Pharmacodynamics

قل تعالوا اتل عليكم ما حرم ربكم عليكم

Dr. Younus.h.johan
College of pharmacy
University of anbar

- Sources
- Lippincott Illustrated Reviews: Pharmacology 7th Edition
- Katzung ; Basic & Clinical Pharmacology 14th Edition
- Bennett & Brown ; Clinical pharmacology 11th edition
- Essentials of Medical Pharmacology; Lafi 09

Pharmacodynamics

- **Pharmacodynamics**
- **Agonist and antagonists**
- **The mechanism of drug receptor interaction**
- **Spare receptors**
- **Types of antagonism**

Pharmacodynamics

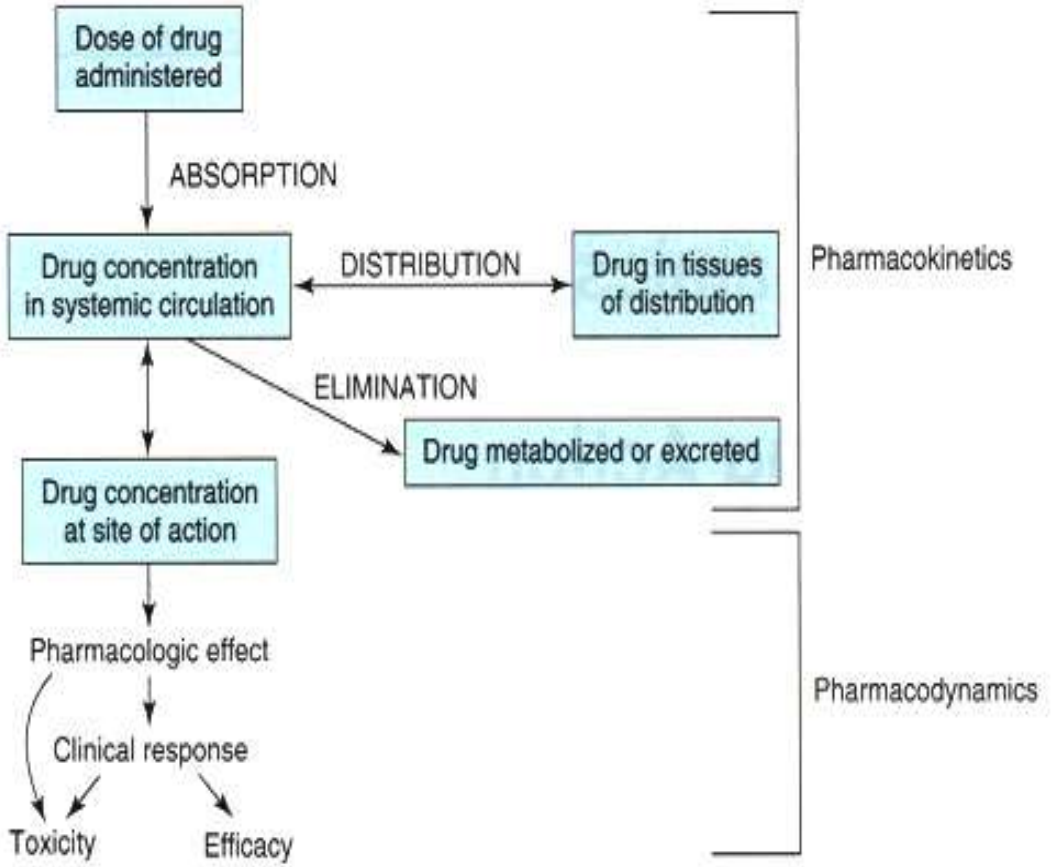
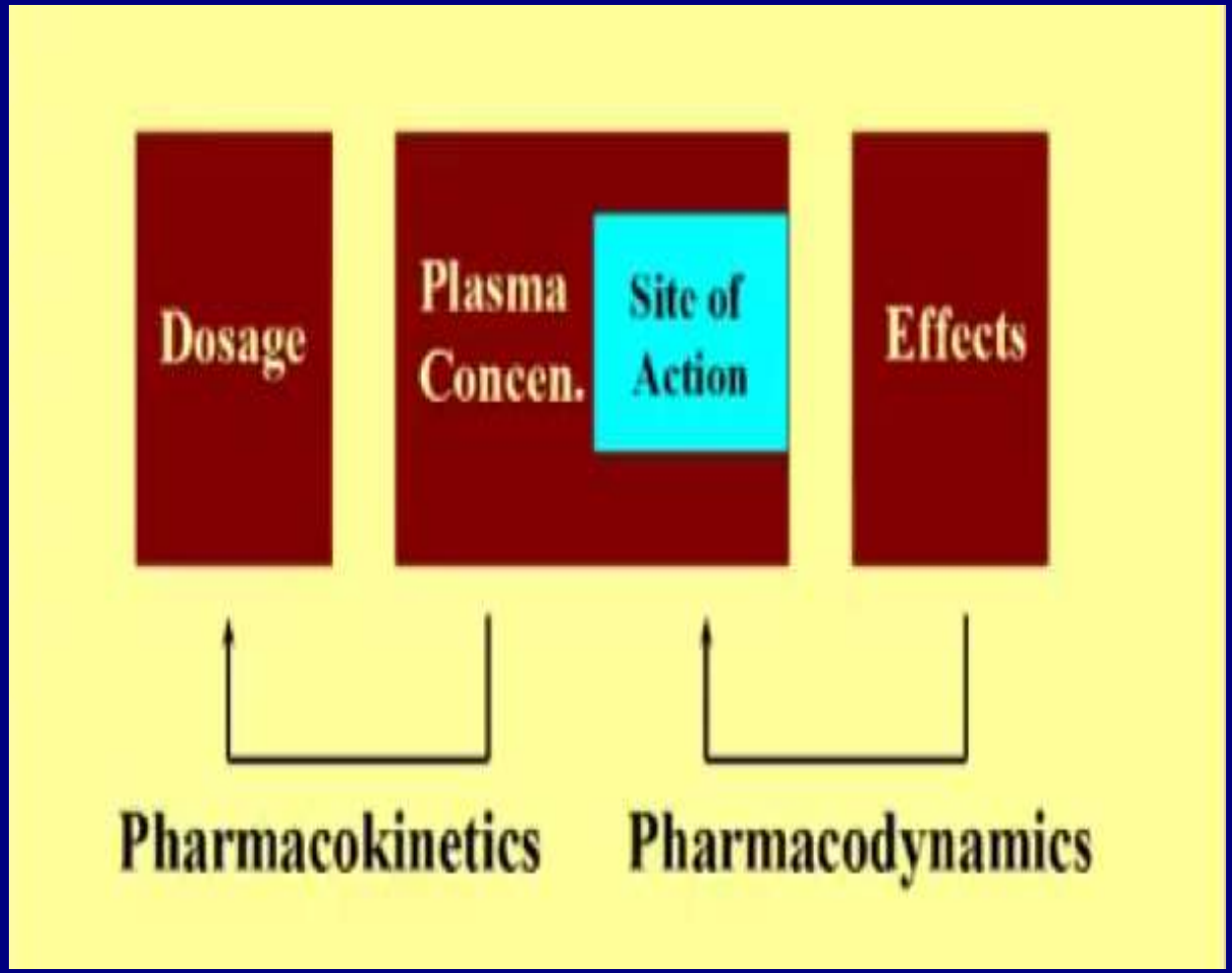
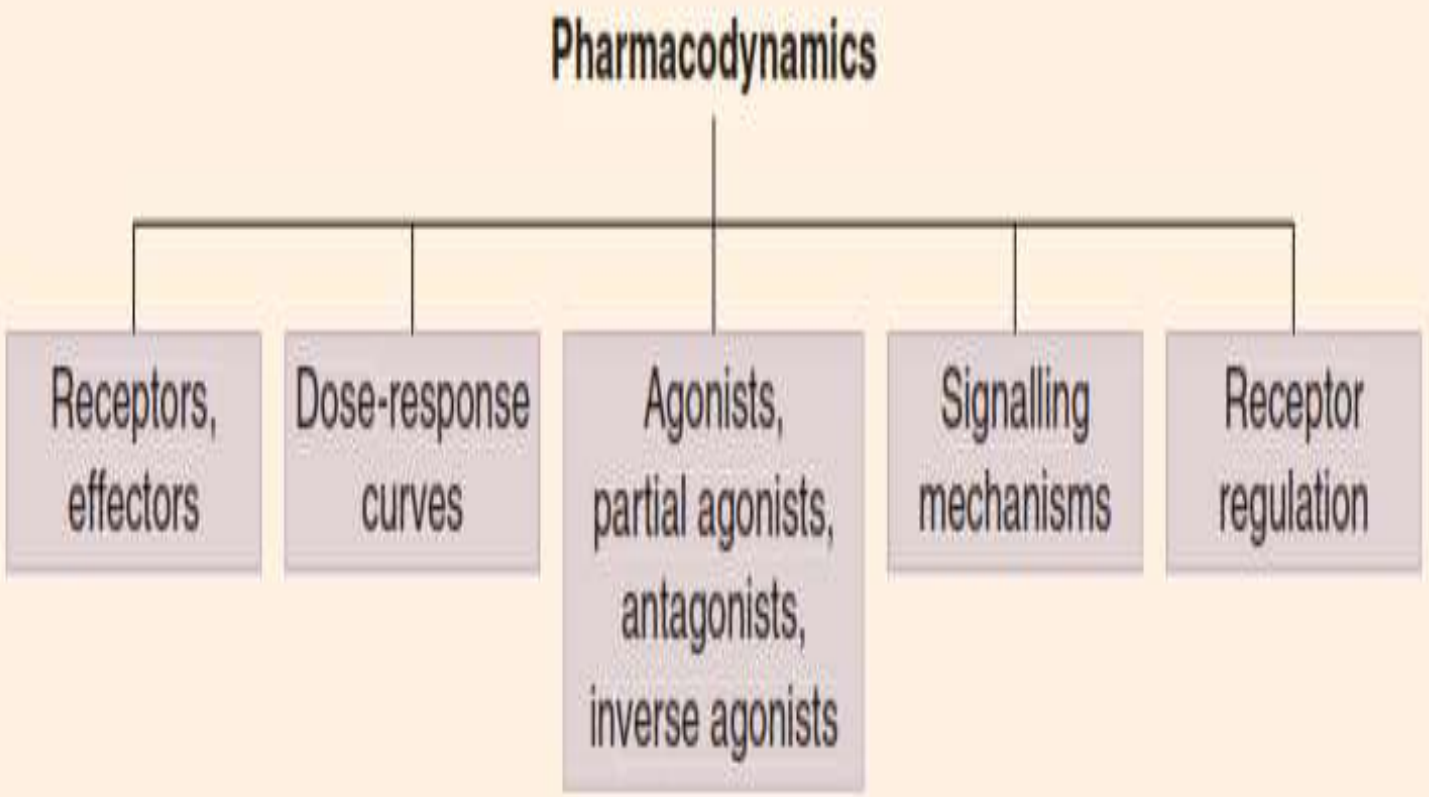


Figure 3–1. The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is the focus of the target concentration approach to rational dosing. The three primary processes of pharmacokinetics are absorption, distribution, and elimination.

Pharmacodynamics



Pharmacodynamics



Pharmacodynamics

Action of a drug on the body

- Receptor interactions
- Mechanisms of therapeutic
- Dose-response phenomena
- Toxic action.

Pharmacodynamics

Most drugs act through Receptors

Drug Receptor

A macromolecular component of a cell with which a drug interacts to produce a response

- ***Usually a protein***

- **Receptors is biologically important molecules**
- **Receptors have structural features that permit drug specificity**
- **Receptors have a drug-binding site and a biologically active site**

Molecules capable of serving as Receptors

- Enzymes
- Membrane proteins

  glycoproteins, lipoproteins)
- Nucleic acids
- Complex polysaccharides

Many drugs inhibit enzymes

- in the patient (ACE inhibitors)
- in microbes (Penicillins)
- in cancer cells (5-FU)

Types of Protein Receptors

Regulatory – mediate the action of endogenous chemicals e.g. hormones, NT,autocoids

Enzymes – may be inhibited or activated e.g. dihydrofolate reductase receptor for methotrexate

Transport – e.g. Na^+ /K^+ ATP'ase for digitalis glycosides

Structural – e.g. tubulin,receptor for colchicine

Pharmacodynamics

Drug receptor interaction

Drug - Receptor Binding

Drug Receptor Interaction

DR Complex ⟶ **Effect**

$D + R \leftrightarrow DR \Rightarrow RESPONSE$

response is proportional to the fraction of occupied receptors

maximal response occurs when all the receptors are occupied

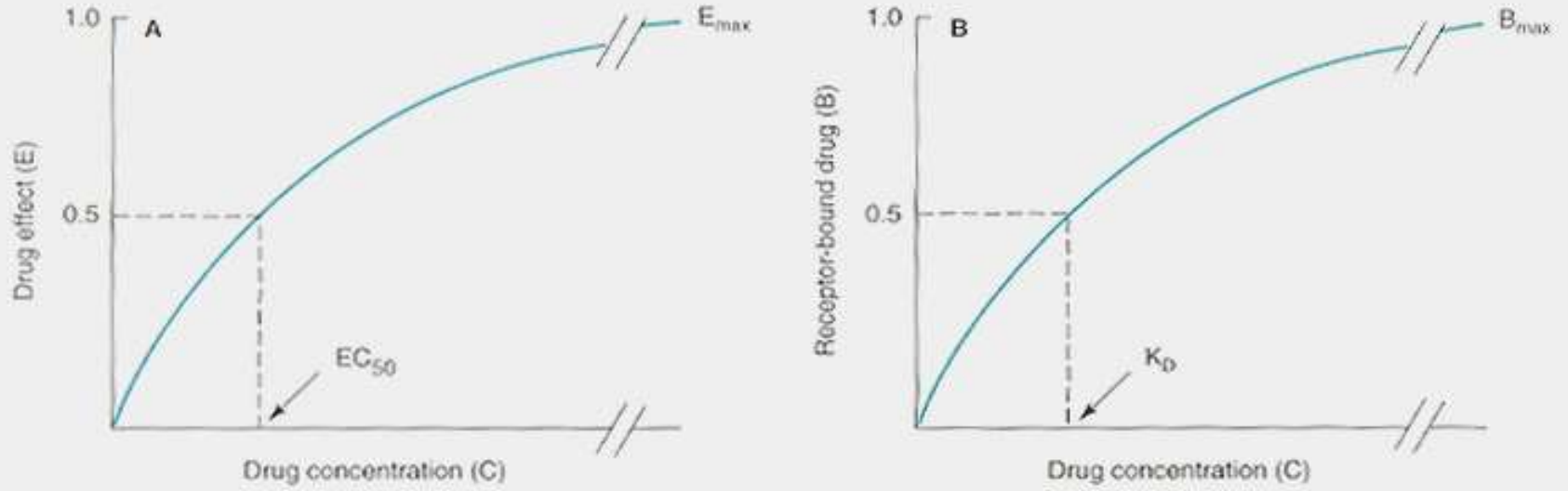
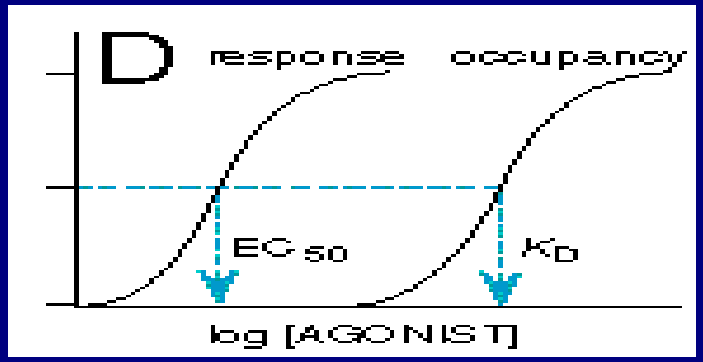


Figure 2–2. Relations between drug concentration and drug effect (panel ***A***) or receptor-bound drug (panel ***B***). The drug concentrations at which effect or receptor occupancy is half-maximal are denoted EC_{50} and K_D, respectively.

Spare receptors



- More receptors available than needed to elicit maximum response

➢ *allow maximal response without total receptor occupancy – increase sensitivity of the system*

➢ Agonist has to bind only a portion of receptors for full effect

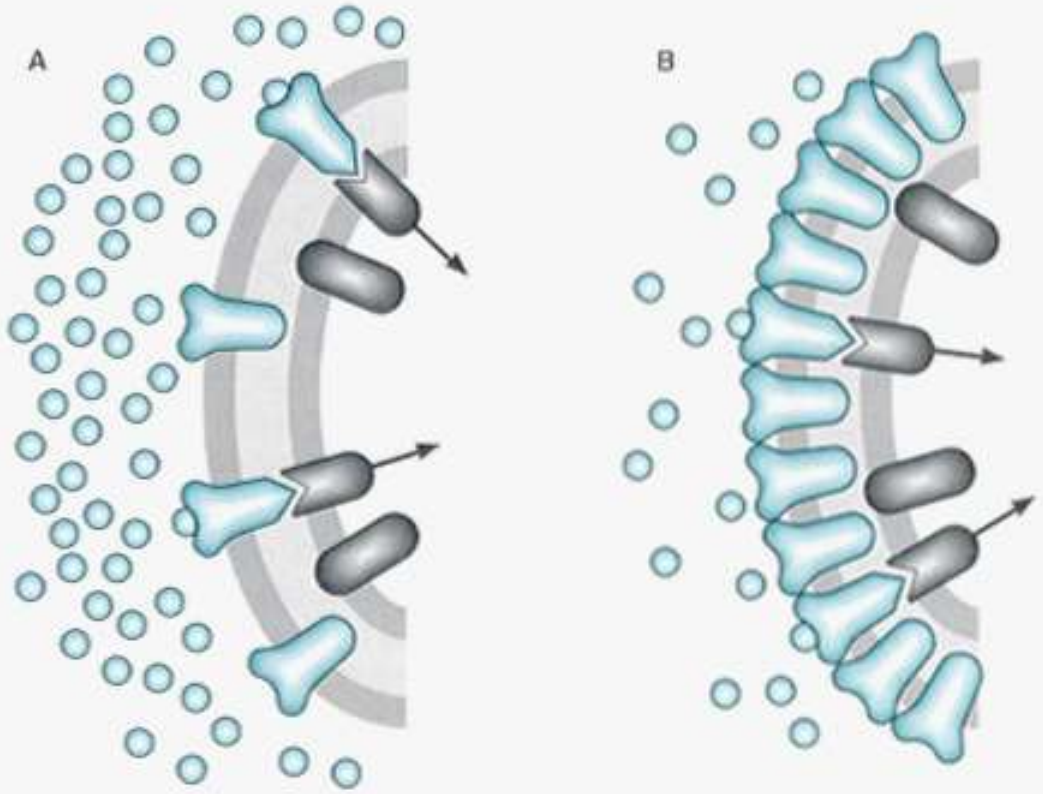


Figure 2–4. Spare receptors increase sensitivity to drug. In panel ***A,*** the free concentration of agonist is equal to the K_D concentration; this is sufficient to bind 50% of the four receptors present, resulting in the formation of two agonist-receptor complexes. (***Note:*** When the agonist concentration is equal to the K_D, half the receptors will be occupied. Remember that $B/B_{max} = C/[C + K_D]$.) Agonist occupancy of these two receptors changes their conformation so that they bind to and activate two effector molecules, resulting in a response. Because two of four effectors are stimulated by agonist-receptor complexes, the response is 50% of maximum. In panel ***B,*** the receptor concentration has been increased tenfold (not all receptors are shown), and the K_D for binding of agonist to receptors remains unchanged. Now a very much smaller concentration of free agonist ($= 0.05 \times K_D$) suffices to occupy two receptors and consequently to activate two effector molecules. Thus, the response is 50% of maximum (just as in panel A), even though the agonist concentration is very much lower than the K_D.

Some terminologies regarding drug receptor interaction

- **Affinity**
- **Efficacy**
- **Potency**
- **Ligand**

Affinity: measure of propensity of a drug to bind receptor; the attractiveness of drug and receptor

Efficacy: Potential maximum therapeutic response that a drug can produce.

Potency: Amount of drug needed to produce an effect.

Which one is important while selecting a drug for therapy ?

POTENCY

OR

EFFICACY

Ligand:

Molecules that binds to a receptor

Classification of Ligands

a. agonist

b. partial agonist

c. antagonist

pharmacological vs. physiological vs. chemical

pharmacological antagonists

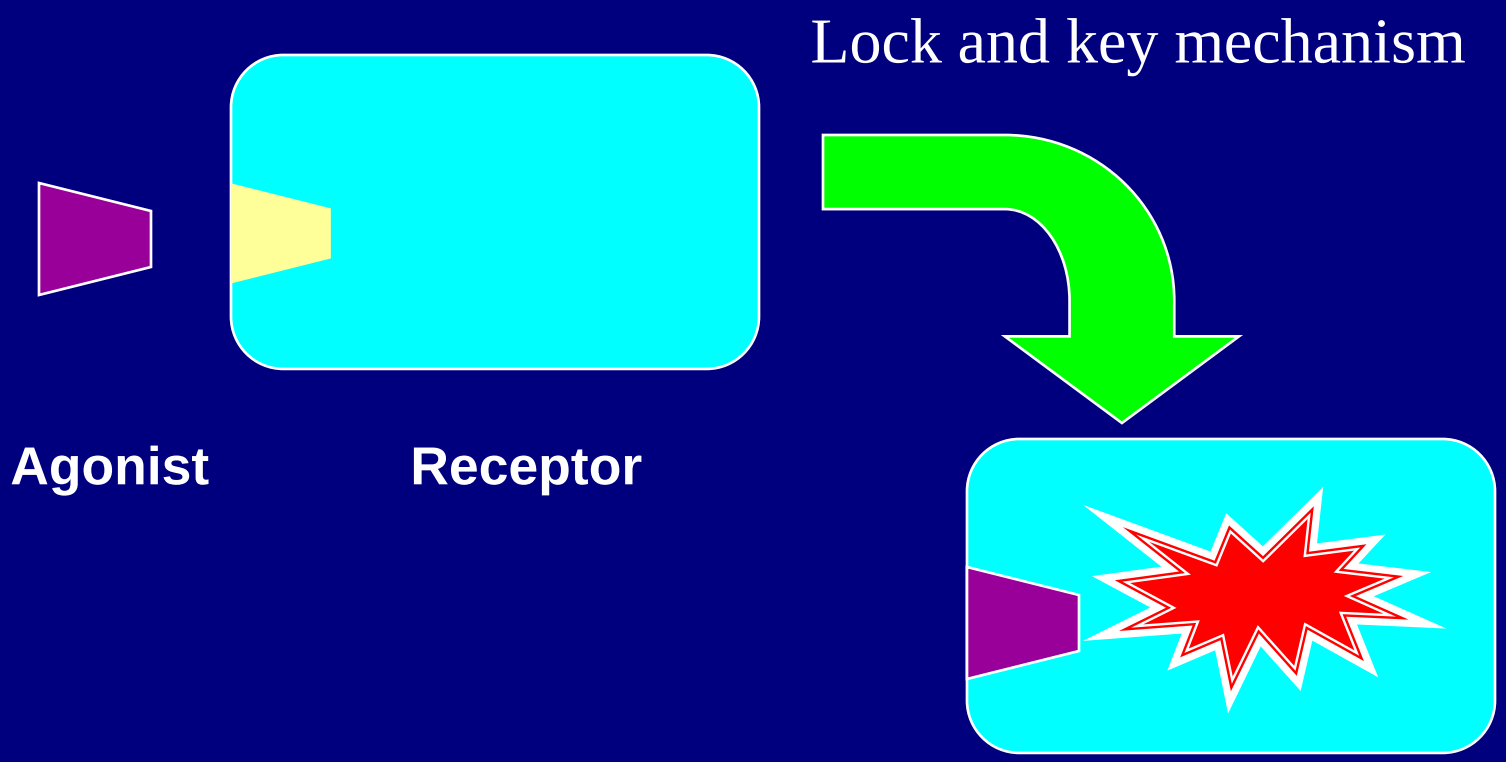
- competitive

  surmountable

- noncompetitive

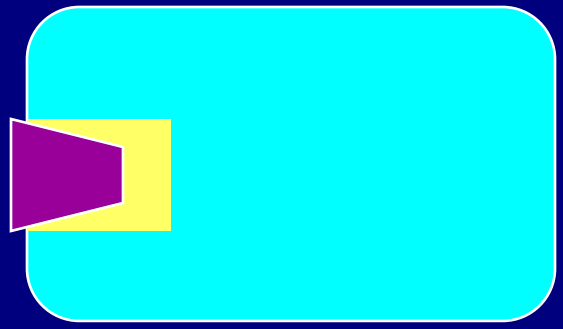
AGONIST

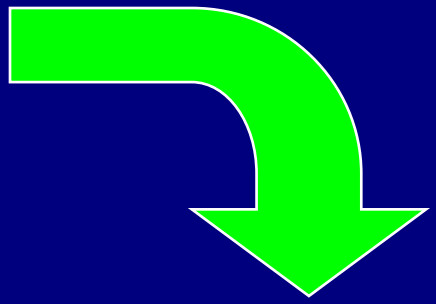
Agonist Receptor Interactions



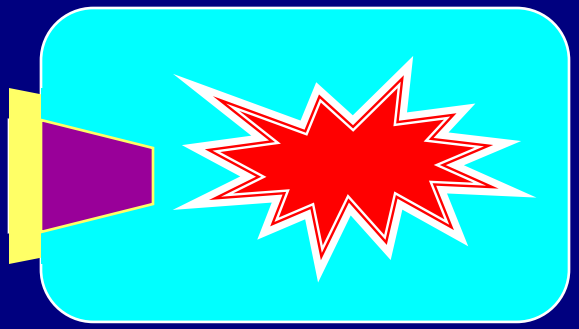
Agonist Receptor Interactions

Induced Fit





Receptor



Agonists

- Drugs that cause a response
- Drugs that interact with and activate receptors;
- They possess ***both affinity and efficacy***

Types

- **Full agonists**

  An agonist with maximal efficacy (response)

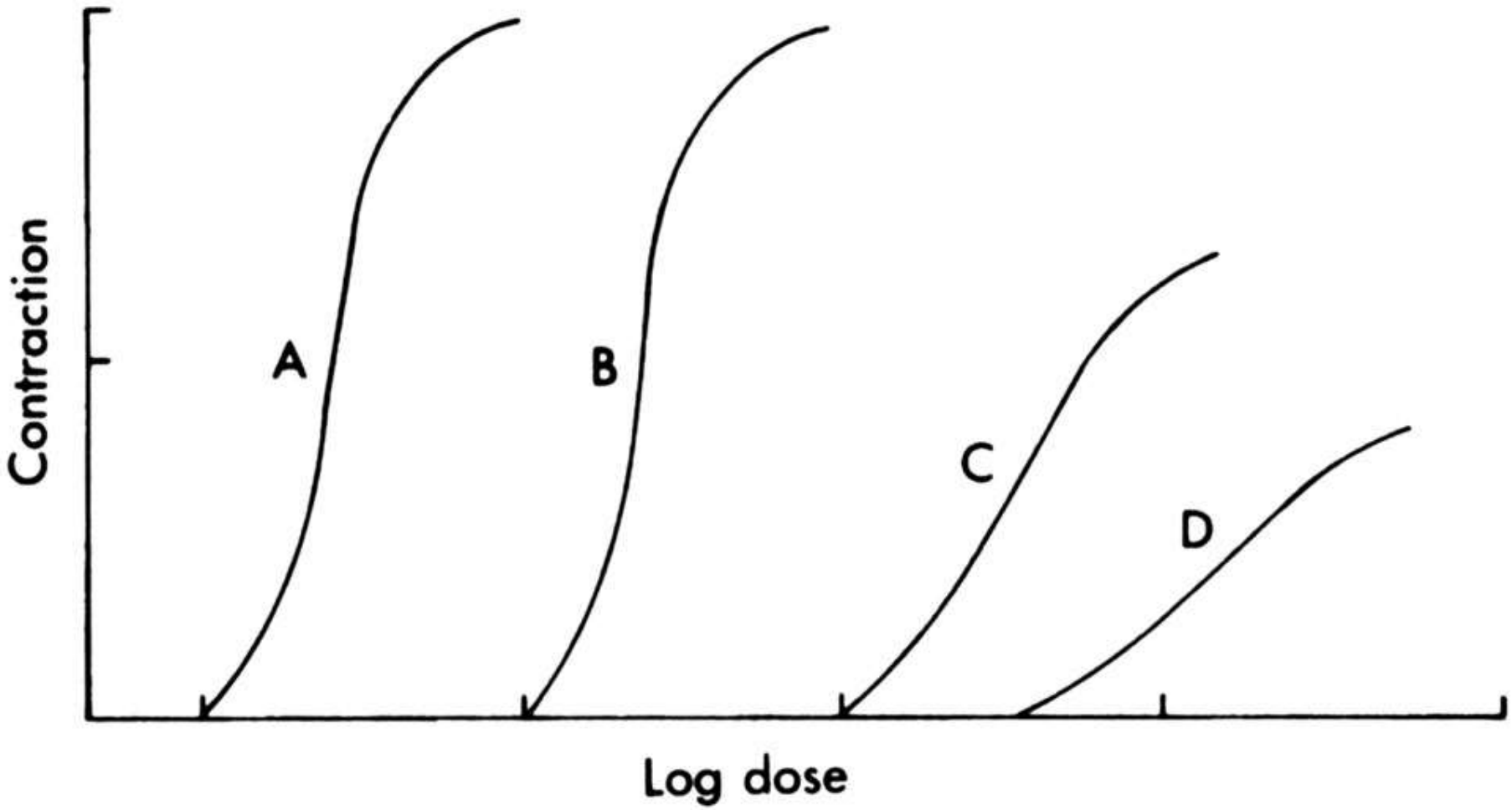
➢ **has affinity plus intrinsic activity**

- **Partial agonists**

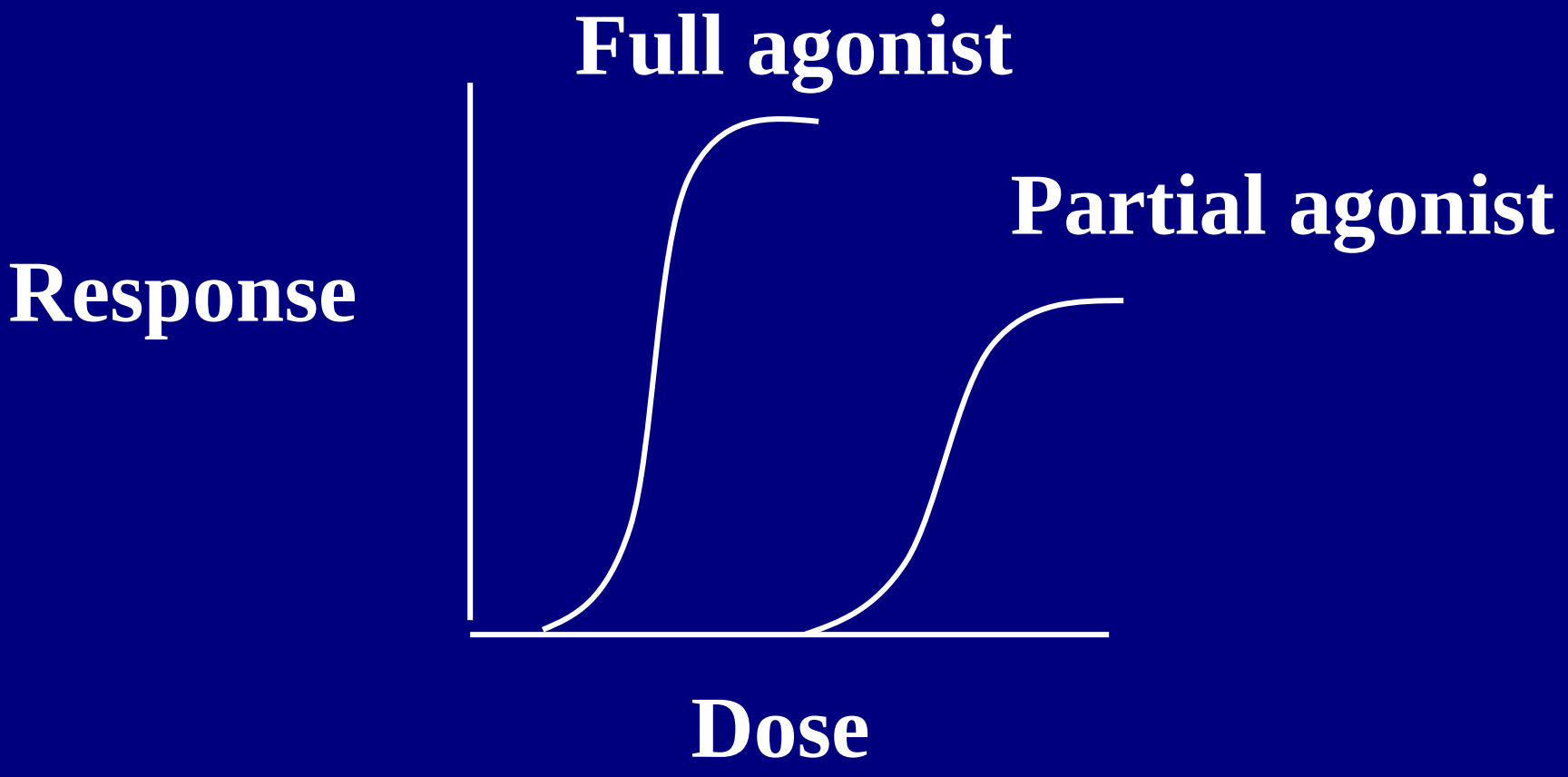
  An agonist with less then maximal efficacy

➢ **has affinity and *less* intrinsic activity**

Agonists differing in potency and maximum efficacy

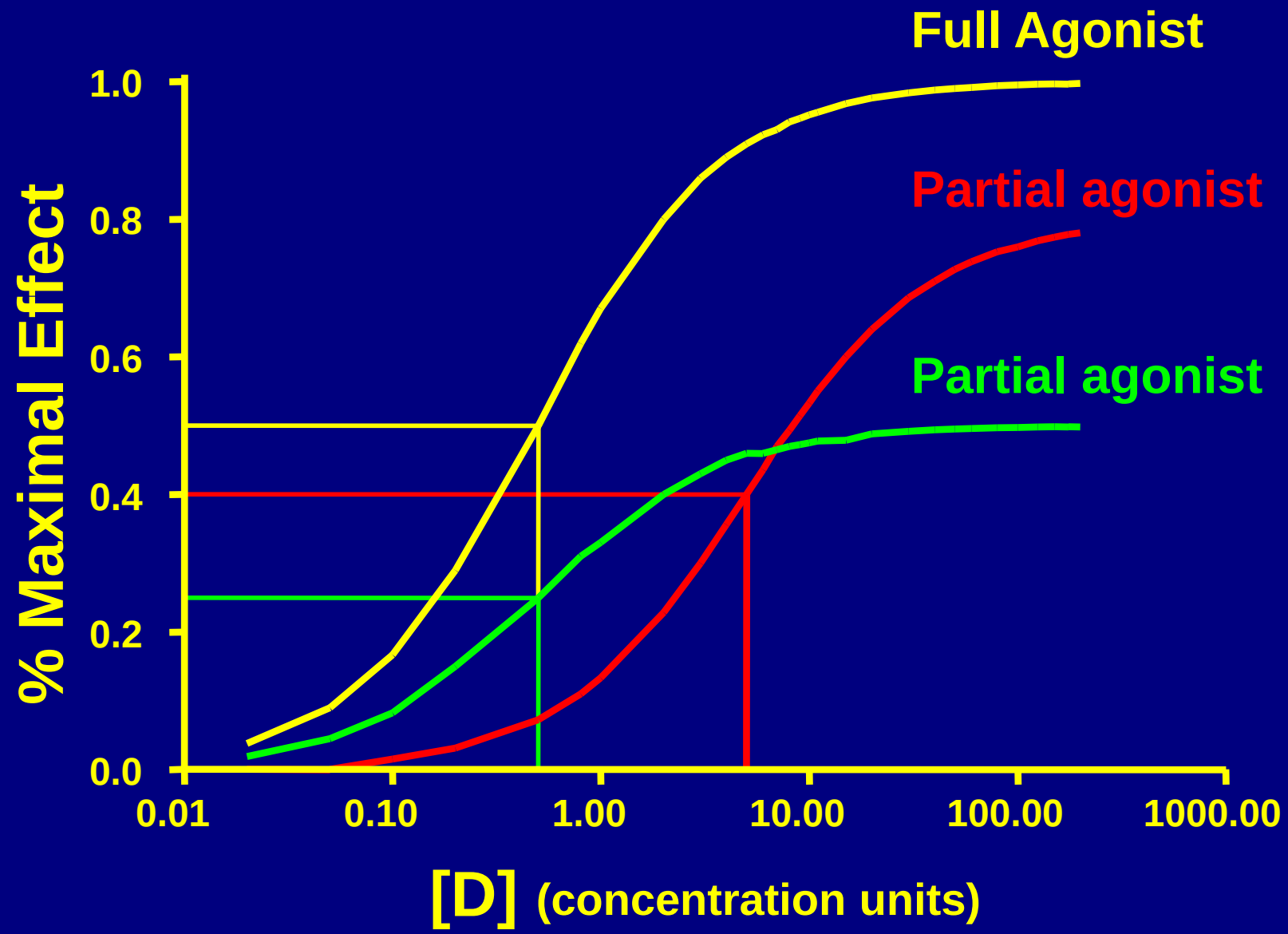


Agonist Dose Response Curves

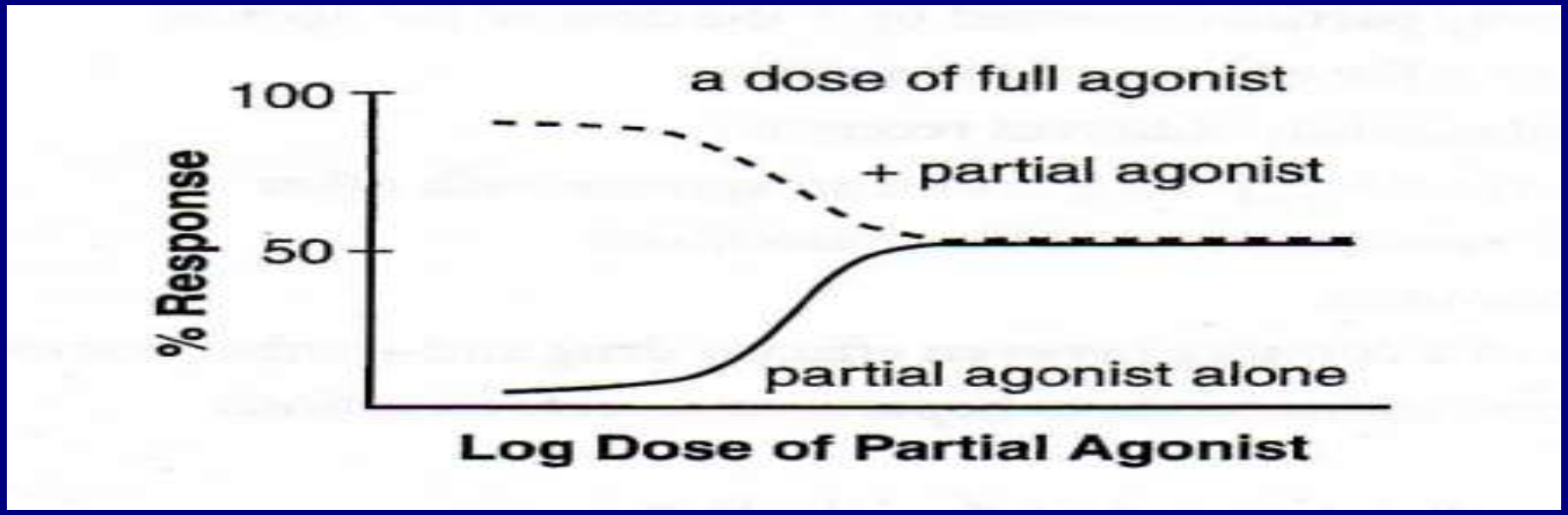


PARTIAL AGONISTS - EFFICACY

Even though drugs may occupy the same # of receptors, the magnitude of their effects may differ.



Agonist : Full VS Partial



Duality of Partial Agonists

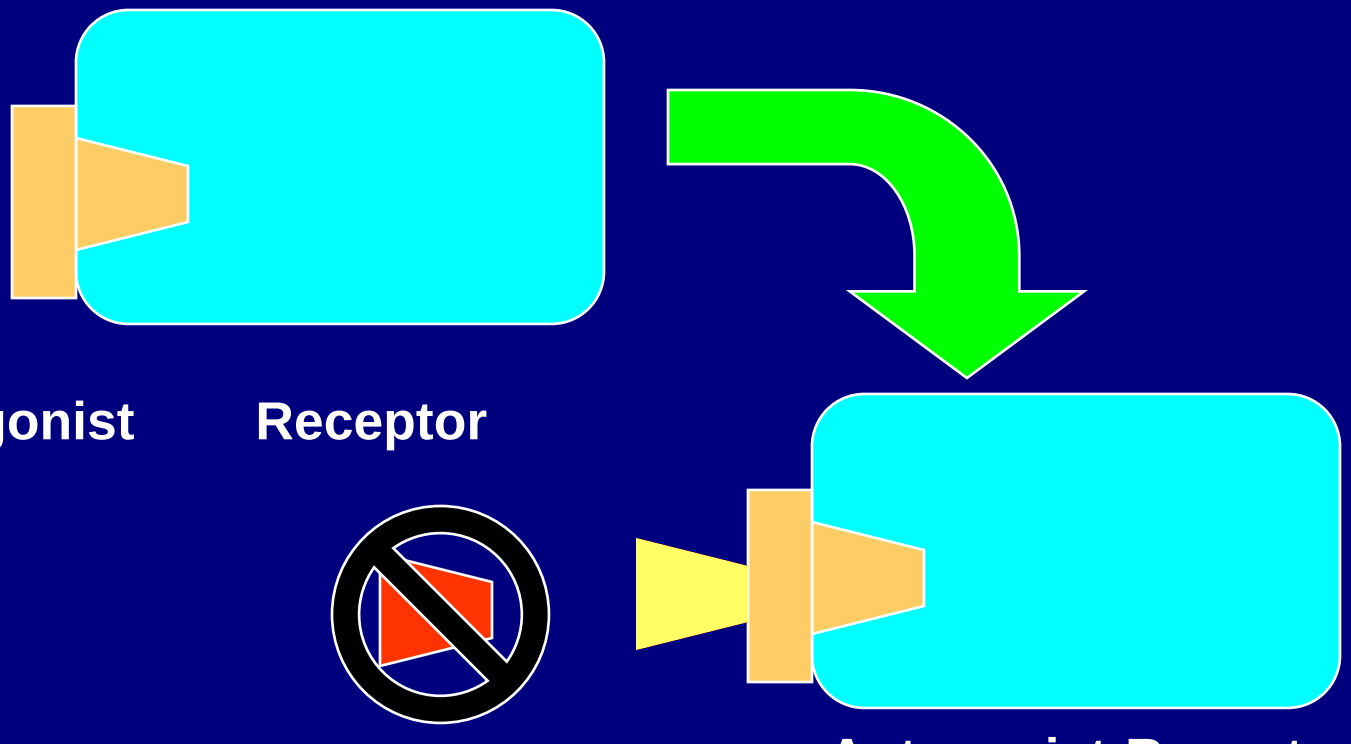
the partial agonist is acting as an antagonist .

Antagonists

- Interact with the receptor but do NOT change the receptor
- Have affinity but NO efficacy
- Block the action of other drugs
- Effect only observed in presence of agonist

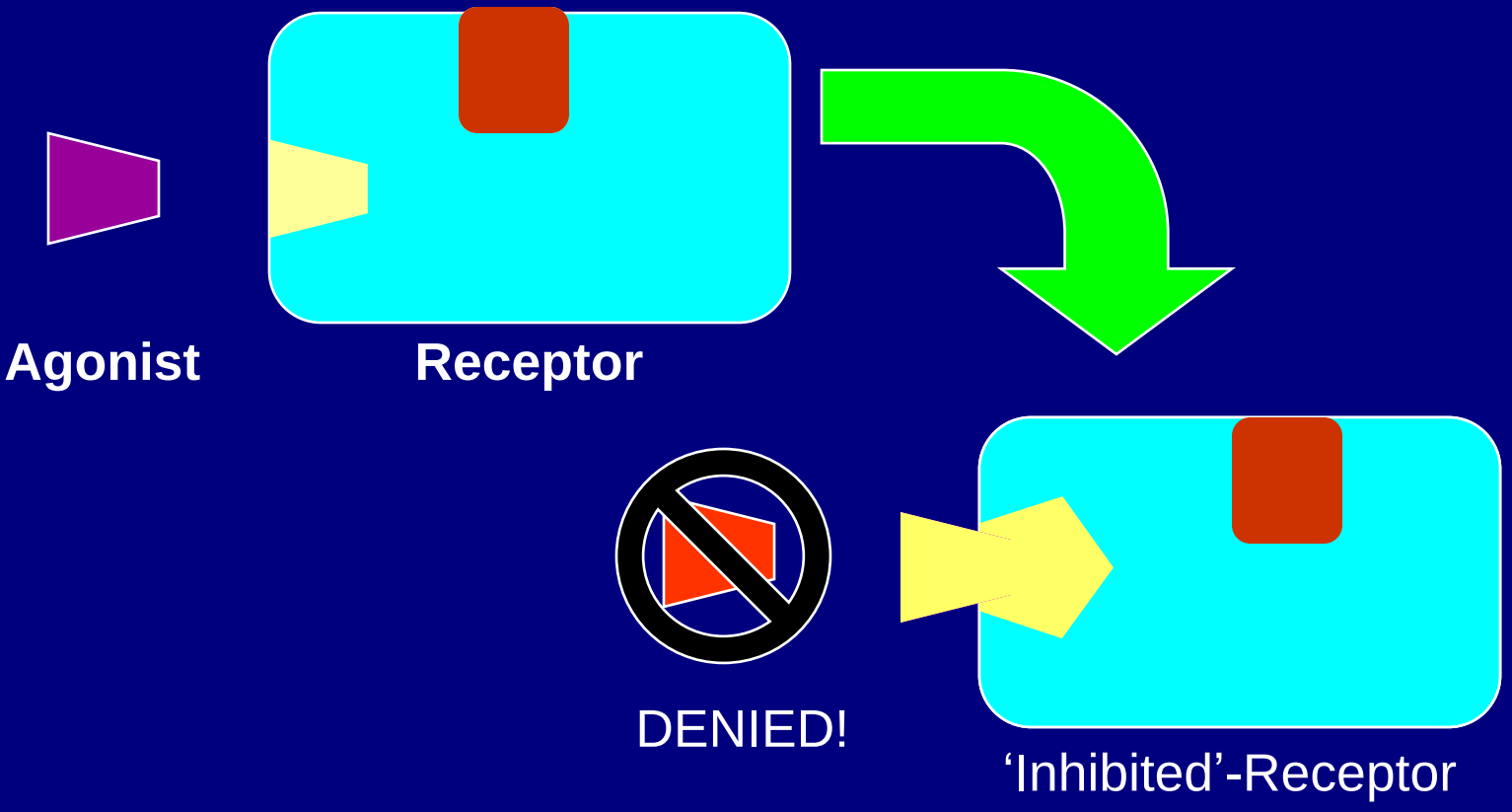
Antagonist-Receptor Interactions

Competitive Inhibition



Antagonist-Receptor Interactions

Non-competitive Inhibition

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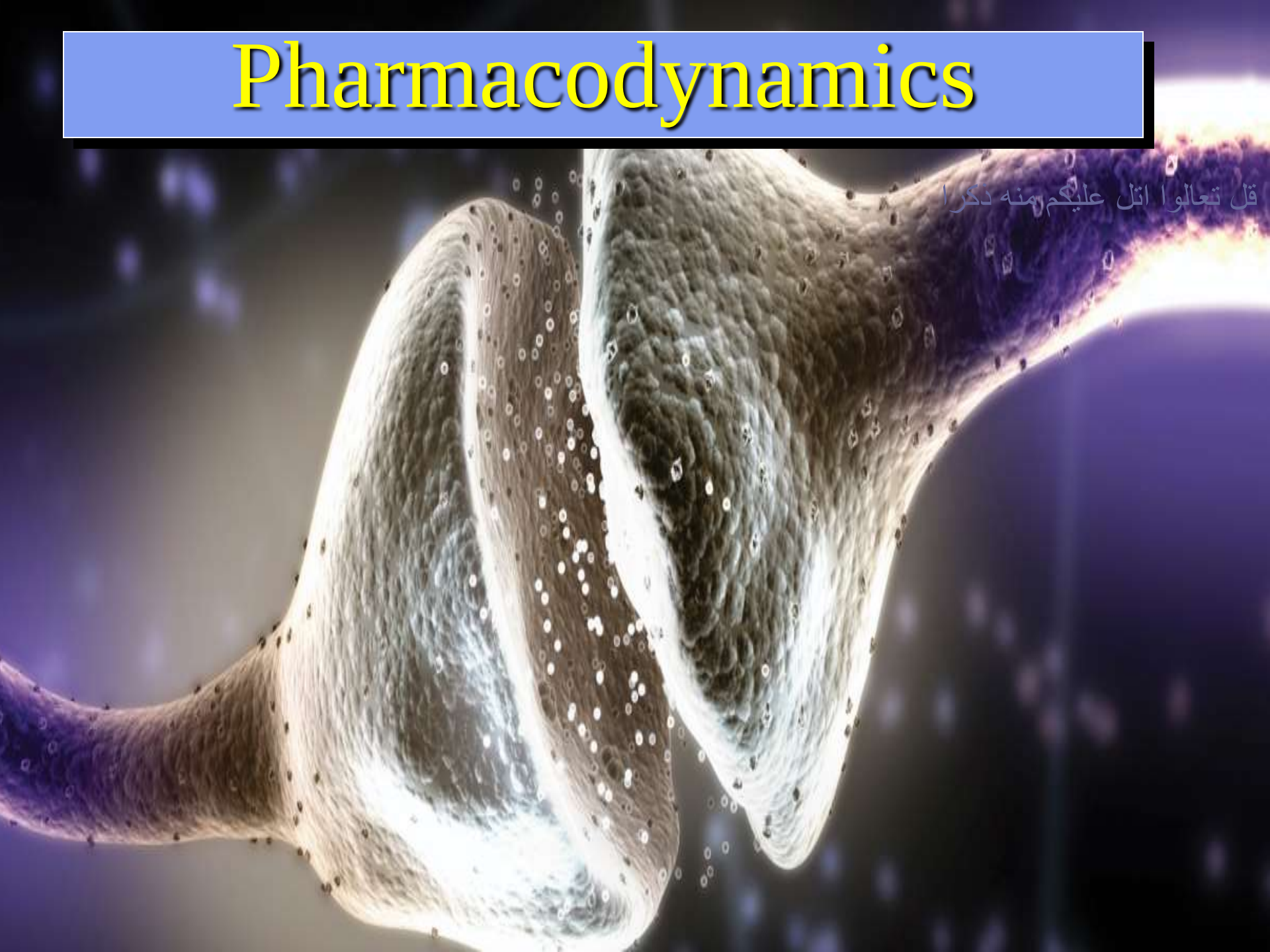
[سورة الروم]

Pharmacodynamics



Antagonists

Antagonist

- pharmacological (shared receptor),
  - competitive
  - noncompetitive
- physiological (acting on different systems having opposing physiologic responses),
- chemical

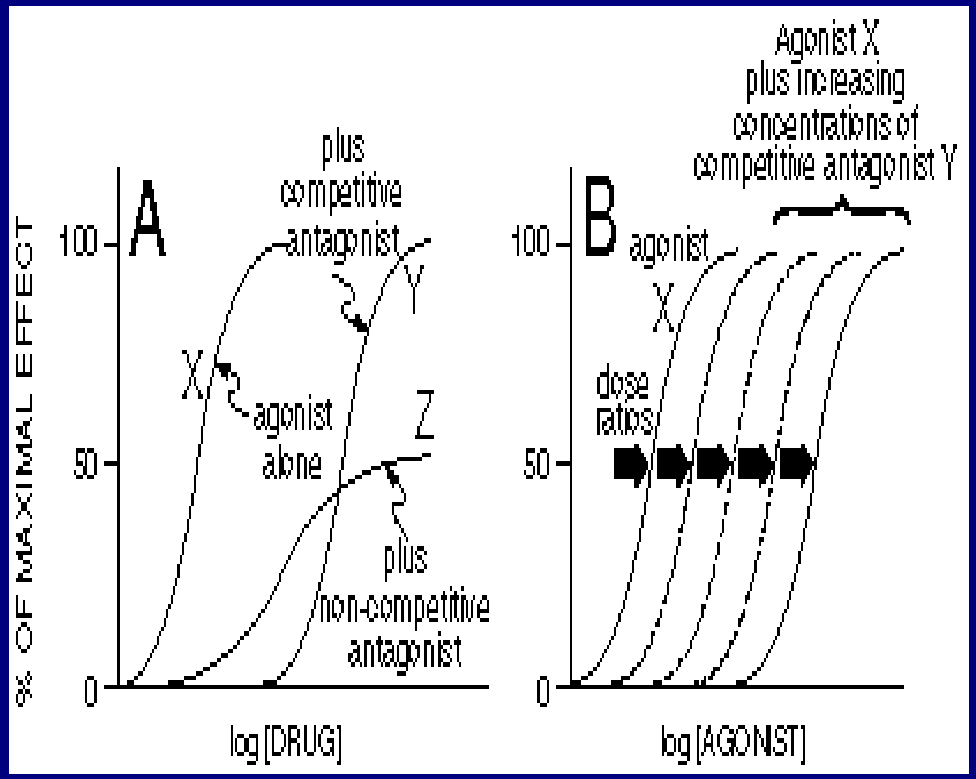
Types of Antagonists

Competitive (Surmountable)

decrease apparent Potency

Noncompetitive

decrease apparent maximum efficacy



Competitive Antagonist

- competes with _____for receptor
- **surmountable** with increasing agonist concentration
- displaces agonist dose response curve to the _____(dextral shift)
- reduces the apparent affinity of the _____.

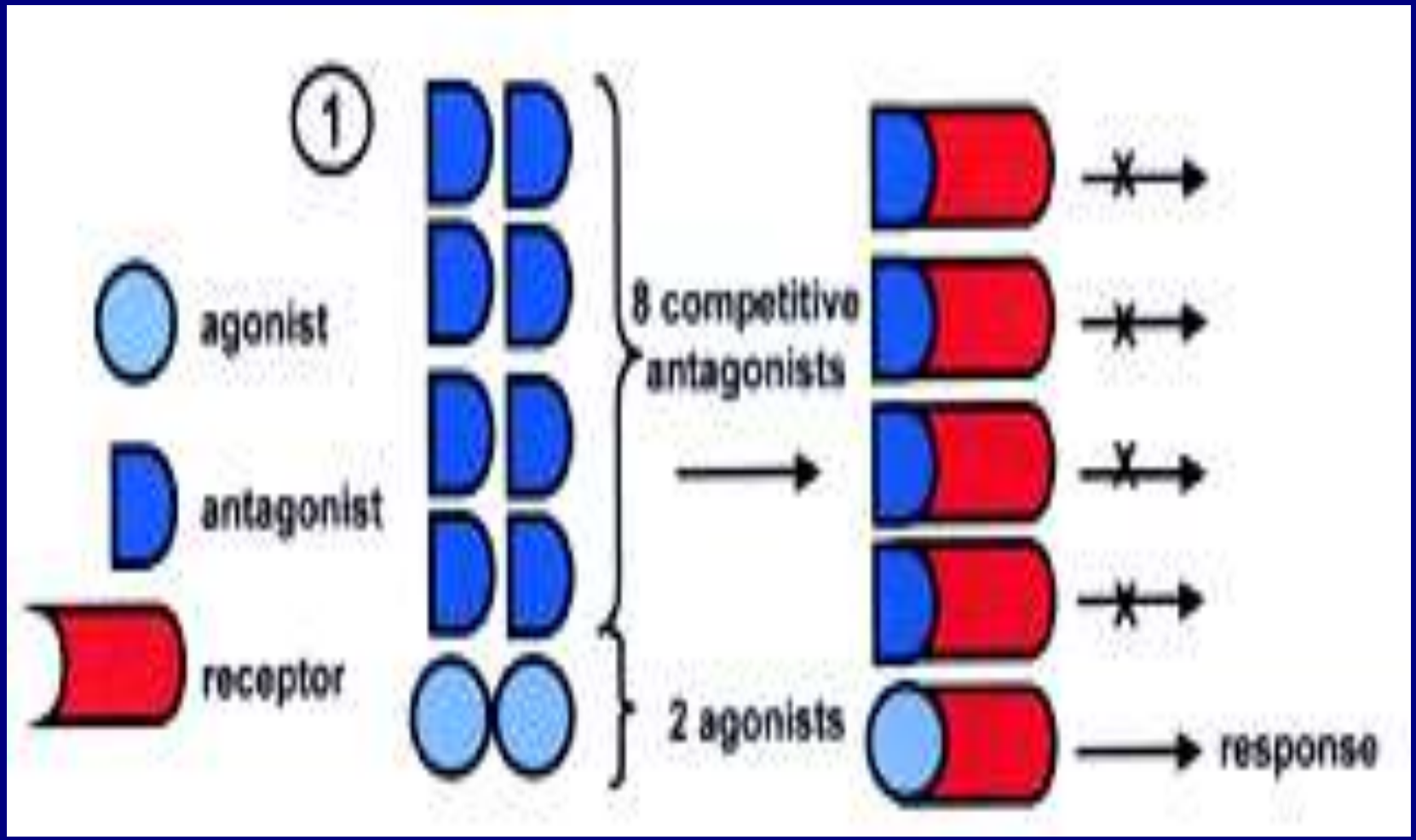
Noncompetitive Antagonist

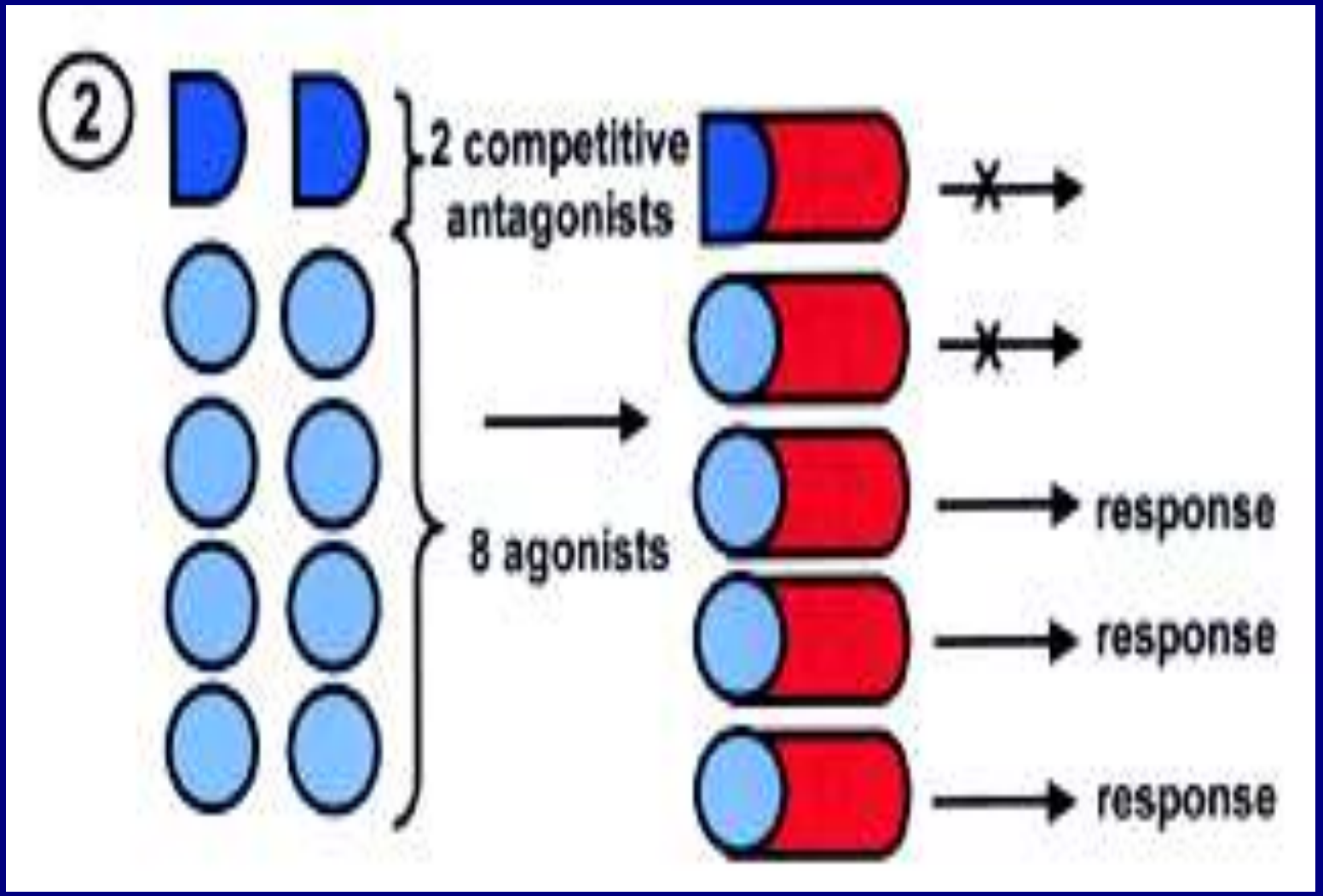
- drug binds to receptor and stays bound
- irreversible – does not let go of receptor

- produces slight dextral shift in the agonist DR curve in the low concentration range

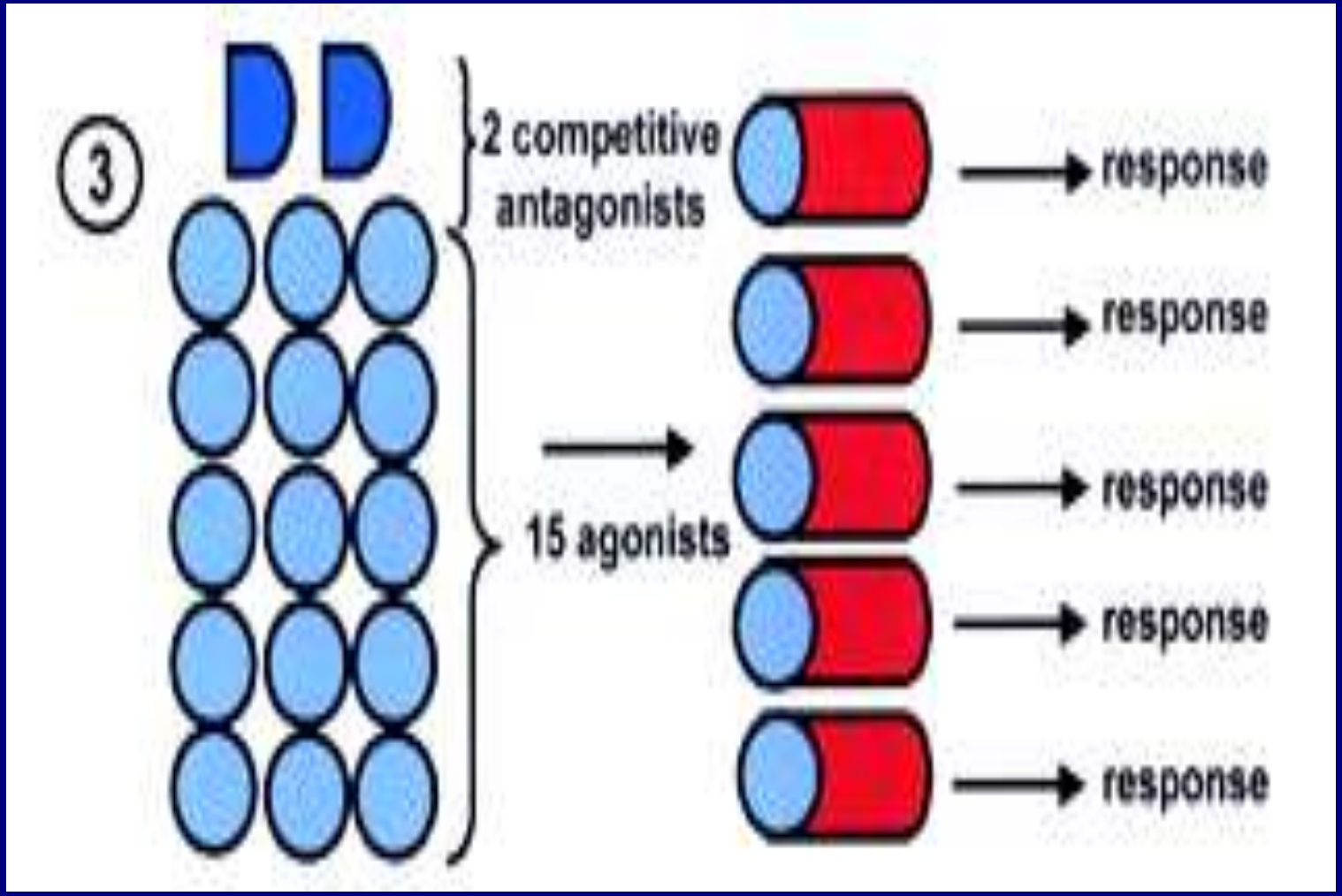
- but, as more and more receptors are bound (and essentially destroyed),
- the agonist drug becomes incapable of eliciting a maximal effect

AGONIST VS ANTAGONIST

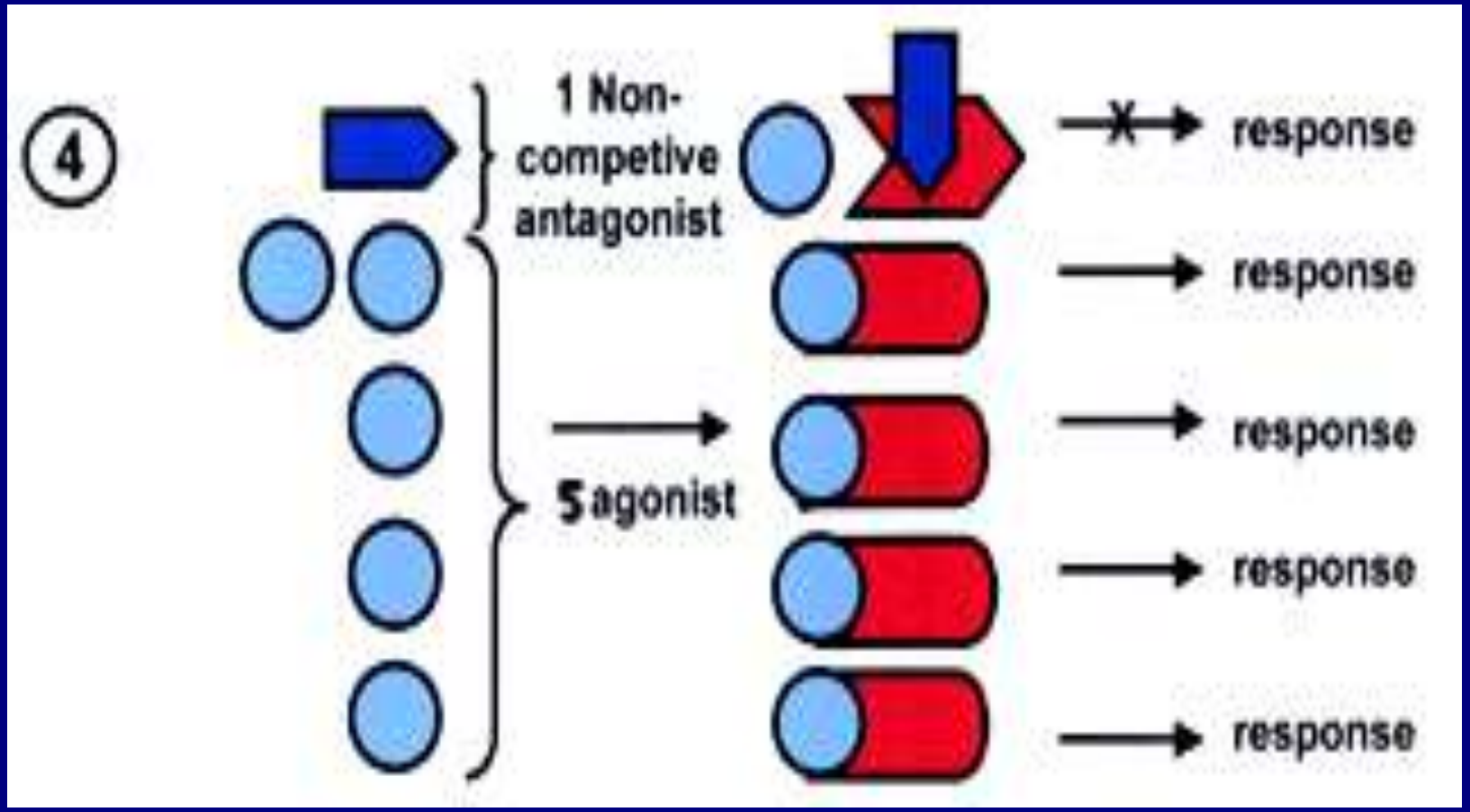



2
2 competitive antagonists
8 agonists
response
response
response

What happen when you increase agonist concentration even higher



How do non competitive antagonist affect receptor function



Physiologic antagonism (different receptor)

Two agonists with opposing action antagonize each other - Example :

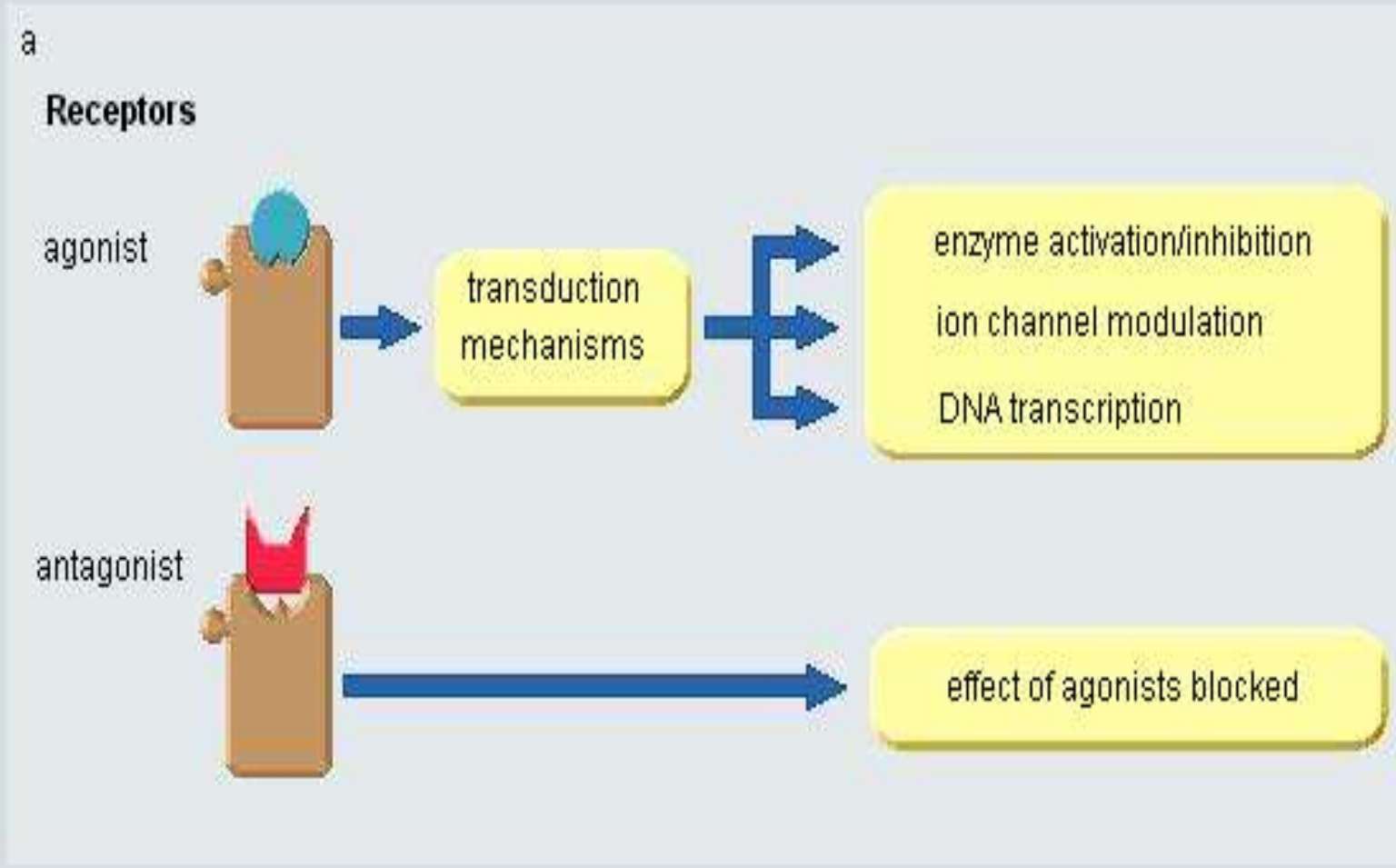
•Adrenaline antagonizes the effect of endogenous histamine on blood vessels and bronchial smooth muscle when used in the treatment of anaphylactic shock.

Chemical antagonism

-The antagonist combines with the agonist away from the receptor, preventing the action of the agonist at this target receptor or tissue.

-Formation of a complex between effector drug and another compound e.g.

- Alkaline antacids neutralise gastric HCl in peptic ulcer;
- Protamine sulphate (base) neutralises the acidic compound heparin preventing its action in overdose.

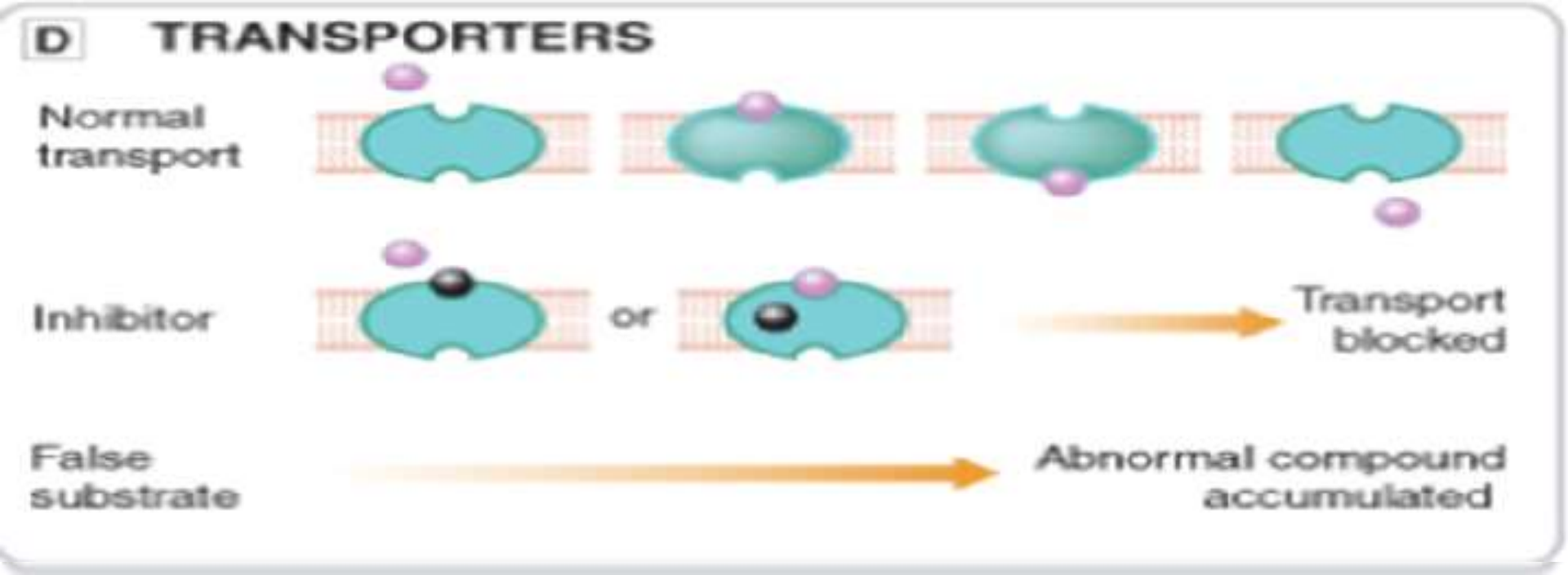

a
Receptors
agonist
transduction mechanisms
enzyme activation/inhibition
ion channel modulation
DNA transcription
antagonist
effect of agonists blocked

QZ

(T or F)

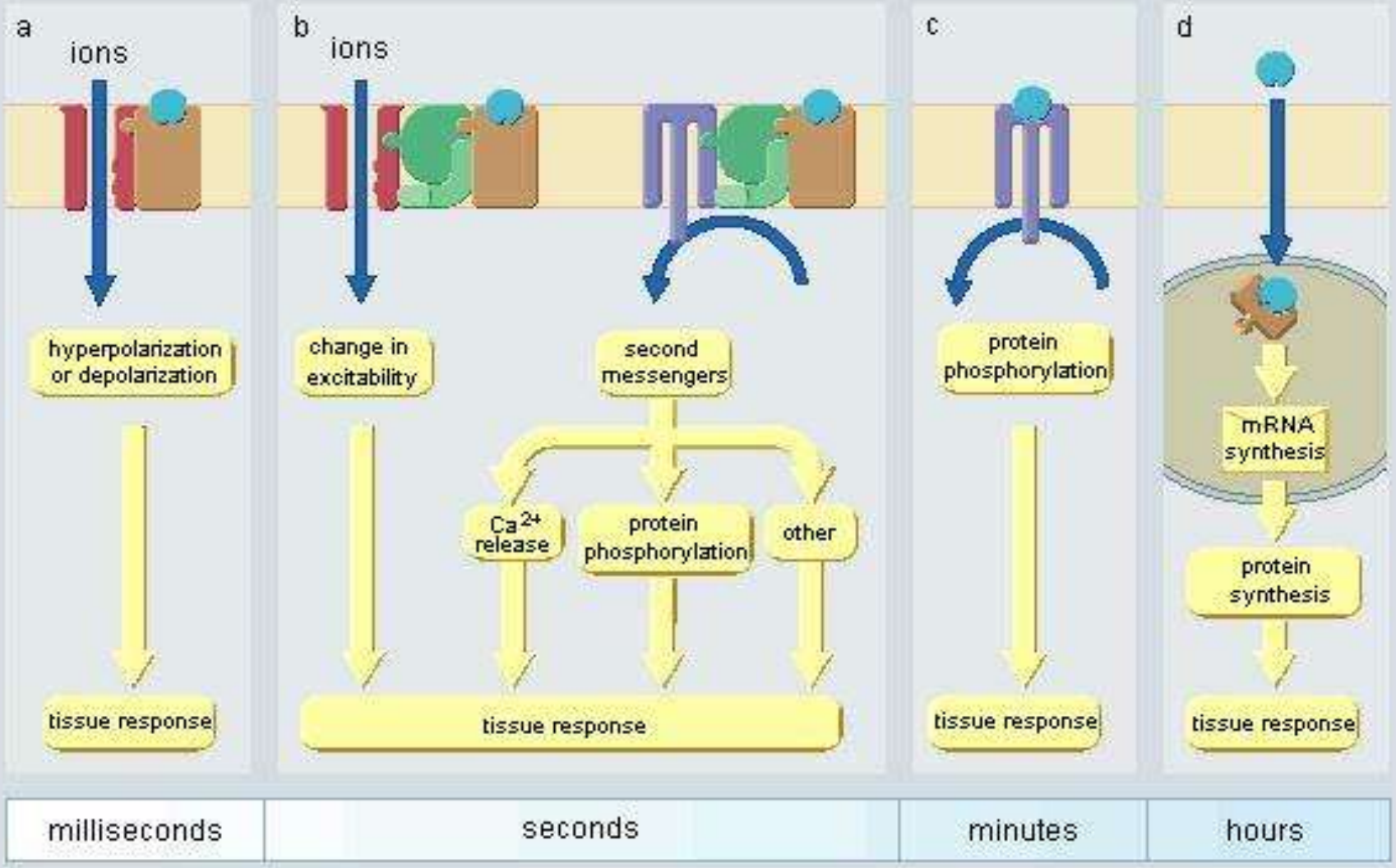
- Pharmacodynamics is the study of absorption, distributio metabolism and elimination of drug.
- Some drugs can act without binding to a receptor
- spare receptors allow maximum response without full receptor occupancy
- Efficacy is the amount of drug needed to produce an effect.
- Affinity is the attractiveness between 2 drug molecules.
- Agonist are the drugs that block the response.
- Partial agonist has affinity and maximum efficacy.
- Antagonist has efficacy but no affinity.
- Competitive antagonist decreases potency
- Non competitive antagonist decreases efficacy

Drugs may act by different mechanisms

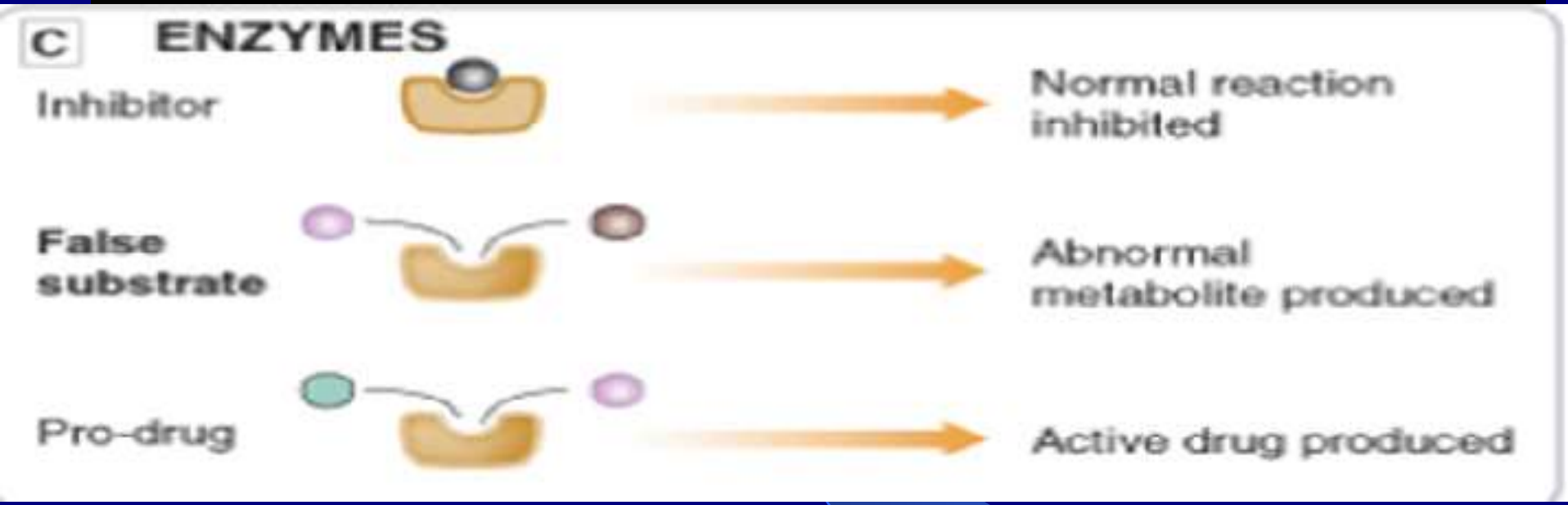


<u>RECEPTOR INTERACTION</u> – Many drugs act by activating or blocking a receptor. Receptors are chemical components mostly on the surface of the cell.

Receptor


a
ions
hyperpolarization or depolarization
tissue response
b
ions
change in excitability
second messengers
Ca2+ release
protein phosphorylation
other
tissue response
c
protein phosphorylation
tissue response
d
mRNA synthesis
protein synthesis
tissue response
milliseconds
seconds
minutes
hours

Drugs may act by different mechanisms



<u>ENZYME INHIBITION</u> – e.g. monoamine oxidase (deprenyl), cholinesterase (neostigmine), cyclooxygenase (aspirin).

Drugs may act by different mechanisms

CHEMICAL INTERACTION – e.g. gastric acid (antacids), heparin (protamine sulphate), alkylating agents.

PHYSICO-CHEMICAL PROPERTIES – e.g. osmotic diuretics, laxatives, volatile anesthetics.

Parallel and Nonparallel D-R Curves

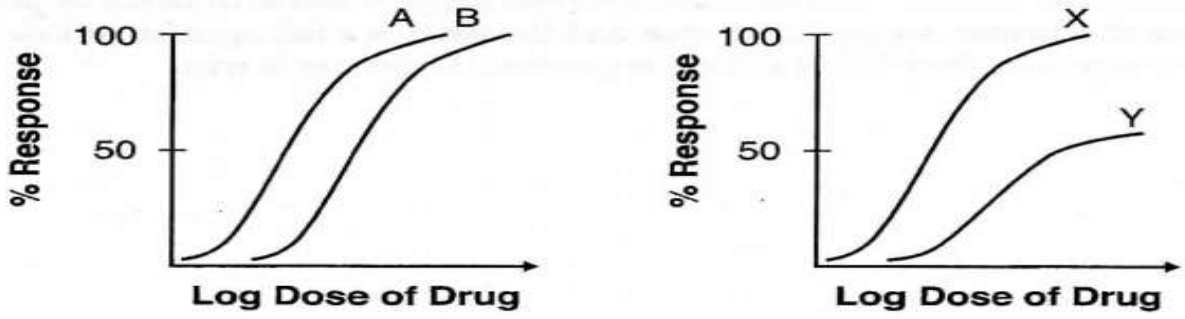
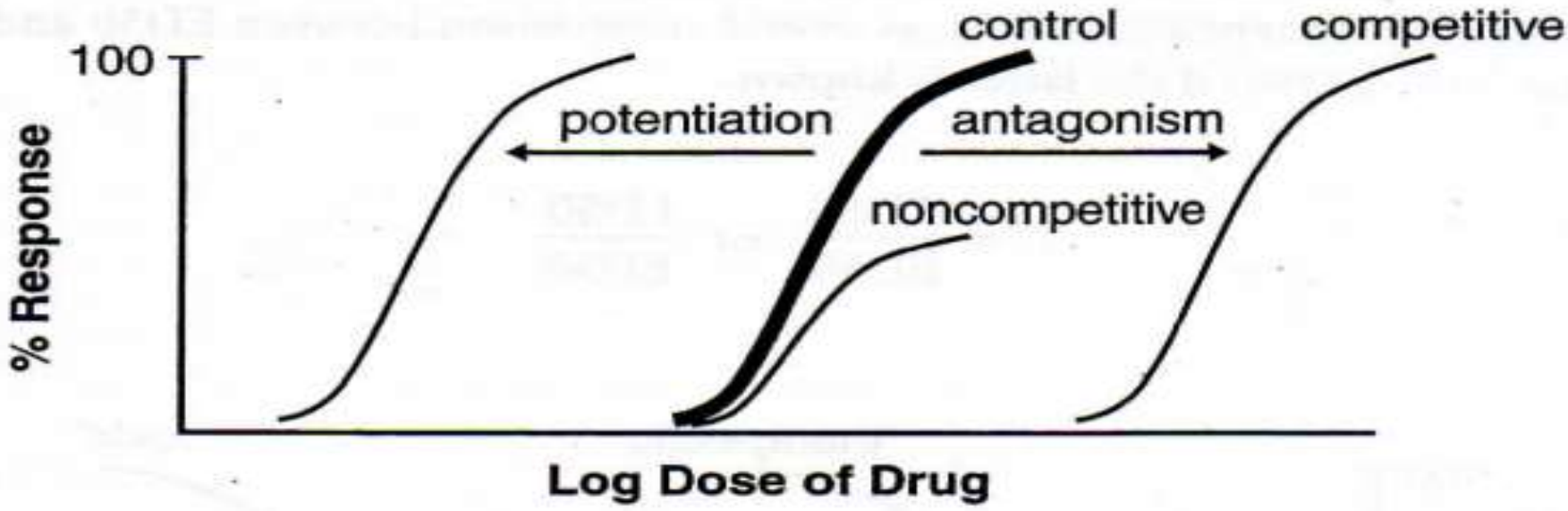


Figure I-2-1. Comparison of D-R Curves for Two Drugs Acting on the Same (*left panel*) and on Different (*right panel*) Receptors

Affinity can be compared only when two drugs bind to the same receptor .Drug A has a greater affinity than drug B.

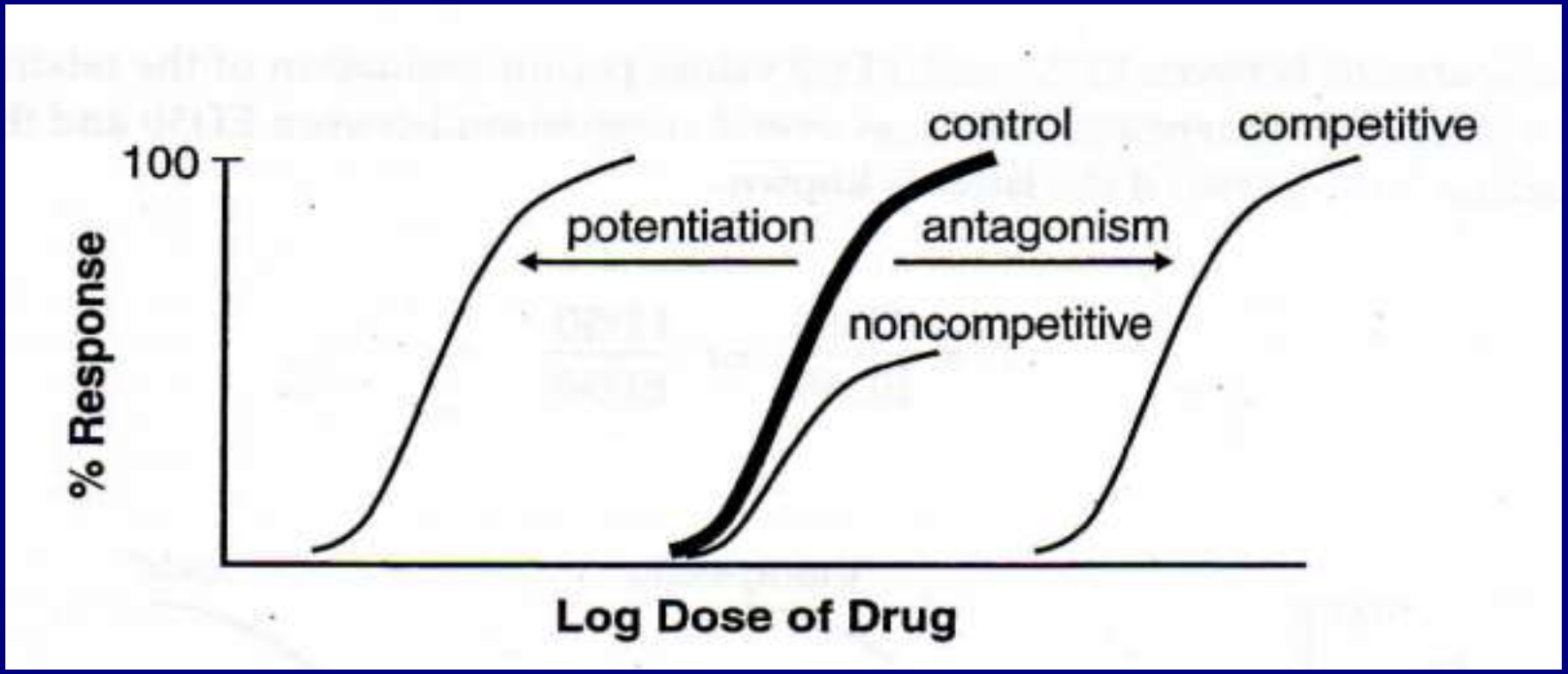
In term s of potency ,
drug A has greater potency than drug B, and X is more potent than Y.

In term s of efficacy,
drug s A and B are equivalent . Drug X has greater efficacy than drug Y.



Antagonism and Potentiation

• Graded dose-response curve s also provide information about antagonists—drugs that interact with receptors to interfere with their activation by agonists .

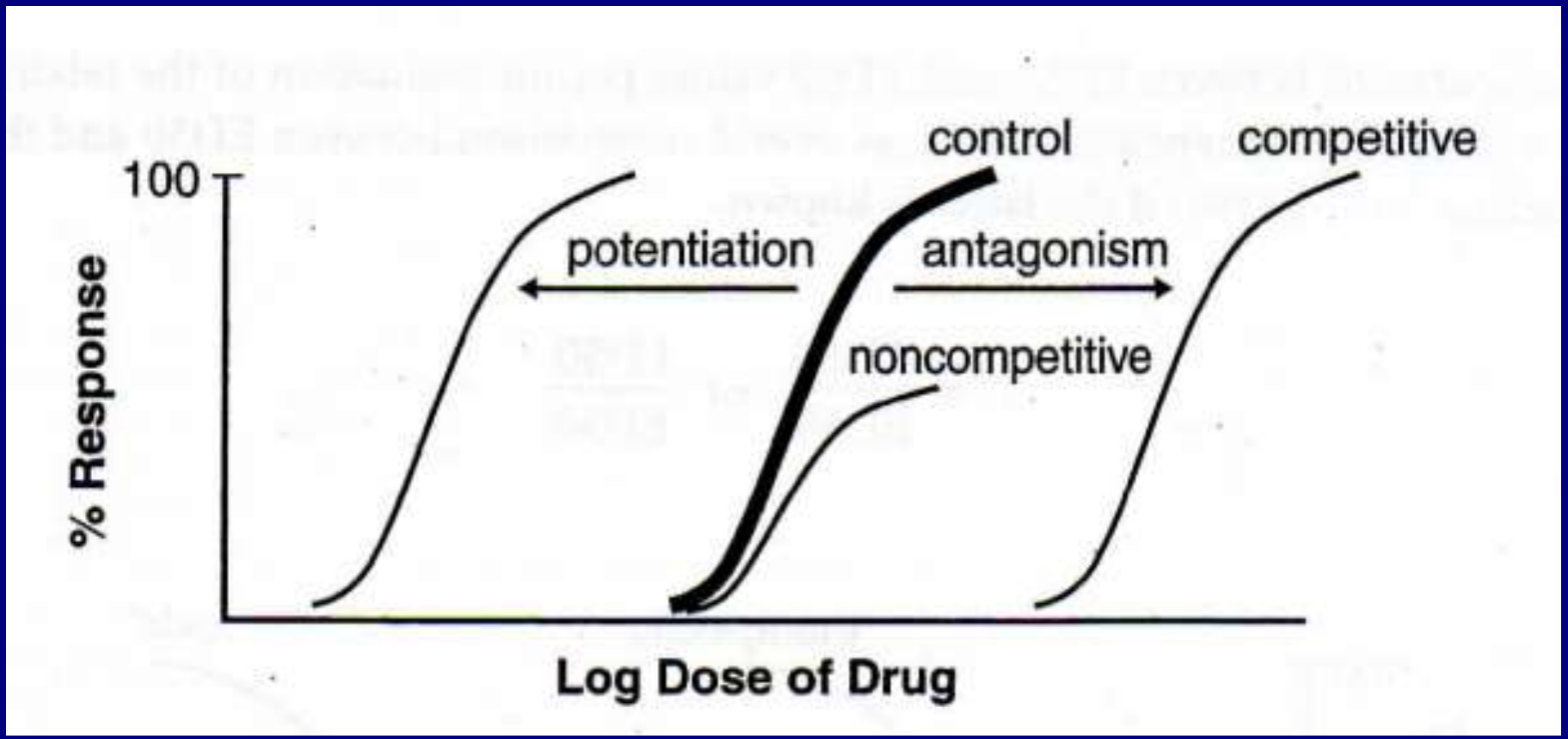


Pharmacologic antagonism (same receptor)

Competitive antagonists :

- Cause a parallel shift to the right in the D-R curve for agonists
- Can be reversed by increase the dose of the agonist drug

- Appears to decrease *the potency of the agonist*



Pharmacologic antagonism (same receptor)

Non competitive antagonists :

- Cause a nonparallel shift to the right
- Can be only partially reversed by increase the dos e of the agonist
- Appear to decrease the efficacy of the agonist

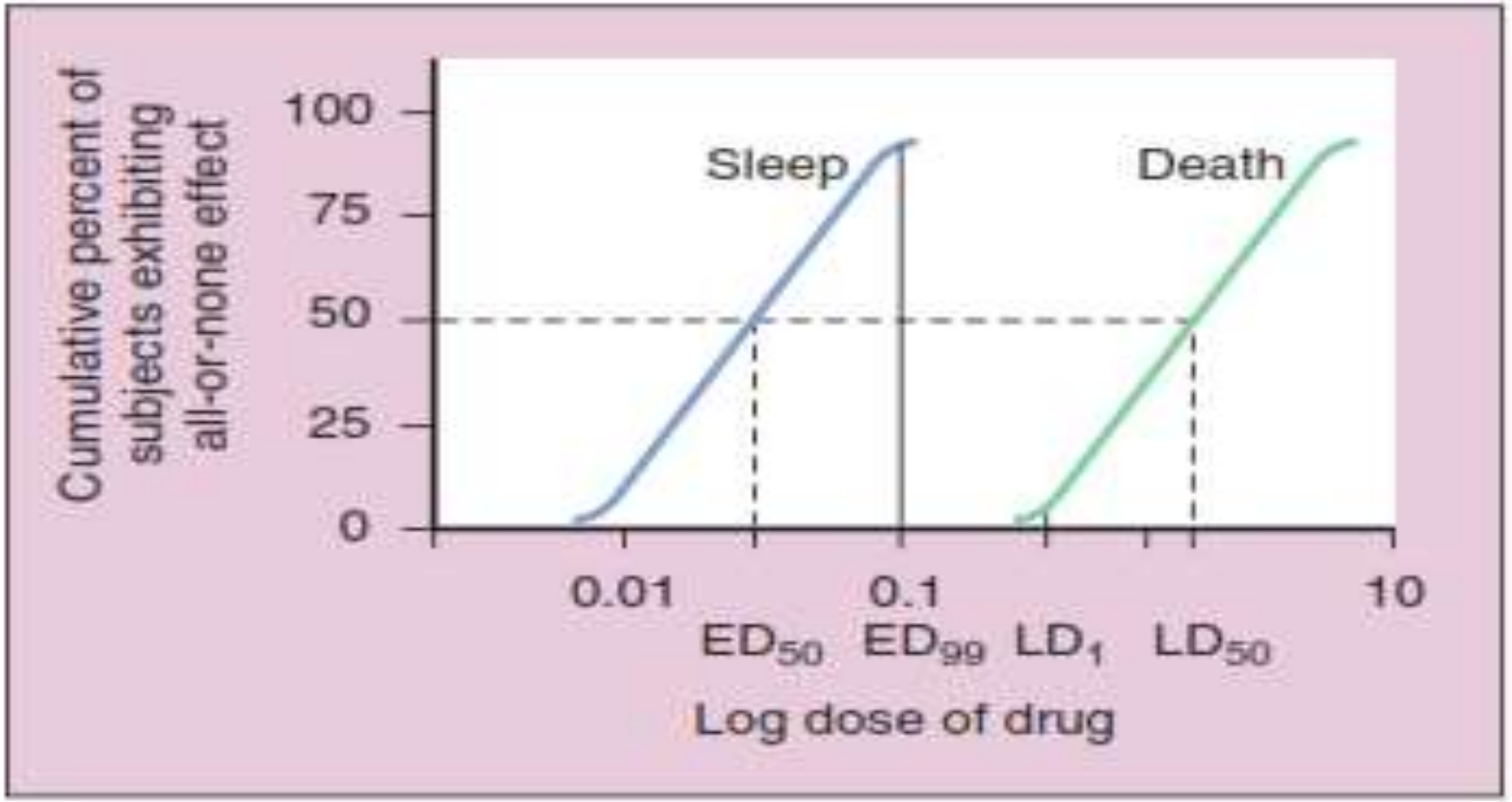


FIGURE 3-6. Quantal dose-response relationships. The dose-response curves for a therapeutic effect (sleep) and a toxic effect (death) of a drug are compared. The ratio of the LD_{50} to the ED_{50} is the therapeutic index. The ratio of the LD_1 to the ED_{99} is the certain safety factor. *ED*, Effective dose; *LD*, lethal dose.

Receptor Regulation

1. Homeostasis

2. Up regulation and
   Down regulation ,
   Desensitization ,
   Tolerance

Receptor Regulation

Persistent exposure to agonist ⇨ tissue receptors numbers decrease probably associated with a loss of receptors from the cell surface due to endocytosis or internal uptake

DOWN REGULATION

decrease in the observed response

Tolerance or desensitisation or Tachyphylaxis

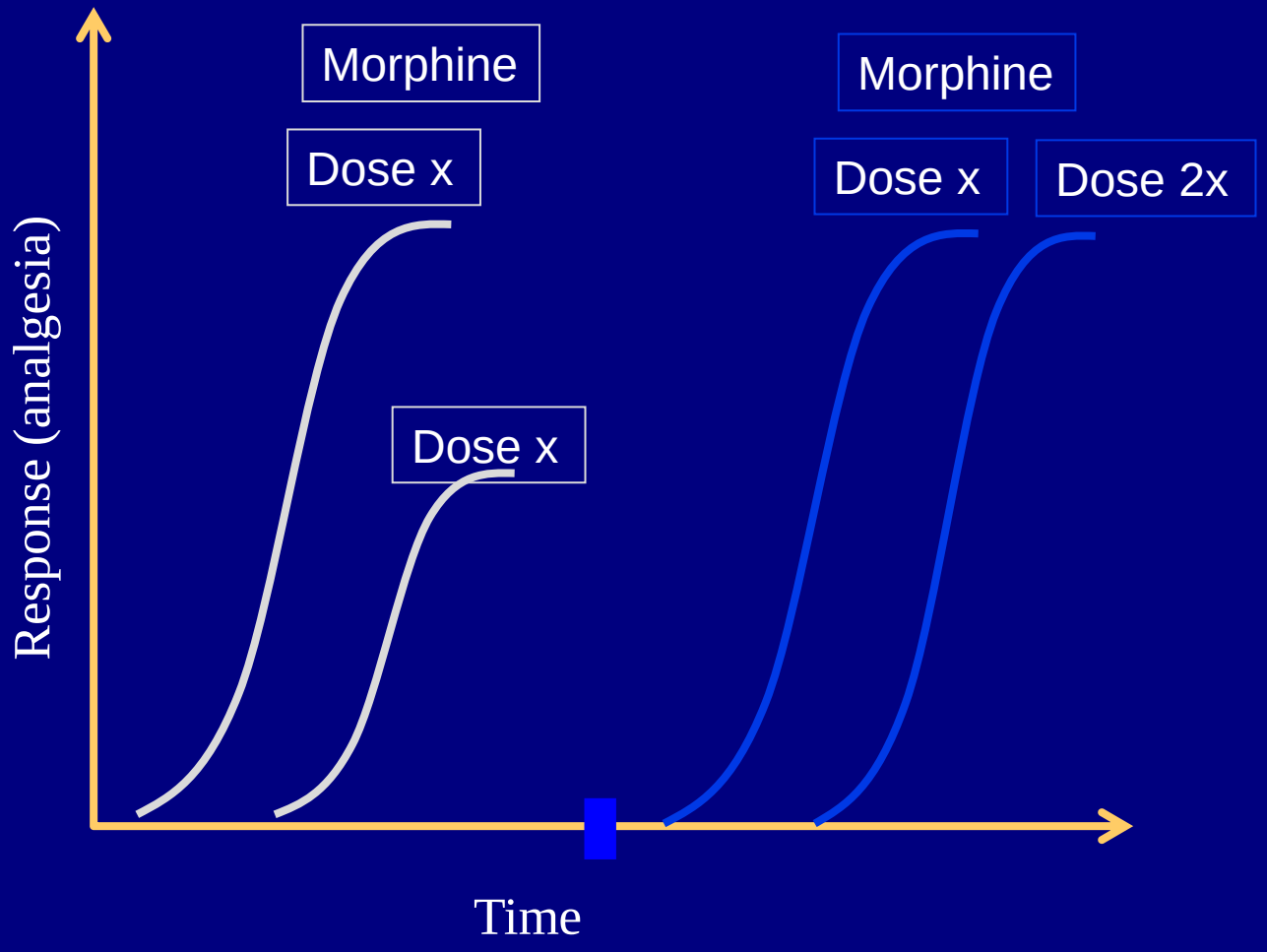
(e.g. morphine)

Tolerance or Desensitisation

The continual administration of drugs sometimes leads to ; a progressive decrease in the observed response

This occurs when increasing amounts of **opiates** (e.g. morphine) , salbutamol ,are required to achieve the same effect.

Tolerance or Desensitisation



Types of tolerance

Pharmacodynamic tolerance

Salbutamol , Morphine

Pharmacokinetic tolerance

Carbamazepine and Alcohol

Tachyphylaxis

(Acute tolerance) is a similar mechanism that develops more rapidly.

This clinically can occur to

- **Lysergide (LSD)**
- **Steroid cream in sever dermatological condition**
- **Local anesthetics (lidocaine) upon repeated administration**
- **Vasopressin** causes smooth muscle stimulant effect (in large non physiological doses).
- **Nor adrenaline when attempting to maintain raised blood pressure in some patients with shock (angiotensin II is suitable in this condition).**
- **Gonadorelins** (GnRH analogues, e.g. goserelin)

Receptor Regulation.

Persistent exposure to antagonist ⇨ tissue receptors numbers increase

UP REGULATION

increase in the observed response

Super sensitivity

rebound phenomina

e.g.(*rebound phenomenon* after clonidine or β-blockers like propranolol)