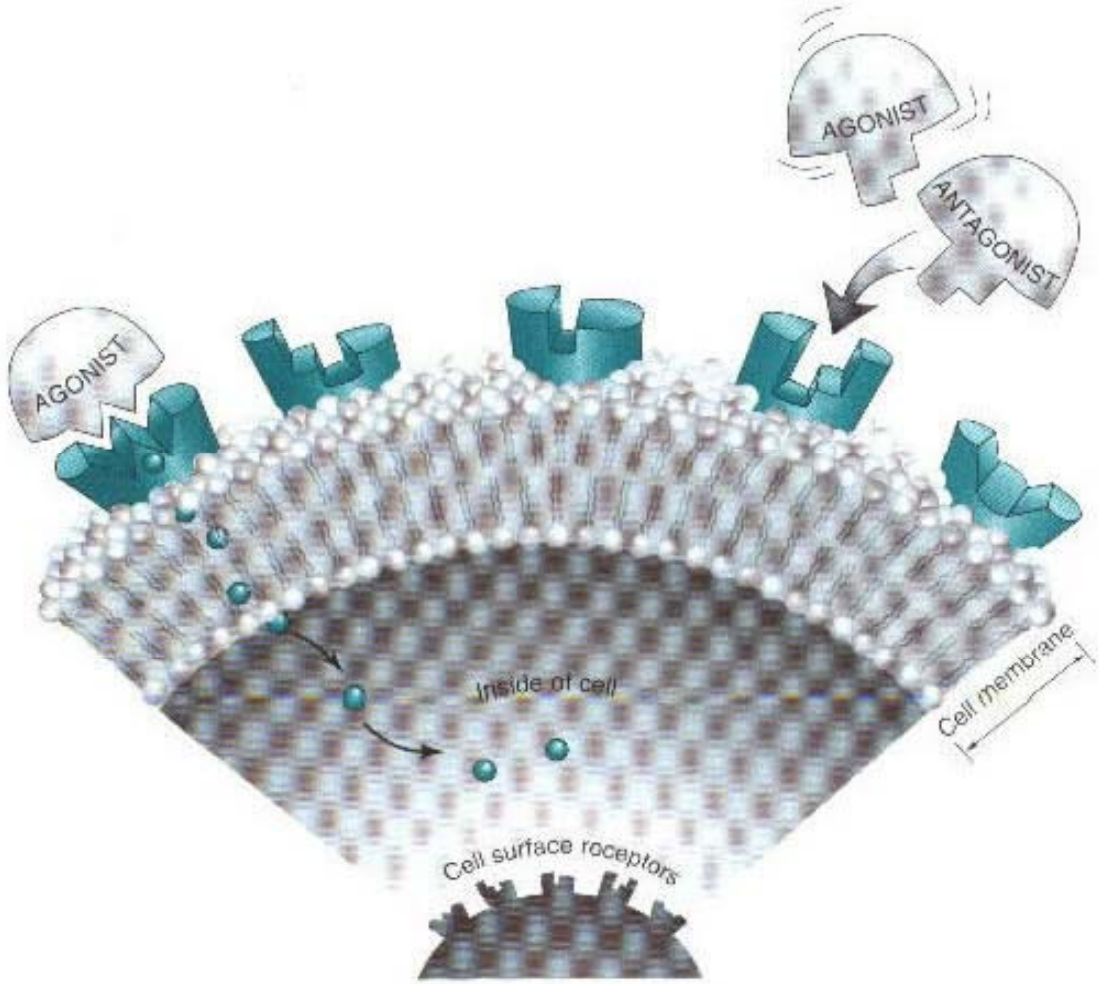
Activates or blocks a receptors that mediates response physiologically opposite to that of the original receptor for agonist



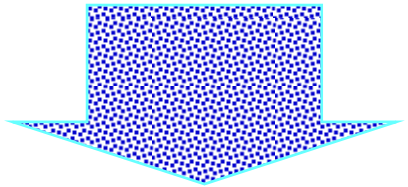
-β adrenergic blocking drugs to counteract the tachycardia effect of endogenous thyroid hormone

- histamin and adrenalin

Inverse agonist



Inverse Agonist



- Acts by abrogating the intrinsic activity of the free (unoccupied) receptor
- Inverse agonist and competitive antagonist:

  The similarities:

  - reduce the activity of a receptor

  - in the presence of full agonist, both act to reduce agonist potency

  The differences :

  - competitive antagonist has no effect in the absence of agonist; whereas, an inverse agonist deactivates receptors that are constitutively active in the absence of agonist

Spare Receptor

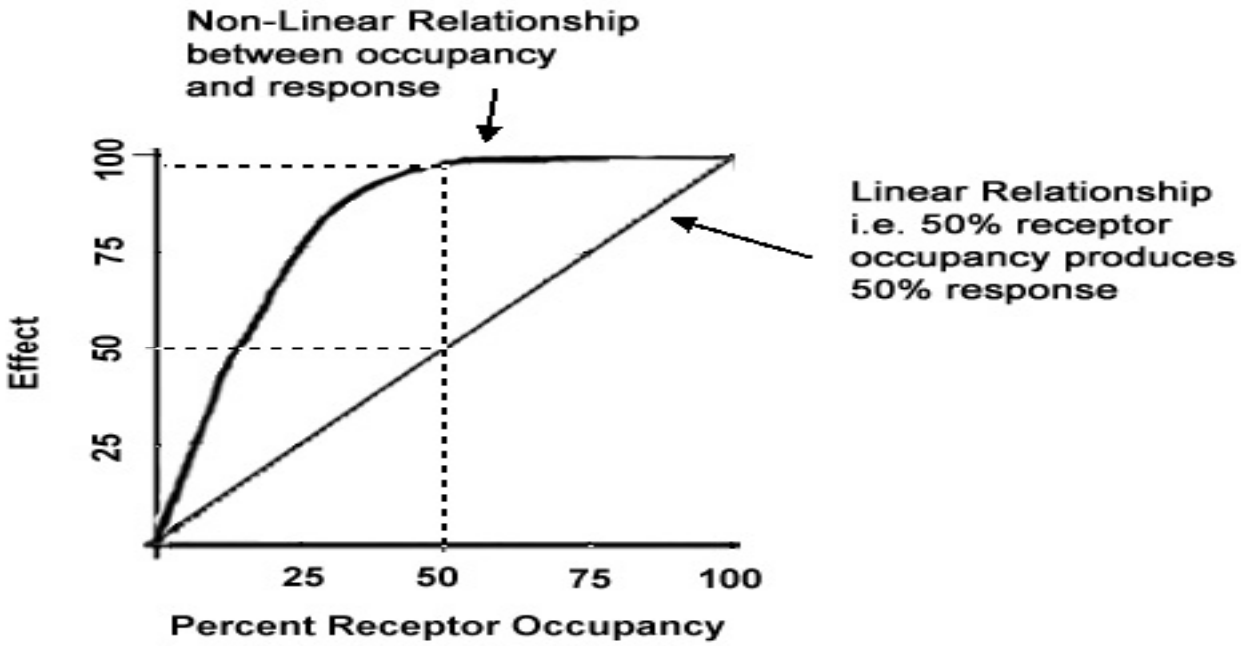
Receptors that do not have to bind drug (occupied) in order for the maximum effect to be produced.

2 possible molecular mechanisms:

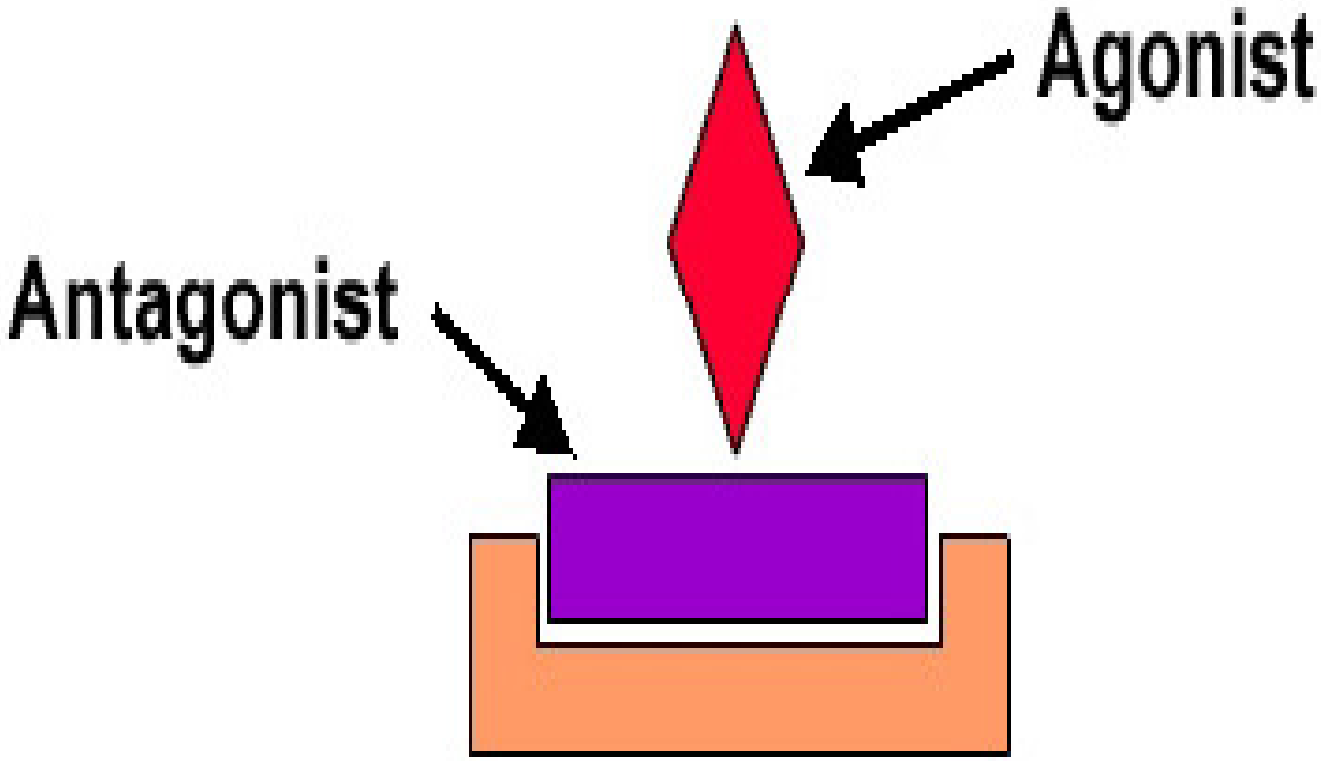
- The rec'r could remain activated after the agonist departs, allowing one agonist molecule to activate several receptor simultaneously
- The cell signaling pathways could allow for significant amplification of a relatively small signal, and activation of only a few rec'r could be sufficient to produce maximal response.

Ex.: G protein-coupled rec'rs ($G\alpha_s$)

THANKYOU



In most physiological systems in which drugs will be administered, the relationship between receptor occupancy and response is not linear but some unknown function f of receptor occupancy. In the graph, this unknown function is presented as being hyperbolic. As the graph depicts in this type of system, all receptors do not have to be occupied to produce a full response. Because of this hyperbolic relationship between occupancy and response, maximal responses are elicited at less than maximal receptor occupancy. A certain number of receptors are "spare." Spare receptors are receptors which exist in excess of those required to produce a full effect. There is nothing different about spare receptors. They are not hidden or in any way different from other receptors.


Agonist
Antagonist