

COMBINED EFFECTS OF DRUGS



Deepankar Ratha
Assistant Professor
Department of Pharmacology
CUTM, Rayagada

Protocol:



Summation

Additive effects

Synergism

Drug antagonism

EFFECT OF COMBINATION OF DRUGS

Combinations of two/ more drugs, simultaneously or in quick succession

1. No interference with each other's effects.
2. May oppose each other's actions (antagonism)
3. May produce similar actions on the same organ (synergism)





Interaction



Pharmacokinetic

Pharmacodynamic



Drug Synergism

Syn-together ; ergon-work

Drug Synergism:



This is facilitation of the effects of one drug by another when given together

Types:

- a. *Additive (summation)*
- b. *Supra-additive (Potentiation)*

Summation / Addition



Effect of drugs A + B = Effect of drug A + Effect of drug B

- Final effect is same as the algebraic sum of the magnitude of individual drugs
- Side effects do not add up

Examples of Summation: Different MOA

Aspirin : (-) PGsynthesis \square analgesia +
Codeine : Opioid agonist \square analgesia +

} Analgesia
++

Examples of Addition: Same MOA

Ibuprofen: (-) PGsynth \square analgesia +
Paracetamol: (-) PGsynth \square analgesia +

} Analgesia
++

Other **Additive** Drug Combinations



Drug Combination	Effect
Amlodipine + Atenolol	Antihypertensive
Glibenclamide + Metformin	Hypoglycemic

Supraadditive (Potentiation)



Effect of drug A+ B > Effect of drug A+ Effect of drug B

When two drugs are given together the final effect is much more than the simple algebraic sum of the magnitude of individuals drugs.

Examples:

Sulphamethoxazole & Trimethoprim--- sequential blockade of two steps in synthesis of folic acid in micro-organisms.

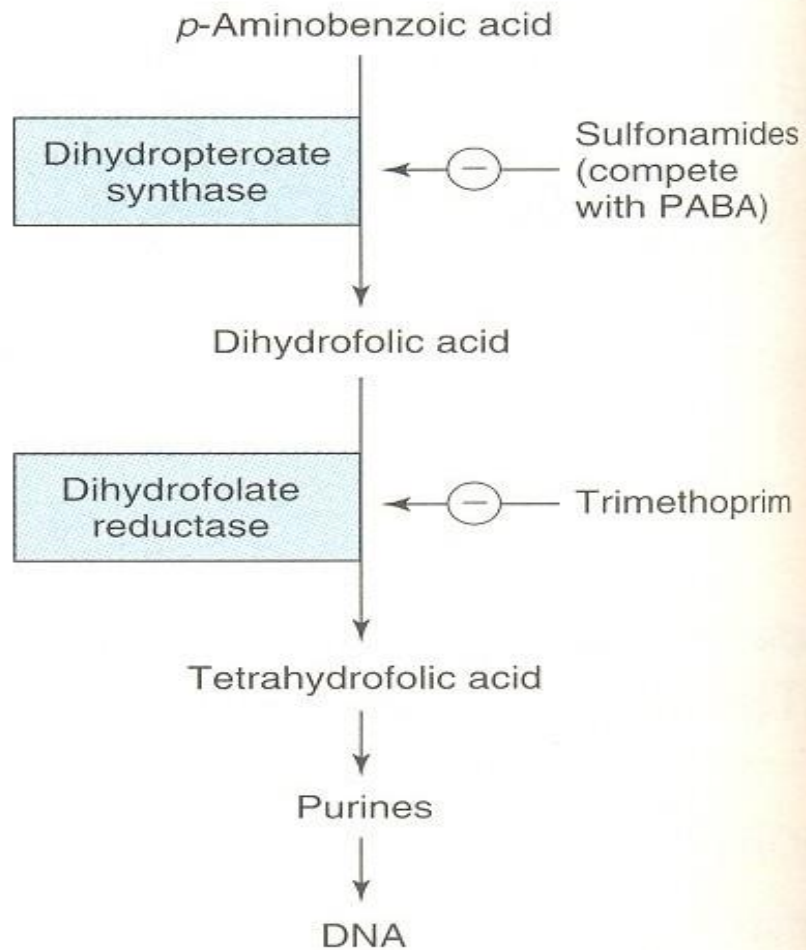
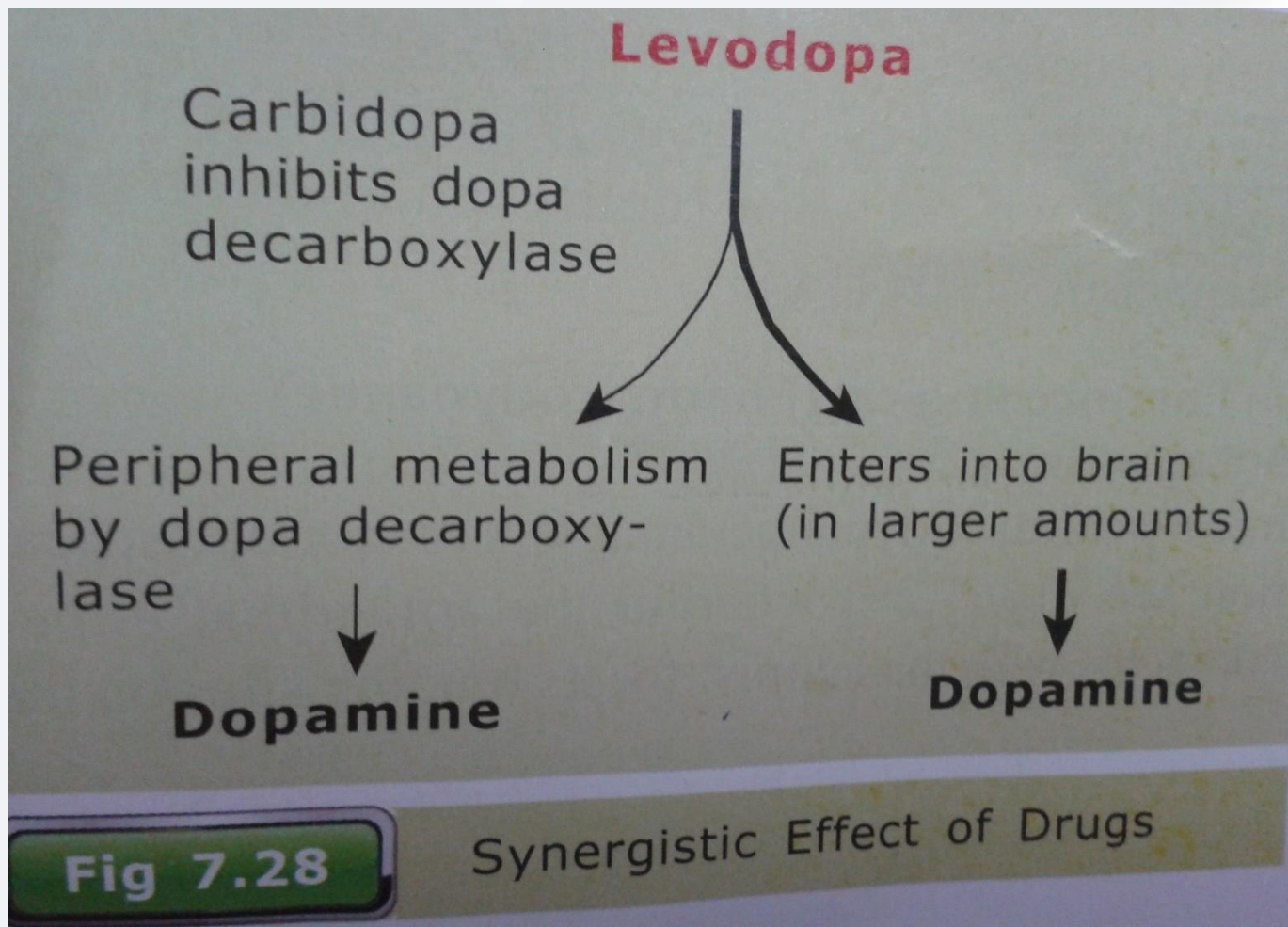


Figure 46-2. Actions of sulfonamides and trimethoprim.

Synergism by altering Pharmacokinetics of the other:



- Levodopa + Carbidopa



Other supraadditive drug combinations



DRUG PAIR

BASIS OF POTENTIATION

Ach + Physostigmine

Inhibition of break down

Adrenaline + Cocaine

Inhibition of neuronal uptake

Tyramine + MAO inhibitors

Increasing releaseable CAT store

Drug Antagonism



Drug Antagonism

Definition:

Combined effect of two drugs is less than the sum of the effects of the individual drugs

Effect of drugs $A + B < \text{Effect of drug } A + \text{Effect of drug } B$

One drug decreases / opposes / reverses / counters the effect of other drug by different mechanisms





Types:

- a. Pharmacological Antagonism :
 - i. Competitive (Reversible)
 - ii. Non-competitive (Irreversible)
- b. Chemical Antagonism
- c. Physiological Antagonism
- d. Physical antagonism

Pharmacological Antagonism:

PHARMACODYNAMIC ANTAGONISM

Competitive

Non Competitive

Reversibly competitive Irreversibly competitive Pseudo-reversibly competitive

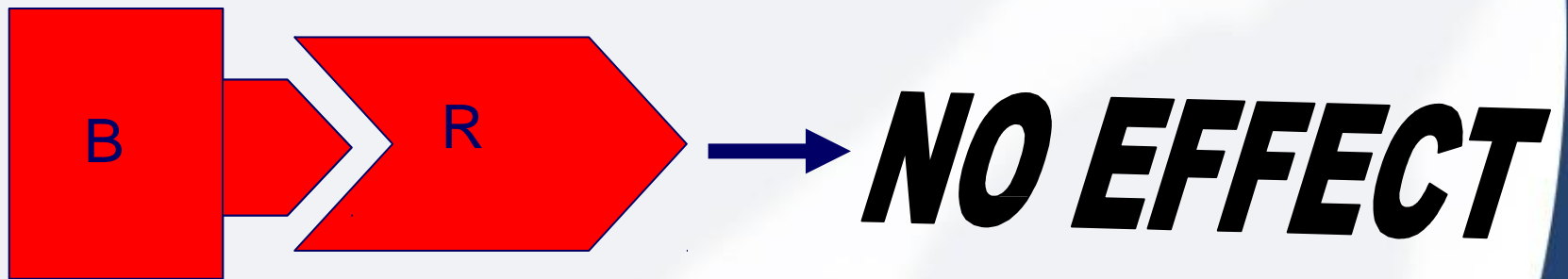
Interfere "Down-stream events"

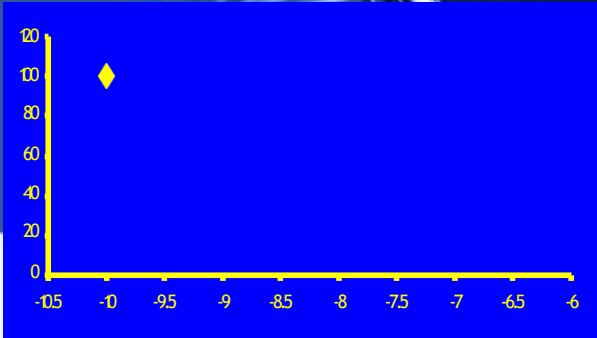
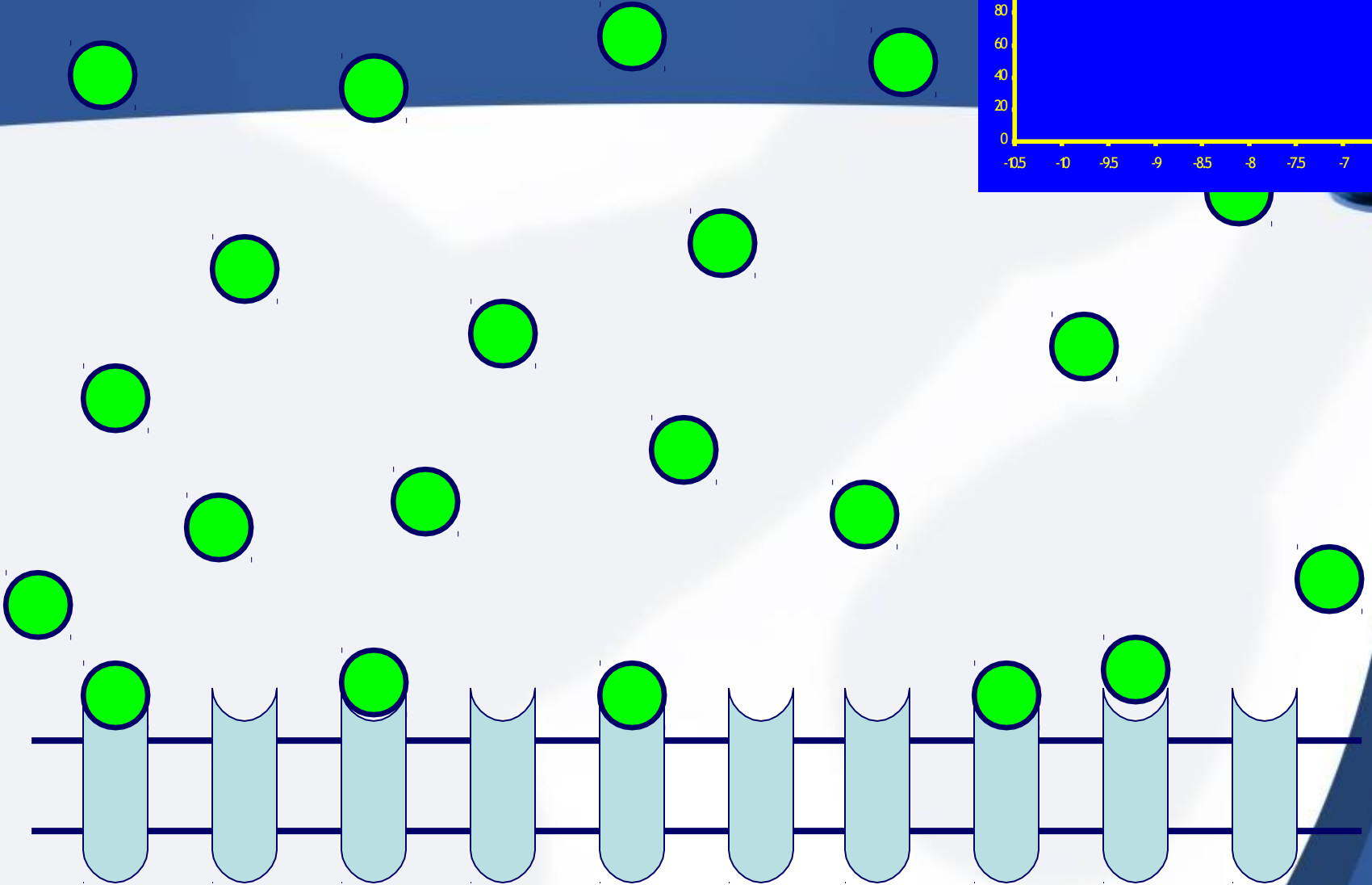
Act on
"allosteric site"



Competitive Antagonism

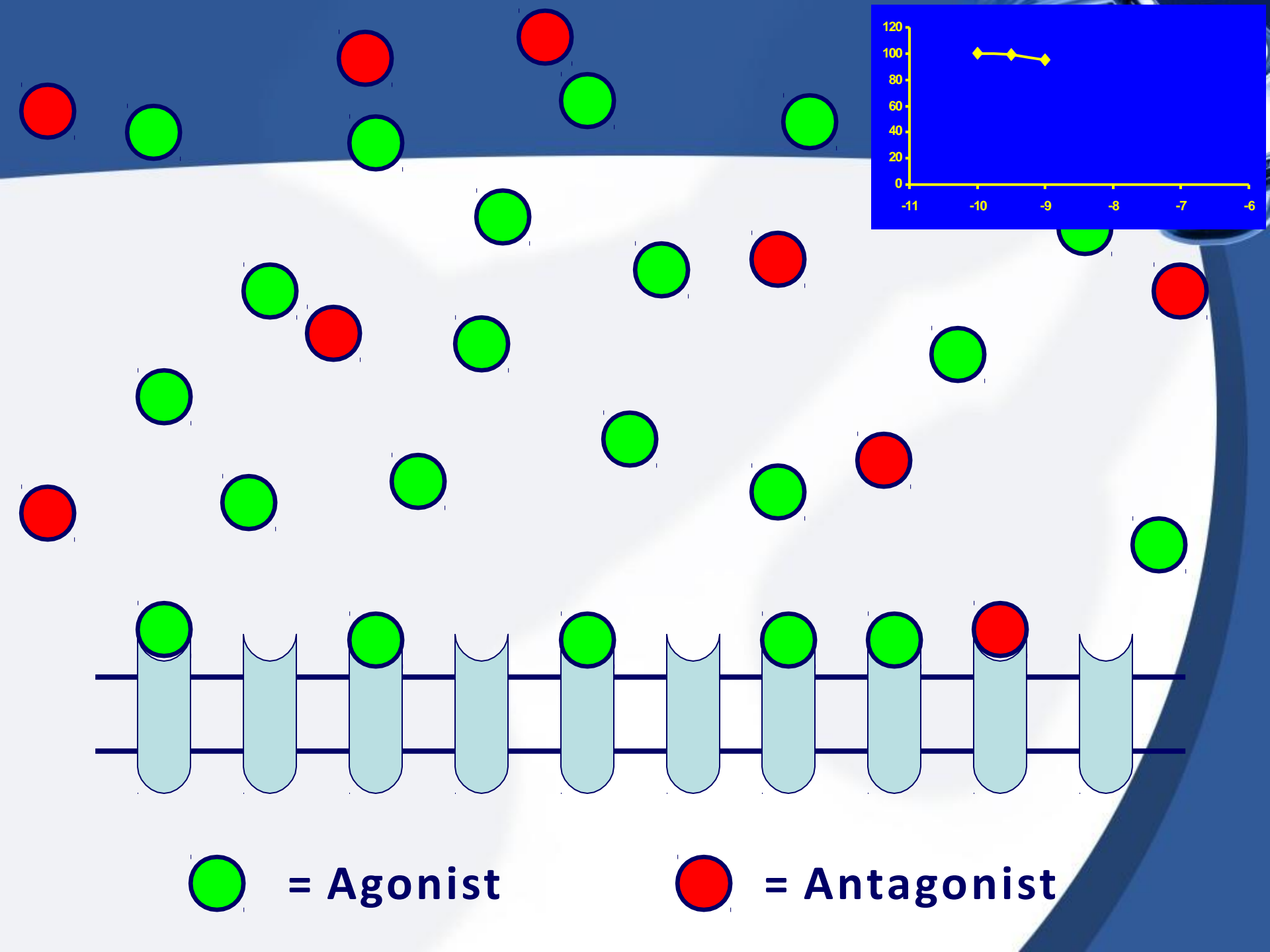
D-R interactions

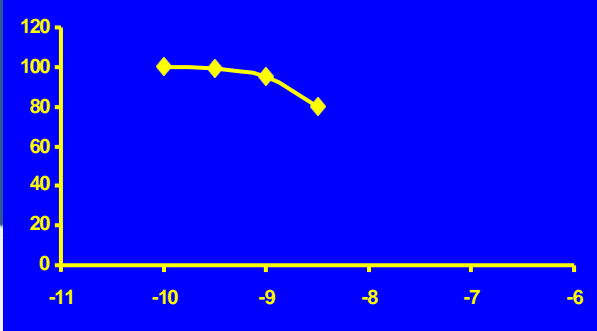
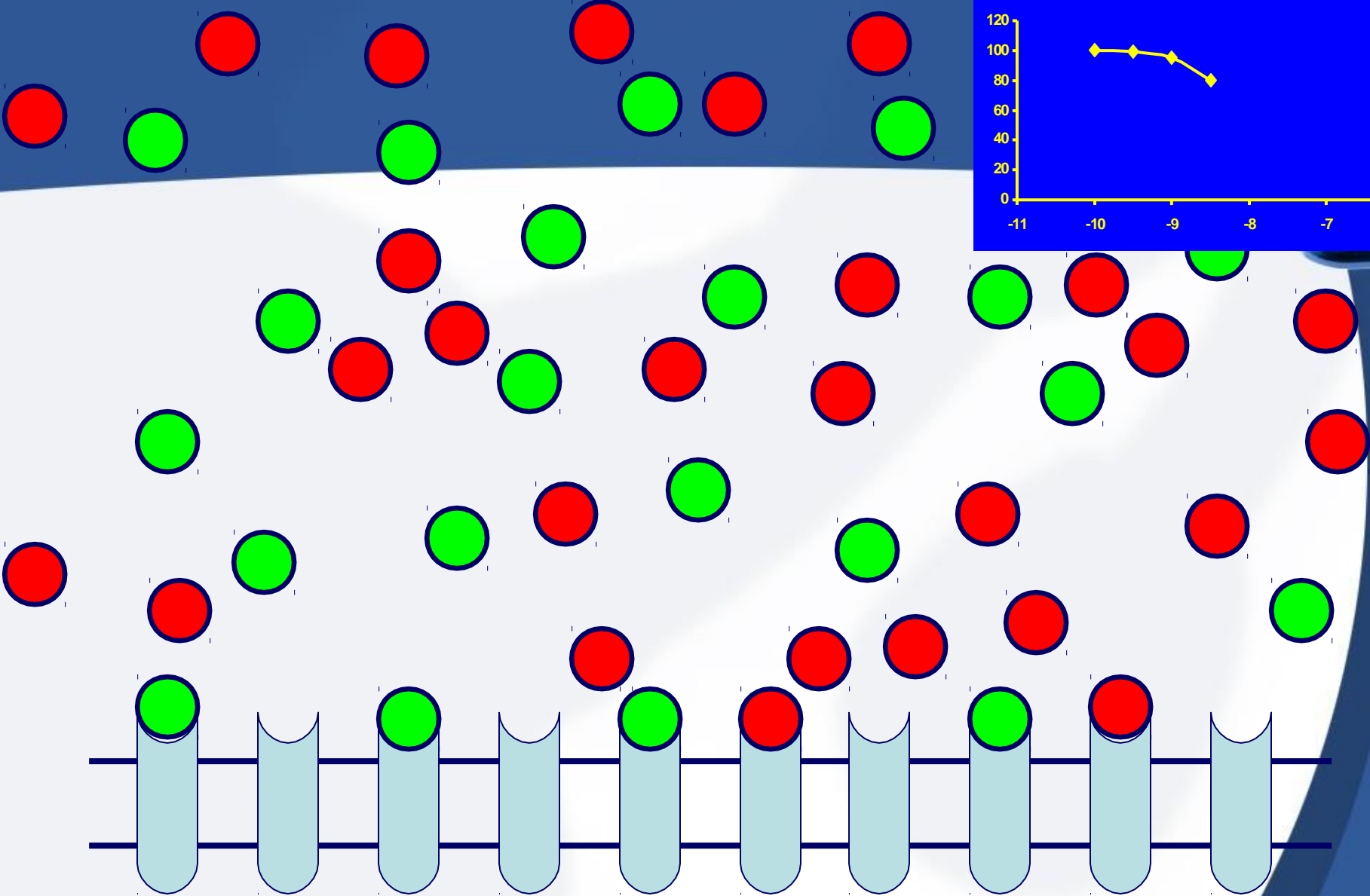




 = Agonist

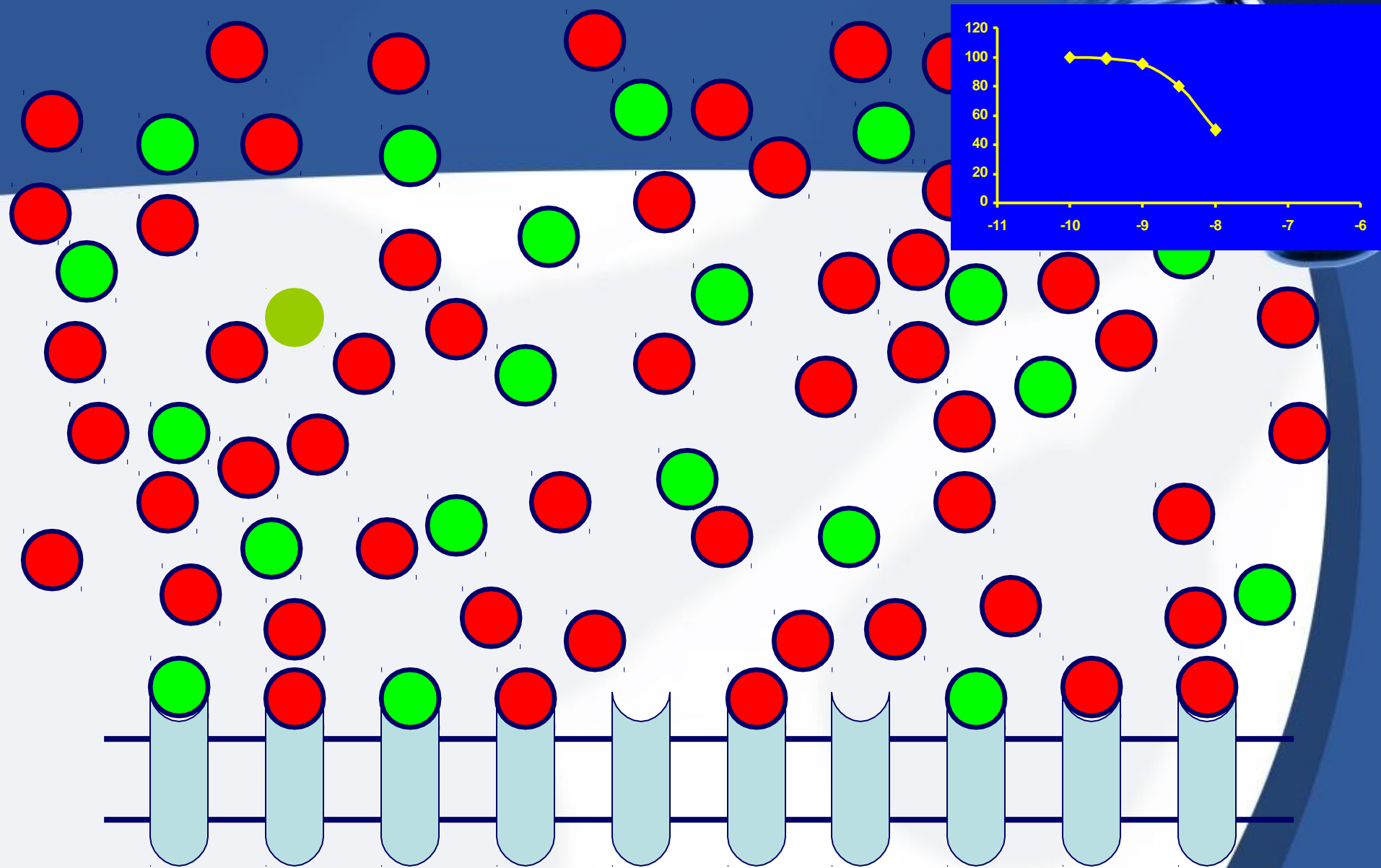
 = Antagonist





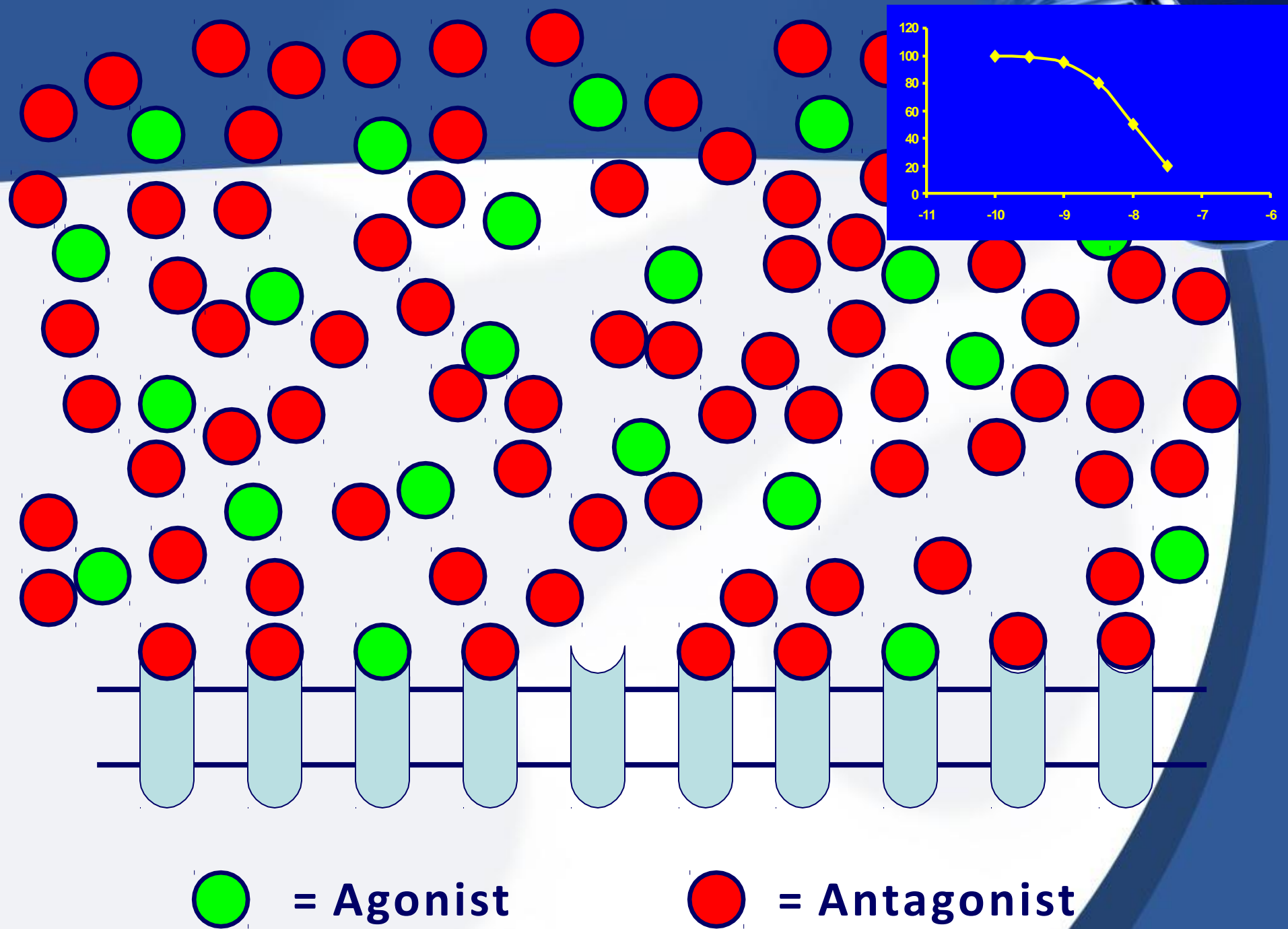
 = Agonist

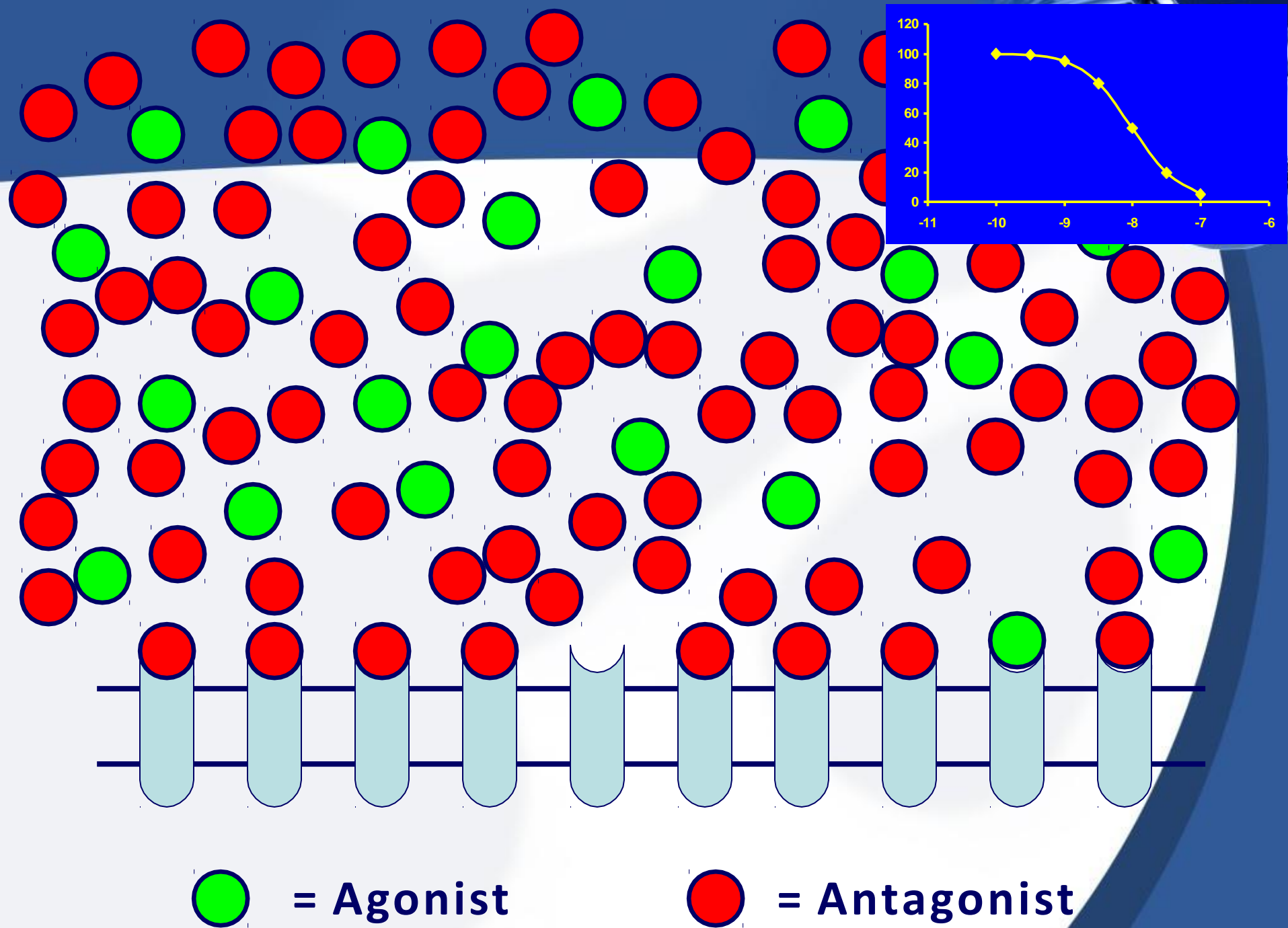
 = Antagonist

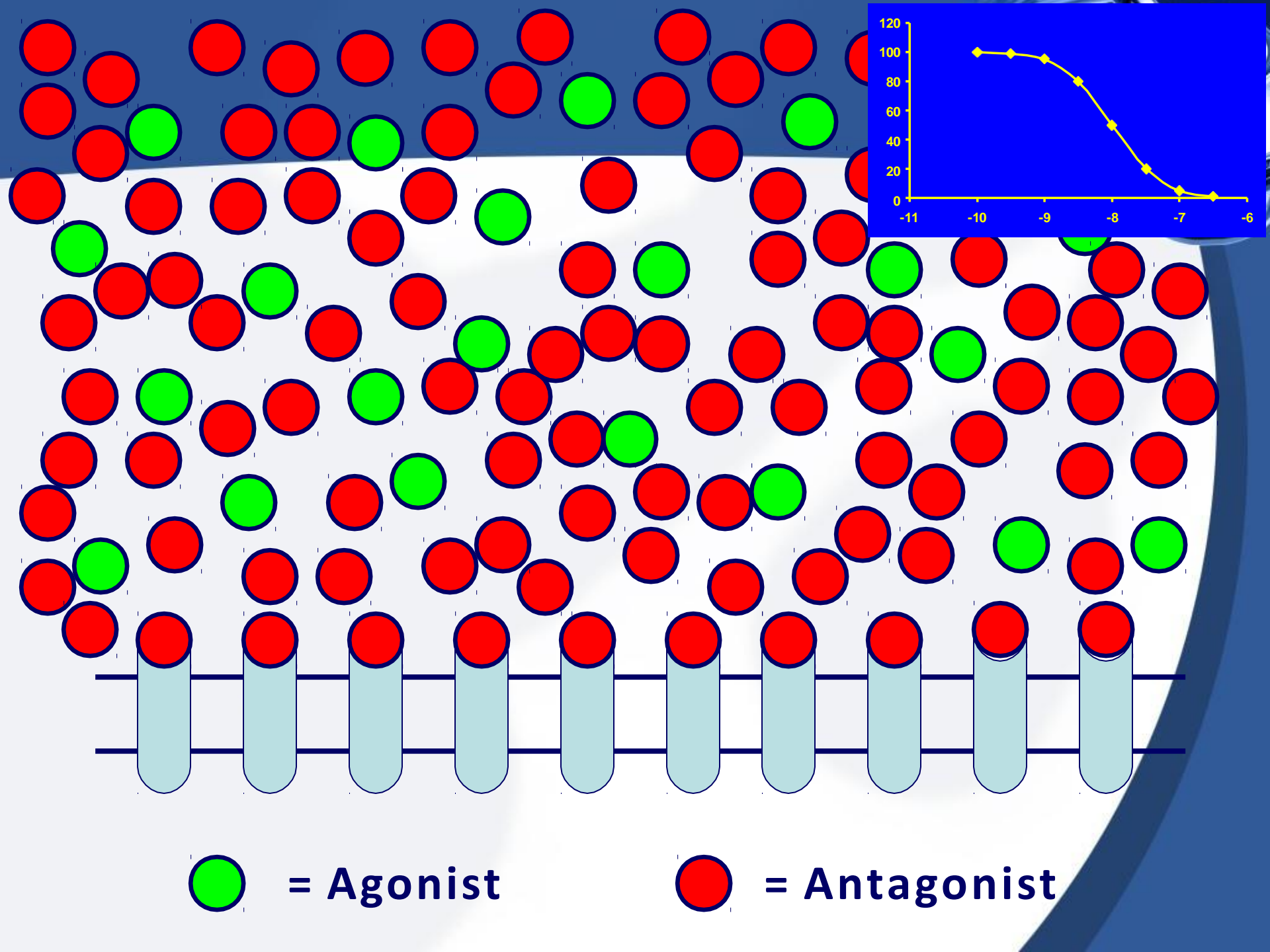


 = Agonist

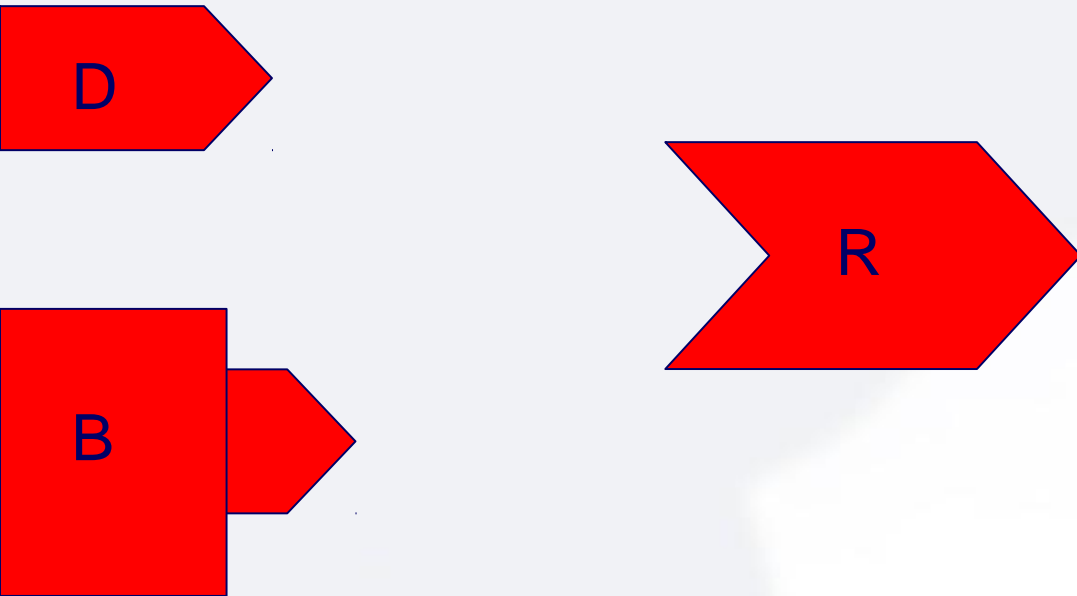
 = Antagonist





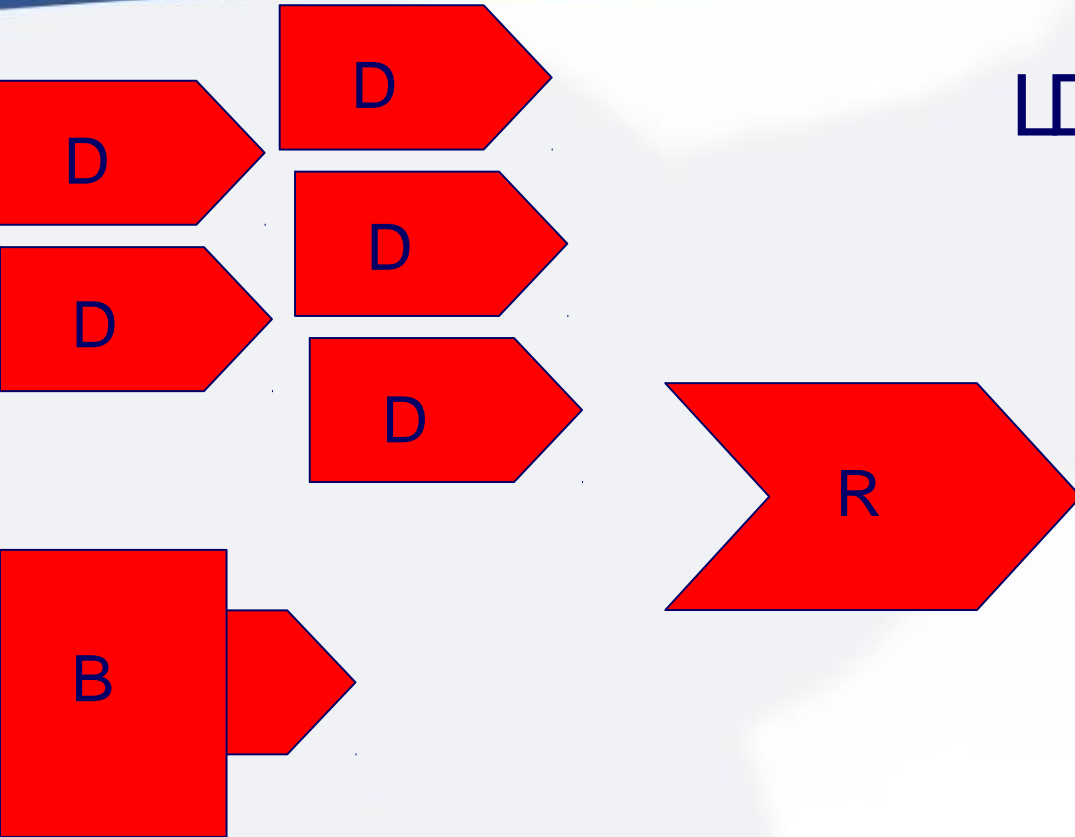


Reversible-Competitive



- Weak bond
- Same agonist site
- Short duration

Reversible-Competitive



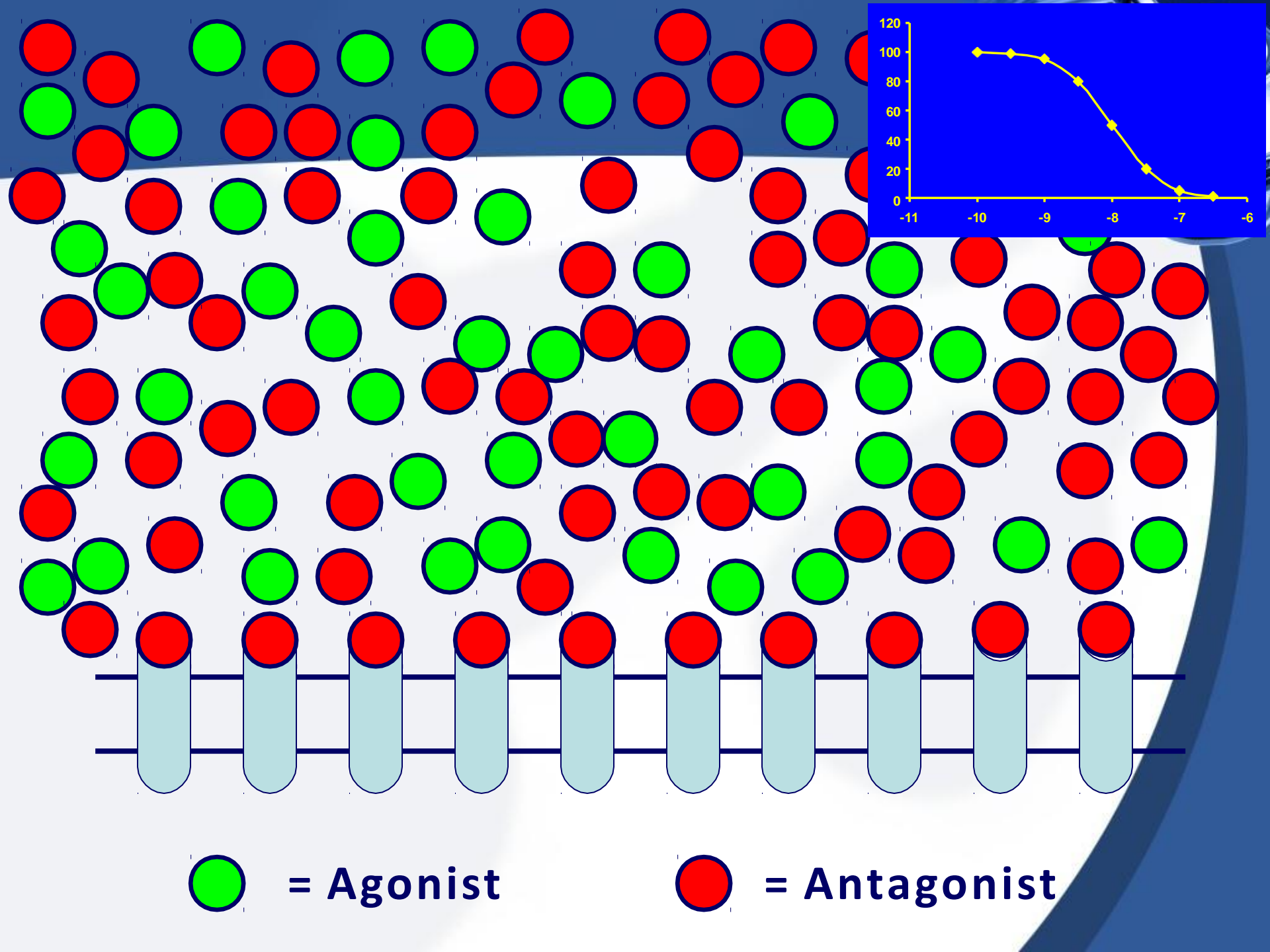
LDRC shift to R

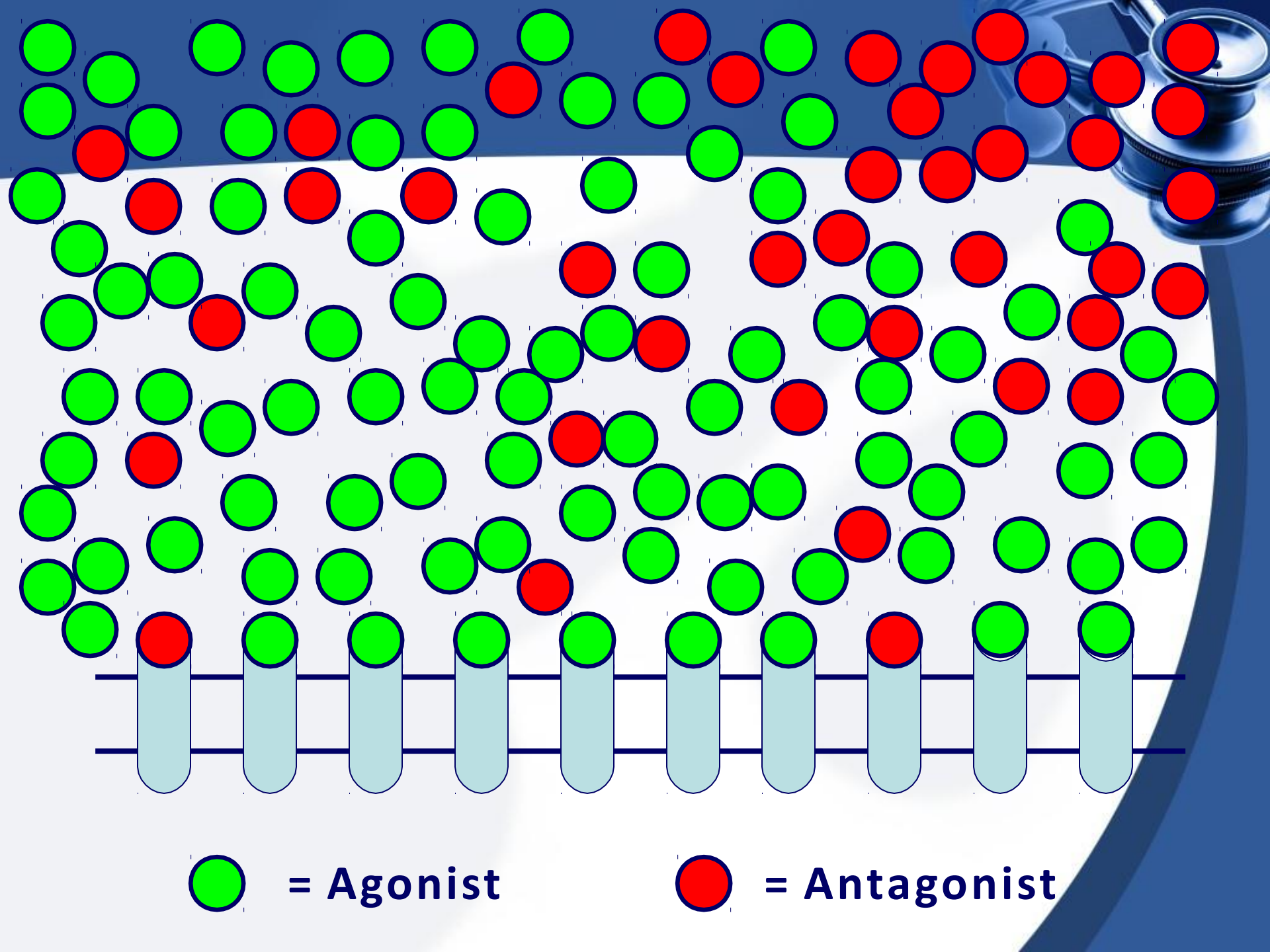
Conc dependant \rightleftharpoons Dynamic Equilibrium

Competitive (Reversible) Antagonism / Competitive (Equilibrium) Antagonism

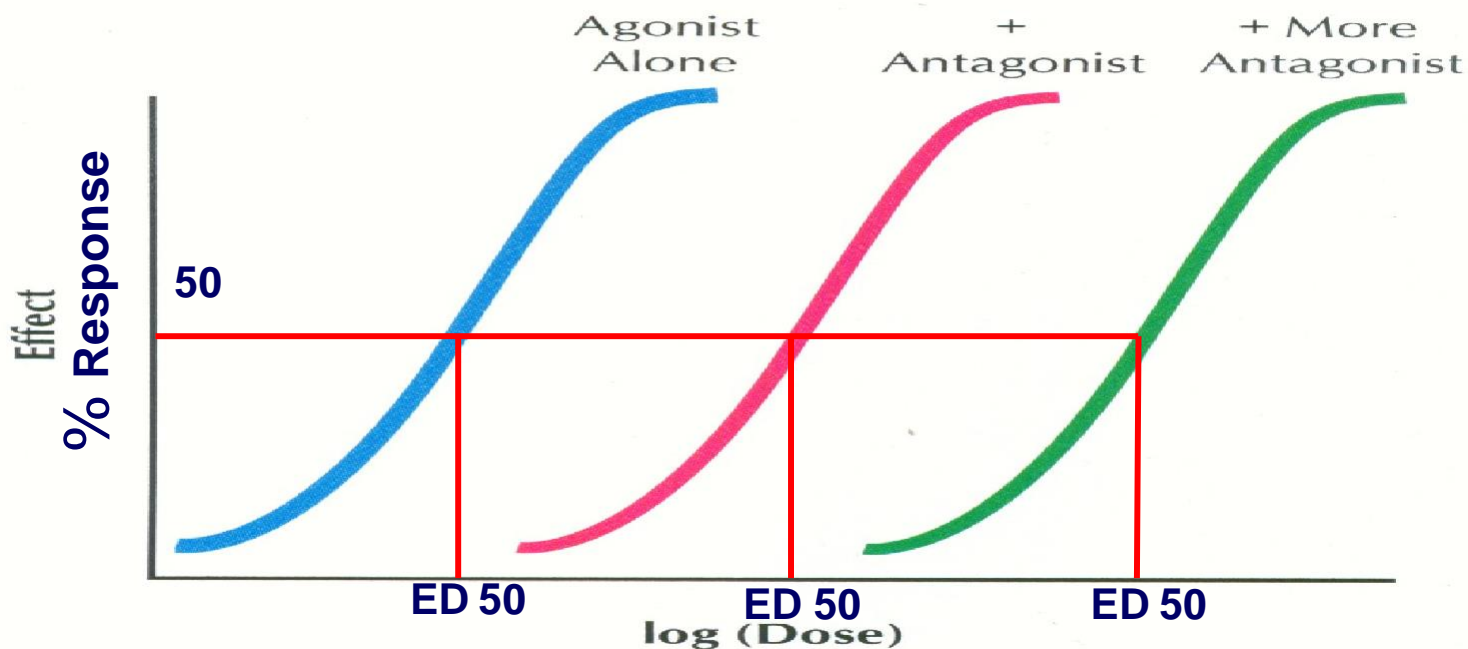


1. Same receptor by forming Weak bonds
2. Maximal response depends on concentration of both agonist and antagonist
3. The effect of antagonist can be overcome by increasing the concentration of agonist. The same **maximal response can be attained** by increasing dose of agonist---It is “surmountable antagonism”.
4. Parallel rightward shift of DRC





Antagonists: Surmountable (Reversible)



Examples: Atropine and Acetylcholine at Muscarinic-R
Naloxone and Morphine at opioid-R
Propranolol and NE at β_2 -R

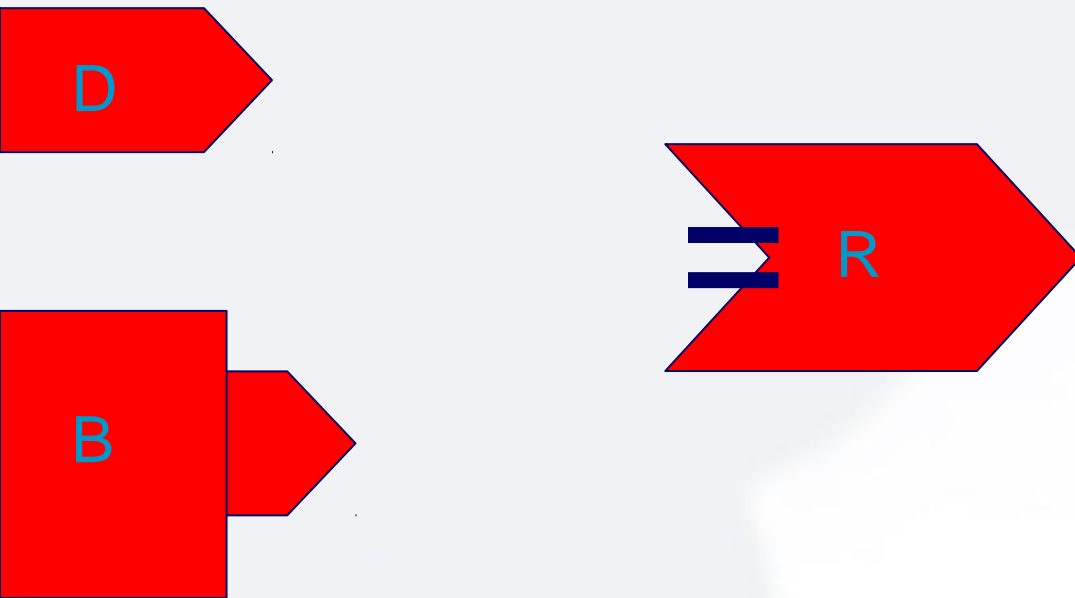
Irreversibly Competitive or Non

Equilibrium Competitive Antagonism:

1. Have affinity for the same receptor sites and bind in an irreversible manner by covalent bond
2. Effects cannot be overcome even by increasing the concentration of the agonist
(unsurmountable)
3. LDR curves of agonist (in presence of antagonist) would show reduced efficacy but unaltered potency



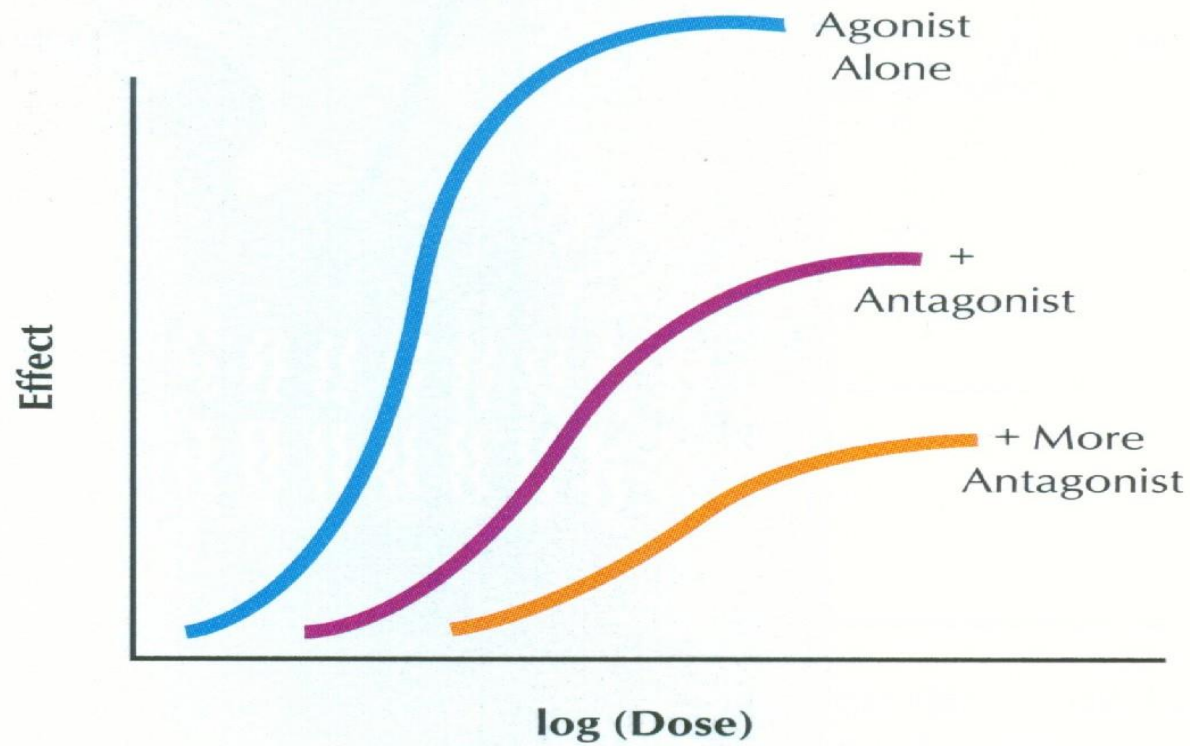
Irreversibly- Competitive



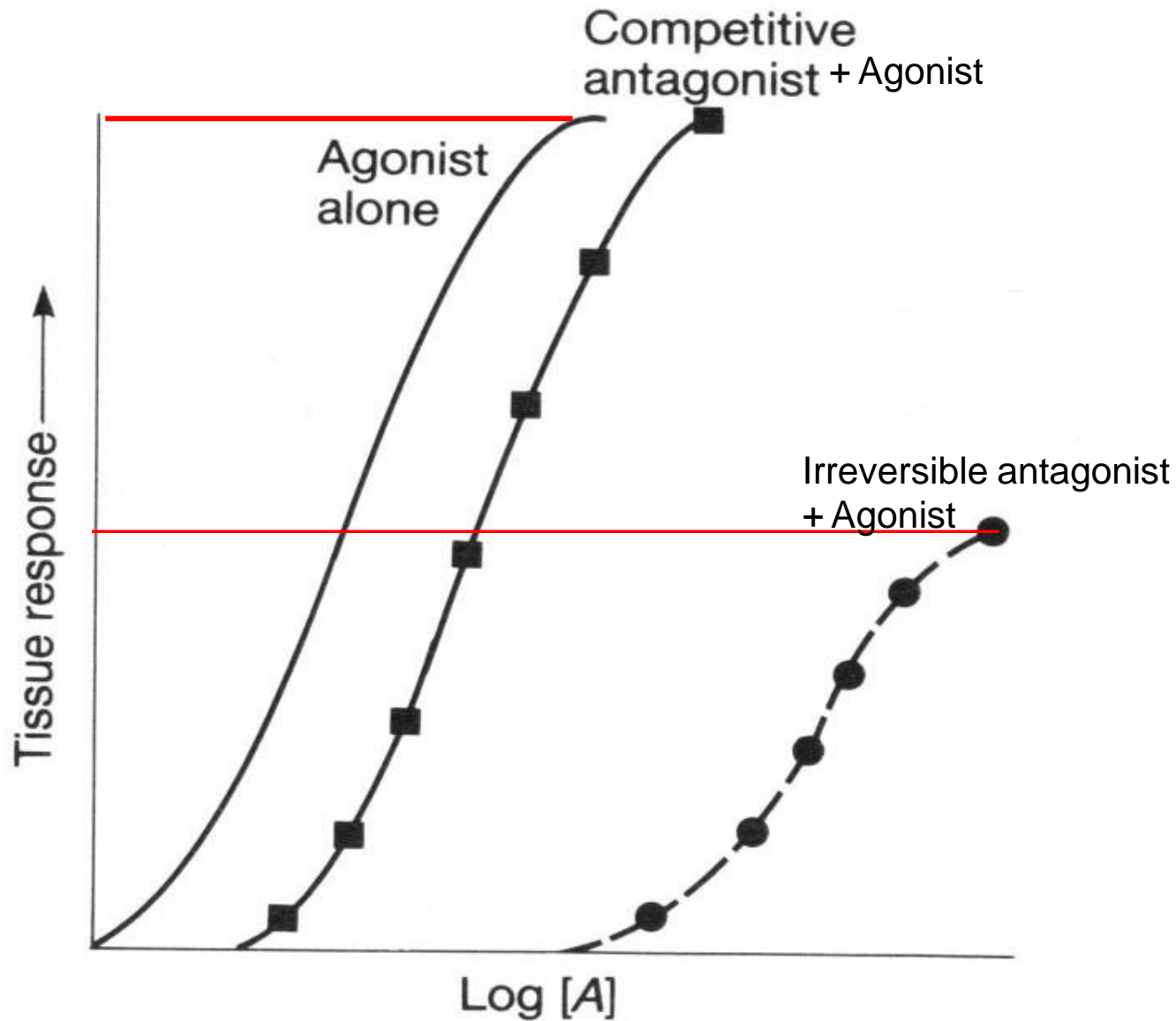
- Same agonist site
- Strong bond
- LDRC₅₀ efficacy (flatten)
- Long duration



Antagonists: Nonsurmountable (Irreversible)



Effect of antagonists





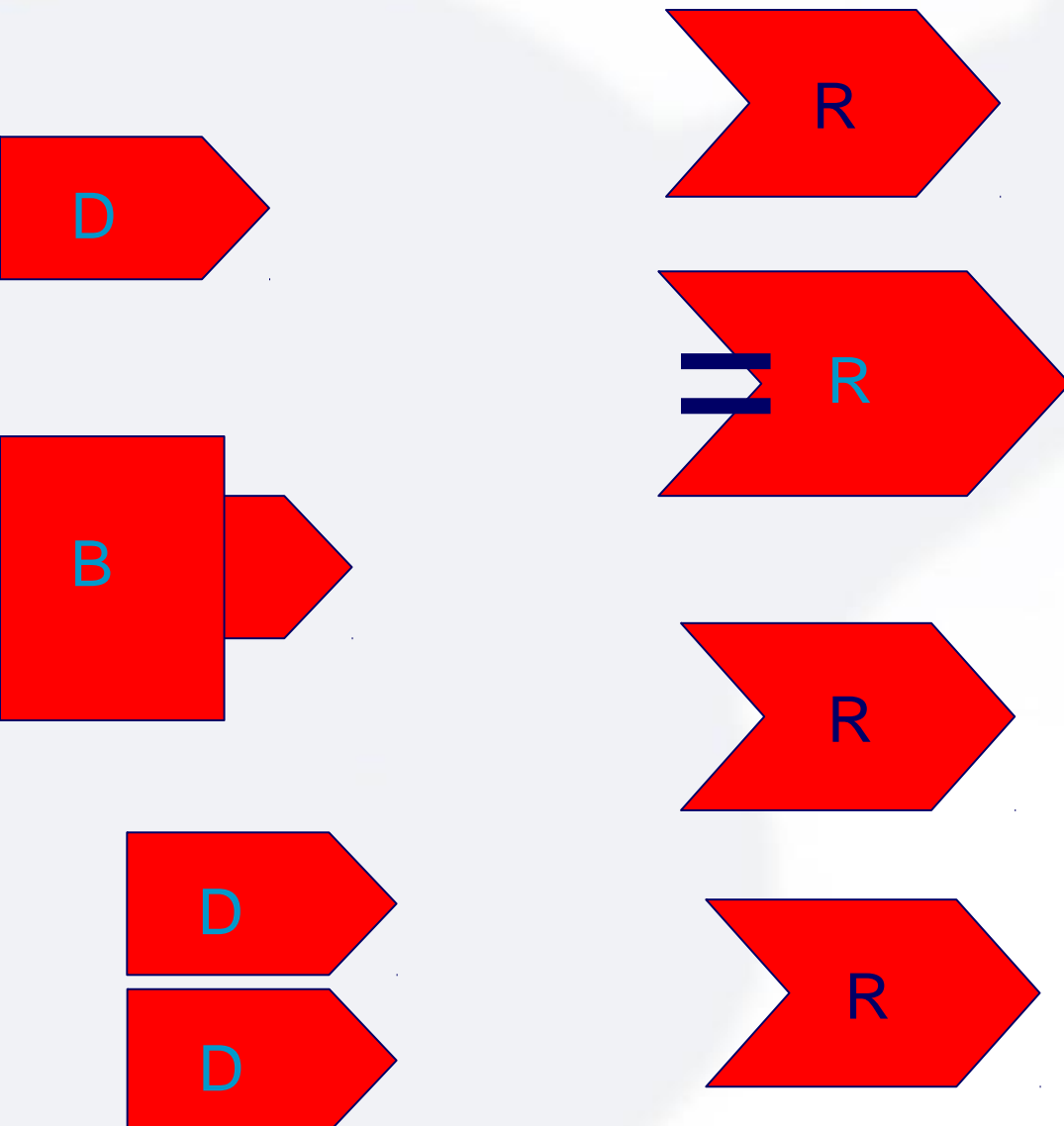
- DOA of irreversible antagonist is longer
- Equilibrium between Antagonist - Agonist cannot be established even after increasing the dose of agonist hence the term “Non-equilibrium competitive antagonism”
- E.g. Dibenamine and NE at α_1 adrenoceptors

Pseudo-reversible Antagonism:

- Lesser degree of receptor occupancy by the antagonist & availability of spare receptors
- Increasing conc. of agonist- shift LD_{50} to right
- Increasing conc. of antagonist- reduction in maximal response.
- Hence the term “Pseudo-reversible Antagonism”

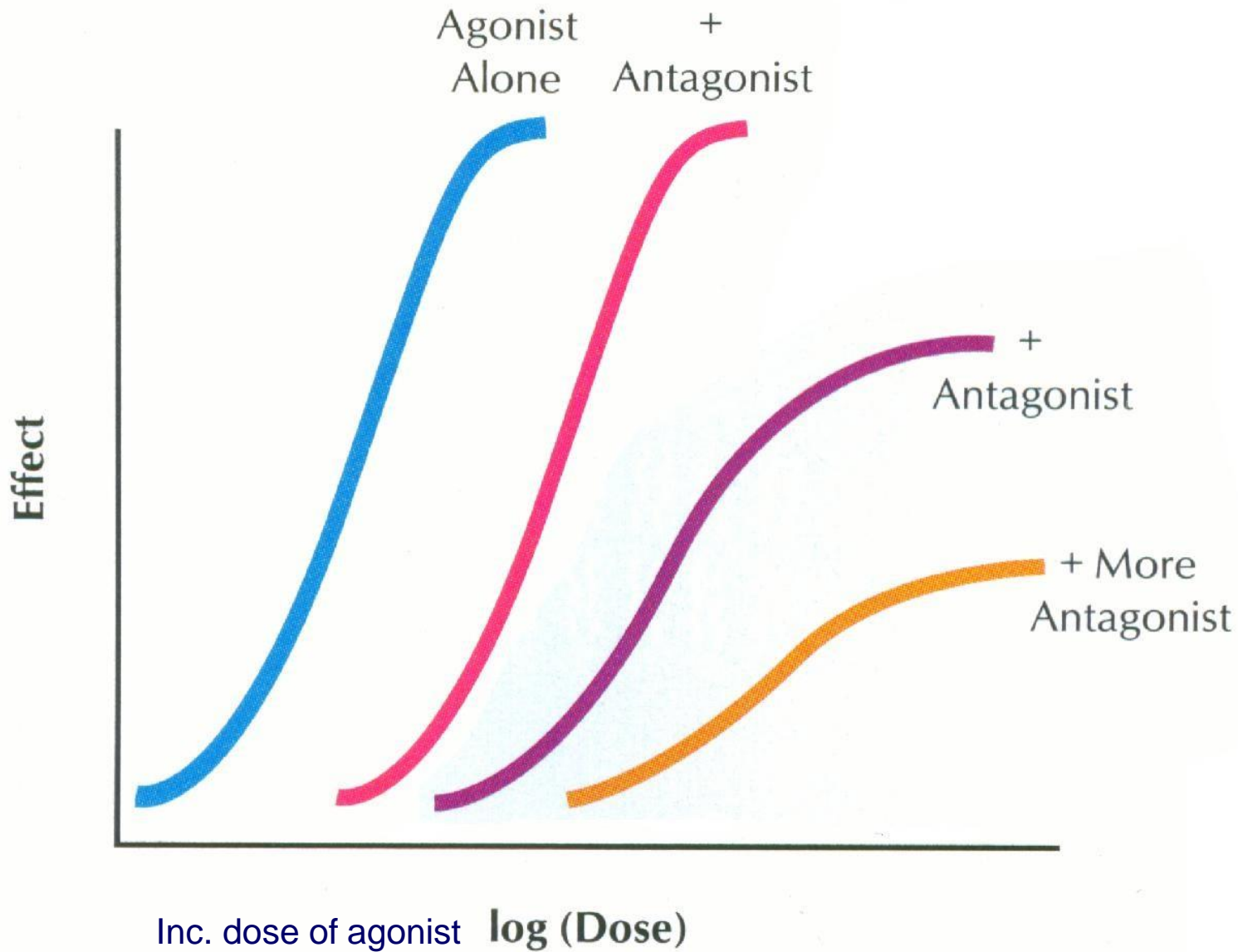


Pseudo-Reversible Competitive



- Strong bond
- Spare receptors
 ☐ Agonist overcomes antagonist
- Same agonist site
- LDRC

Antagonists: Pseudo-irreversible Competitive



Pseudo-Reversible Competitive



E.g.

Phenoxybenzamine - at α_1 adrenoceptor

Methysergide - at 5HT receptor

(5HT receptor blocker)

A blue stethoscope is positioned in the top right corner of the slide, partially overlapping the white background. The background features a faint, large-scale pattern of interlocking puzzle pieces.

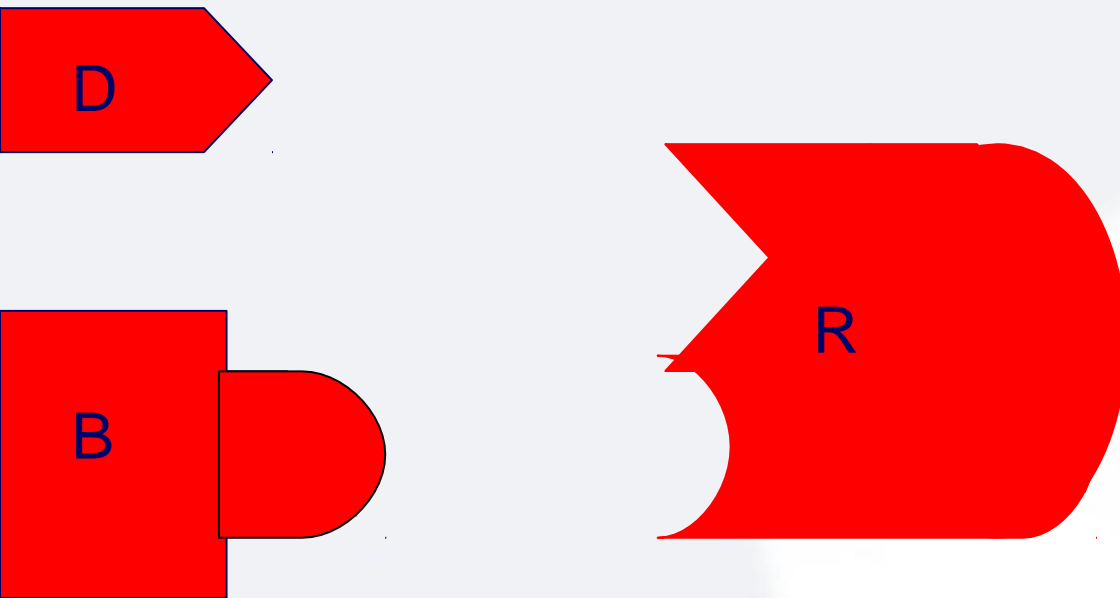
Non Competitive Antagonism

Non Competitive Antagonism

- Via Allosteric Modulation
- Receptor-Effector pathway modulation
(Down-stream regulation)

NO Competition
for Agonist site

Antagonism through Allosteric receptor site binding:



- Different Receptor site
- DR interaction ineffective
- No Reversal
- LDRC \square flatten

Antagonism through Allosteric receptor site binding:

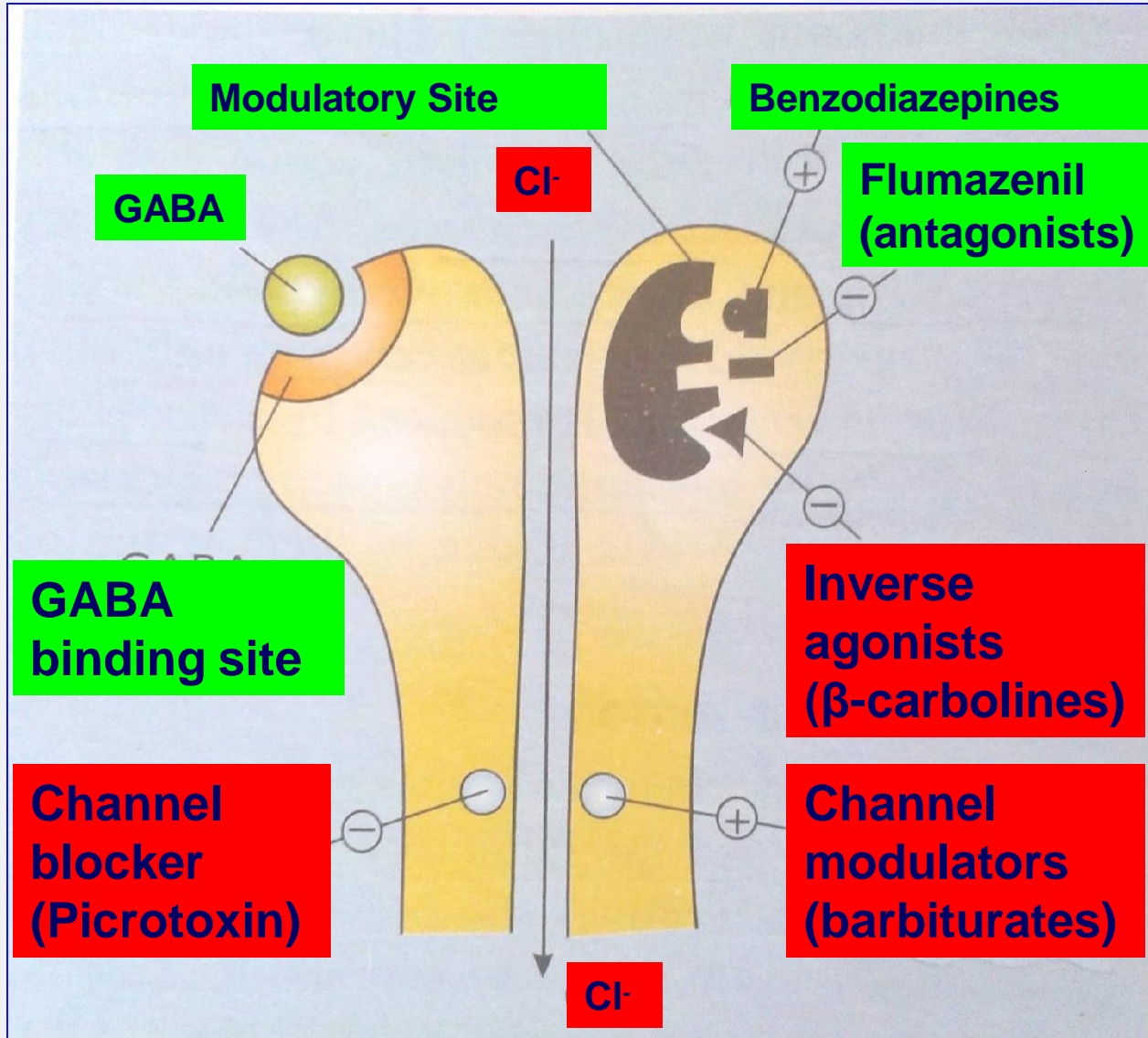


- i. Binds to site other than the agonist site
- ii. Prevent the receptor activation by the agonist

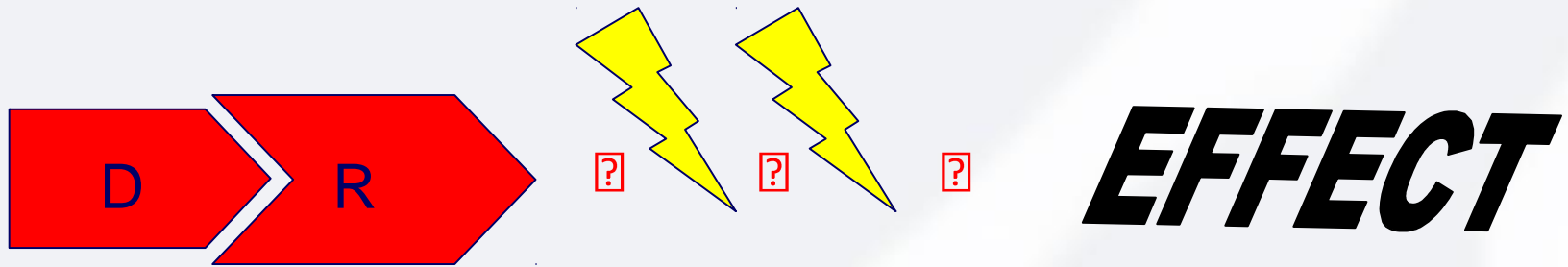
E.g.

- Flumazenil by binding to BZD site antagonises the effects of BZD by preventing the binding of GABA to GABA_A receptor
- Bicuculline and BZD

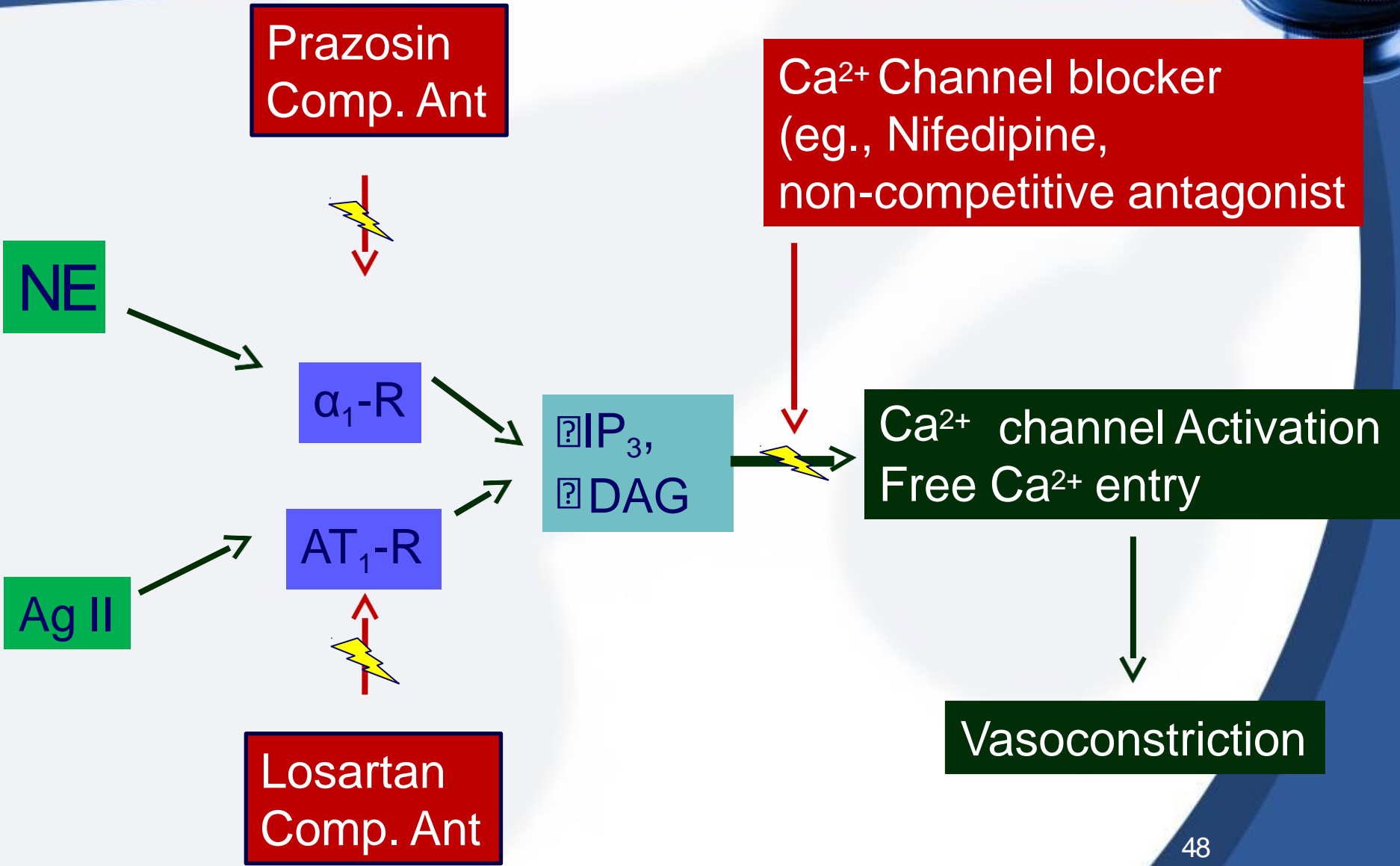
Antagonism through Allosteric receptor site binding:



Receptor-Effector pathway modulation (Down-Stream Regulation)

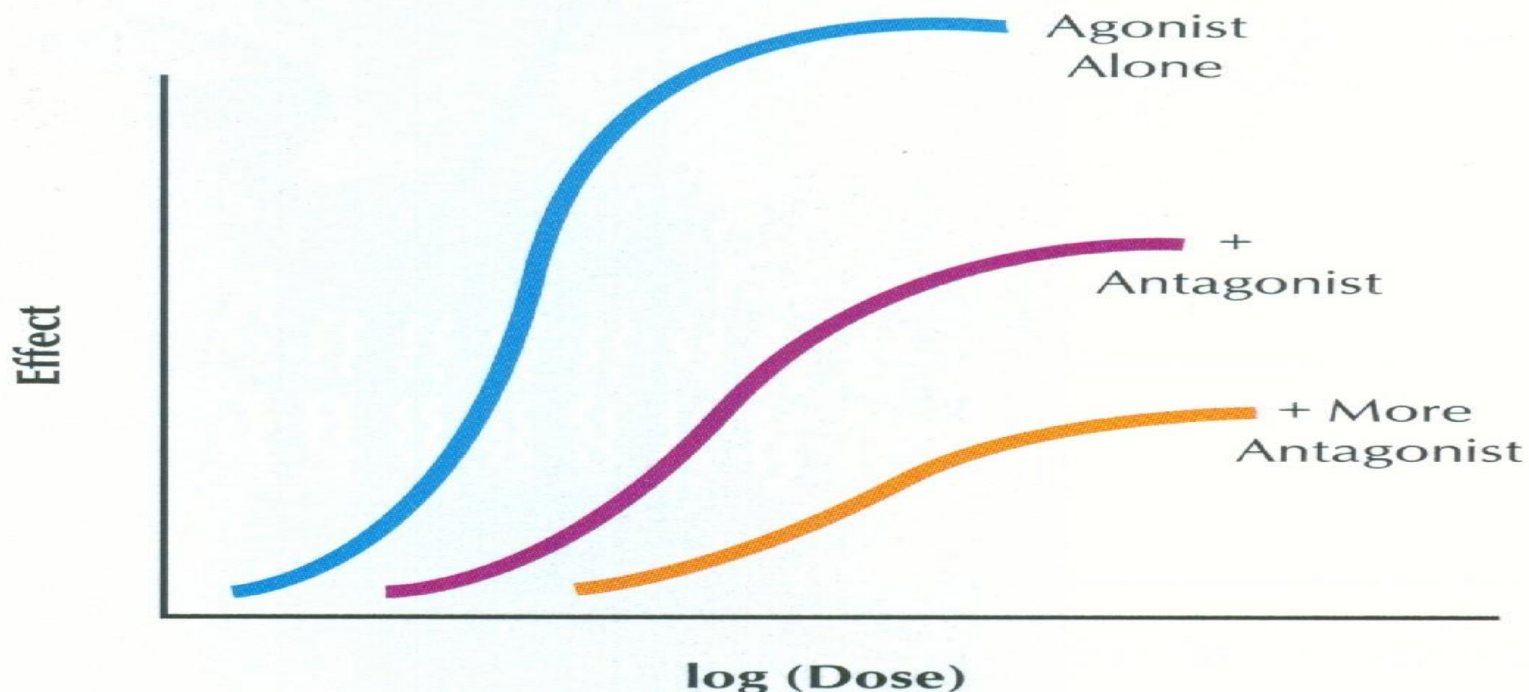


Receptor-Effector pathway modulation (Down-stream regulation)



Effects on log DRC

- There is downward shift .The slope is reduced and maximum response is diminished
- The parallelism is not maintained
- No shift of curve on dose axis





- Competitive Antagonism (equilibrium or reversible)

- ☐ Action of agonist is blocked if conc. of antagonist is ☐
- ☐ Antagonism can be overcome by ☐ conc. of agonist
- ☐ Agonist can produce max. response in higher conc.
- ☐ Competitive antagonist shifts LDRC of agonist to right
- ☐ ED₅₀ of agonist ☐ in presence of antagonist, e.g., *Ach & atropine; Adr & Prop.; Morphine & Naloxone*

- Non-competitive (non-surmountable Antagonist)

- ☐ Antagonist binds to another site of receptor
- ☐ LDRC is flattened + max. response is ☐
- ☐ e.g. Diazepam and bicuculline

Chemical Antagonism



A type of antagonism where a drug counters the effect of another by simple chemical reaction / neutralization (not binding to the receptor)

1. Protamine sulphate & Heparin
2. Calcium sodium edetate form insoluble complexes with arsenic / lead
3. Neutralization of gastric acid by antacids like Aluminium hydroxide, Magnesium hydroxide, Sodium bicarbonate

Physiological Antagonism



Definition:

A type of antagonism **in which one** drug opposes / reverses the effect of another drug by binding to a different receptor and producing opposite **physiological effects**

Examples:

1. Histamine and adrenaline on **bronchial muscles and BP**
2. Glucagon and insulin on **blood sugar level**

Physical antagonism

- Based on the physical property of drug e.g. Charcoal adsorbs alkaloids and can prevent their absorption- used in alkaloidal poisonings