PHARMACODYNAMICS

- In Greek

Pharmacon = Drug

Dynamics = Action/Power

It covers all the aspects relating to
“What a drug does to the body”

Mechanism of action

- Action: How and Where the effect is produced is called as Action.

- Effect: The type of response producing by drug.

Site of Drug Action

- Where:

1. Extra cellular
2. Cellular
3. Intracellular

Types of Drug Action

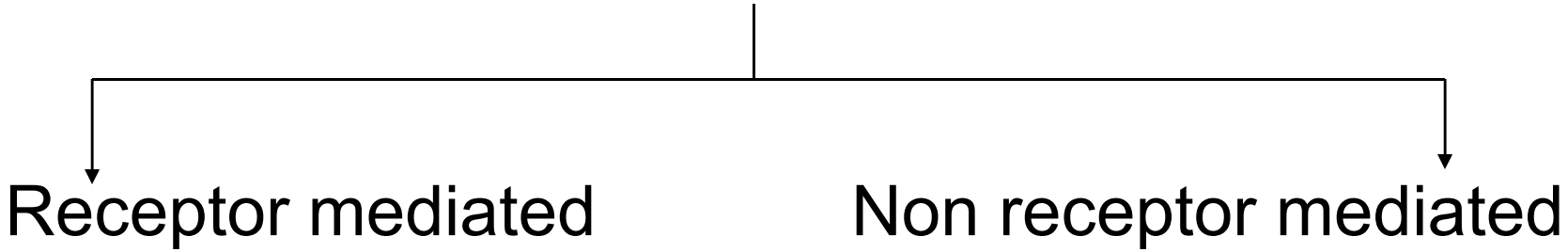
EFFECT (Type of responses):-

1. Stimulation
2. Inhibition/Depression
3. Replacement
4. Irritation
5. Cytotoxic

Mechanism of Action of Drugs

- Drug act either by receptor or by non receptor or by targeting specific genetic changes.

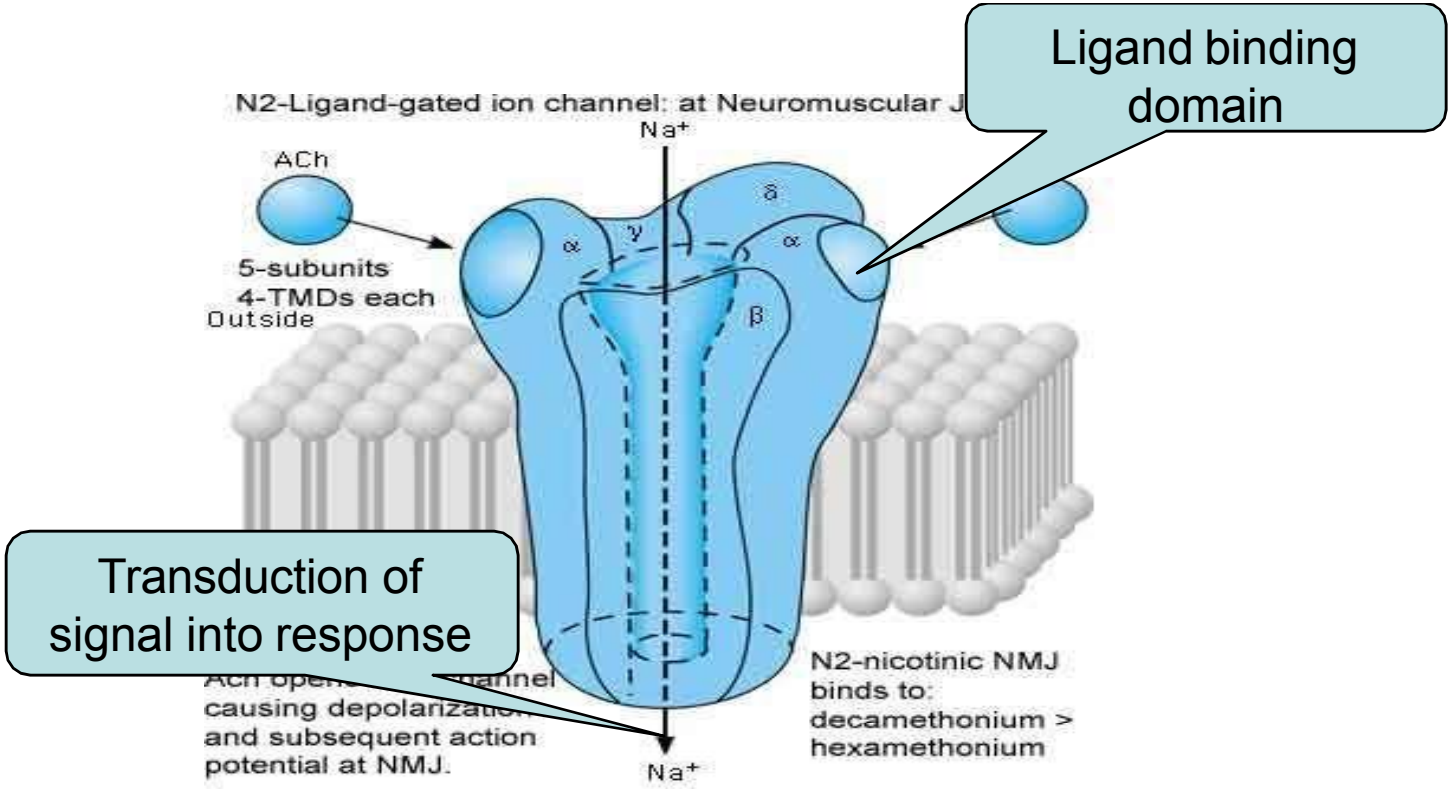
Majority of drugs acts by (HOW)



Receptor Mediated action

- Drug produce their effect through interacting with some chemical compartment of living organism c/s Receptor.

- Receptors are macromolecules
- Most are proteins
- Present either on the cell surface, cytoplasm or in the nucleus



Receptor Functions : Two essential functions

- 1. Recognization of specific ligand molecule (Ligand binding domain)
- 2. Transduction of signal into response (Effector domain)

Drug(D) +Receptor® ⟷ Drug receptor complex ⟶ Response

Drug receptor interaction:-

1. Selectivity:- Degree of complimentary co relation between drug and receptor.

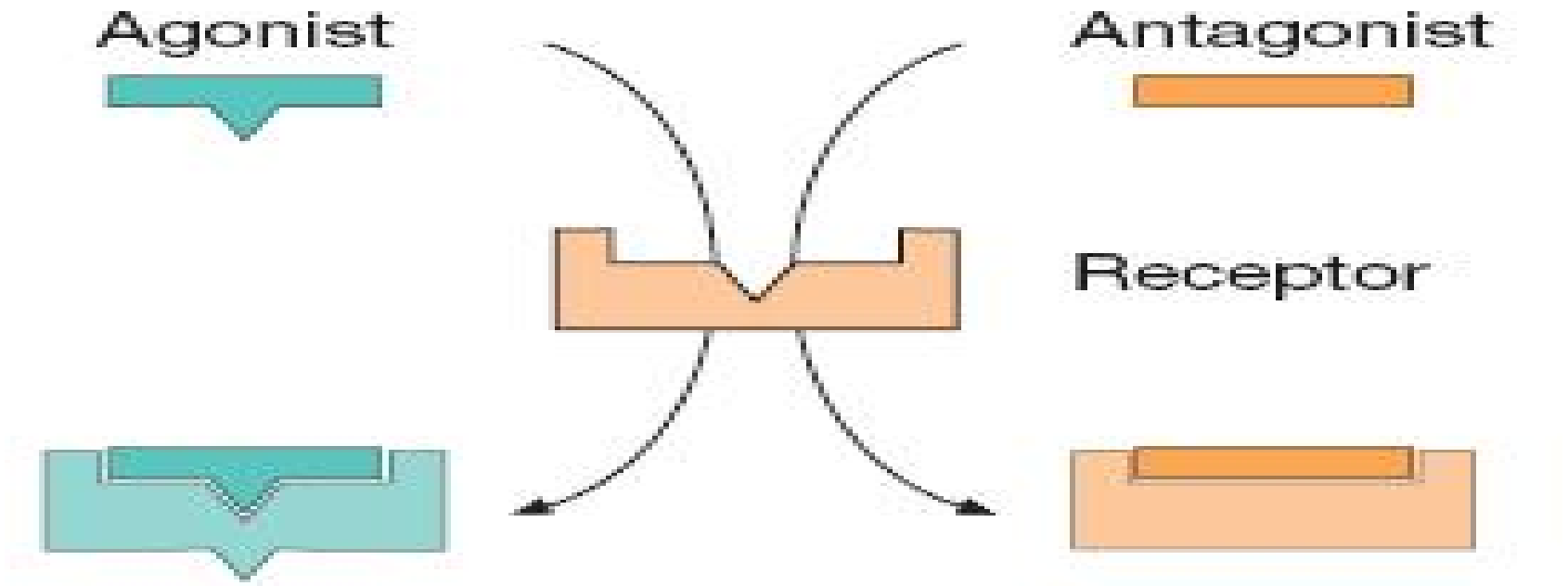
Ex:- Adrenaline Selectivity for α, ß Receptor

2. Affinity:- Ability of drug to get bound to the receptor.

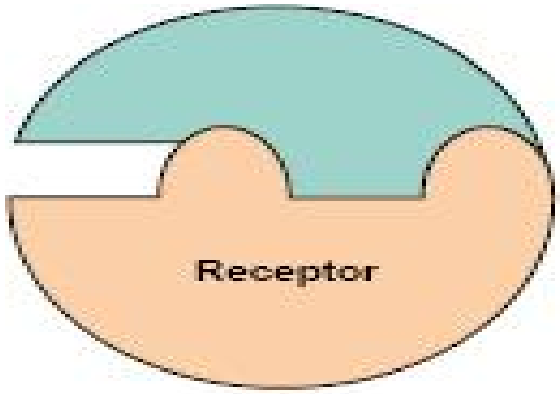
3. Intrinsic activity (IA) or Efficacy:- Ability of drug to produce a pharmacological response after making the drug receptor complex.

Drug classification

(on the basis of affinity & efficacy)


Agonist
Antagonist
Receptor
Agonist induces active conformation of receptor protein
Antagonist occupies receptor without con-formational change
Response
No response

- Partial agonist :These drug have full affinity to receptor but with low intrinsic activity (IA=0 to 1).
- These are only partly as effective as agonist



C. Some drug-receptor fit. Slight therapeutic response possible.

(Affinity is lesser when comparison to agonist)

Ex: Pindolol, Pentazocine

- Inverse agonist: These have full affinity towards the receptor but intrinsic activity is zero to -1 i.e., produces effect is just opposite to that of agonist.

Ex:- ß-Carboline is inverse agonist for Benzodiazepines receptors.

Receptor families

Four types of receptors families

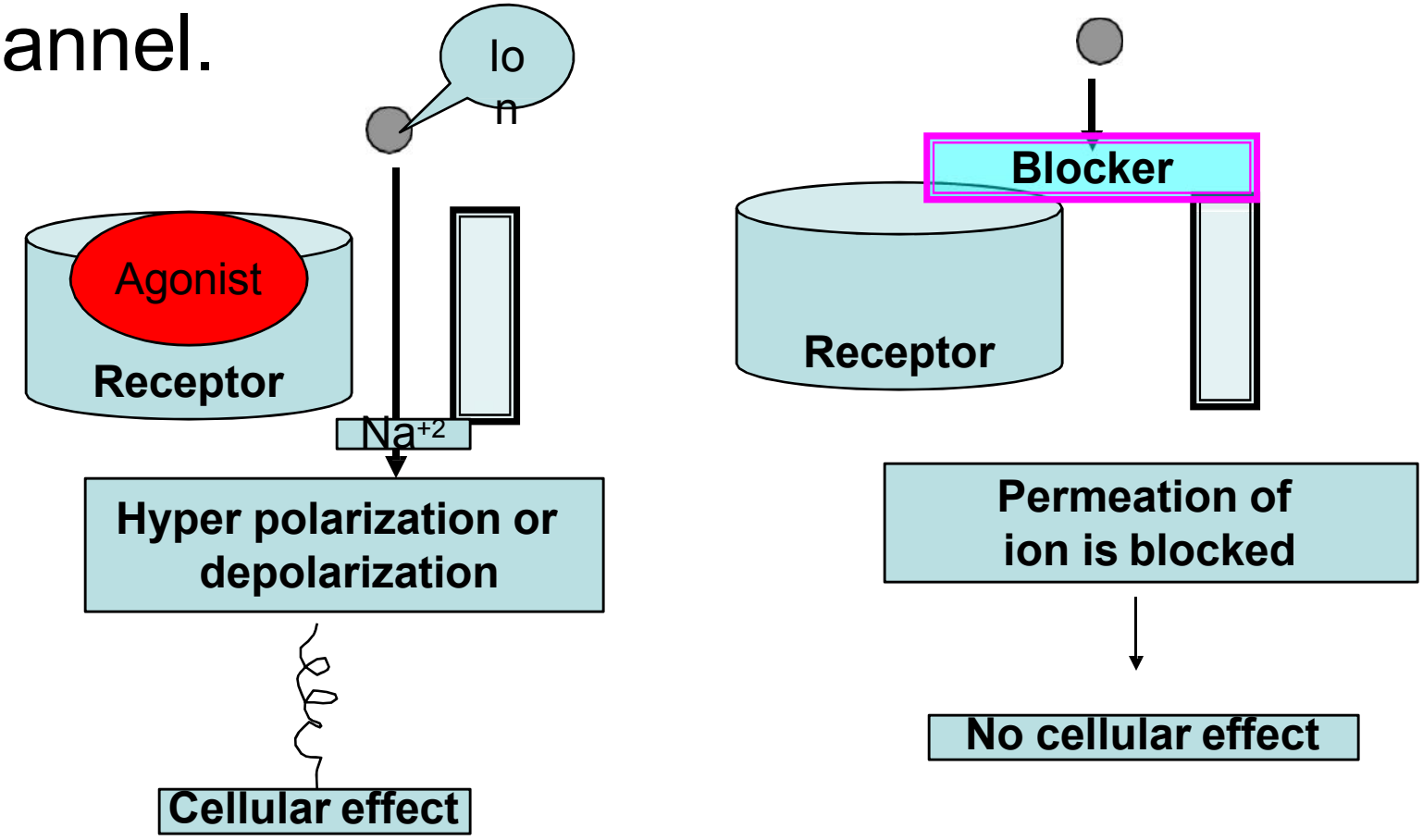
1. Ligand-gated ion channels (inotropic receptors)
2. G-protien coupled receptor (Metabotropic receptors)
3. Enzymatic receptors (tyrosinekinase)
4. Receptor regulating gene expression (transcription factors/ Steroid)

Characteristics of receptor families

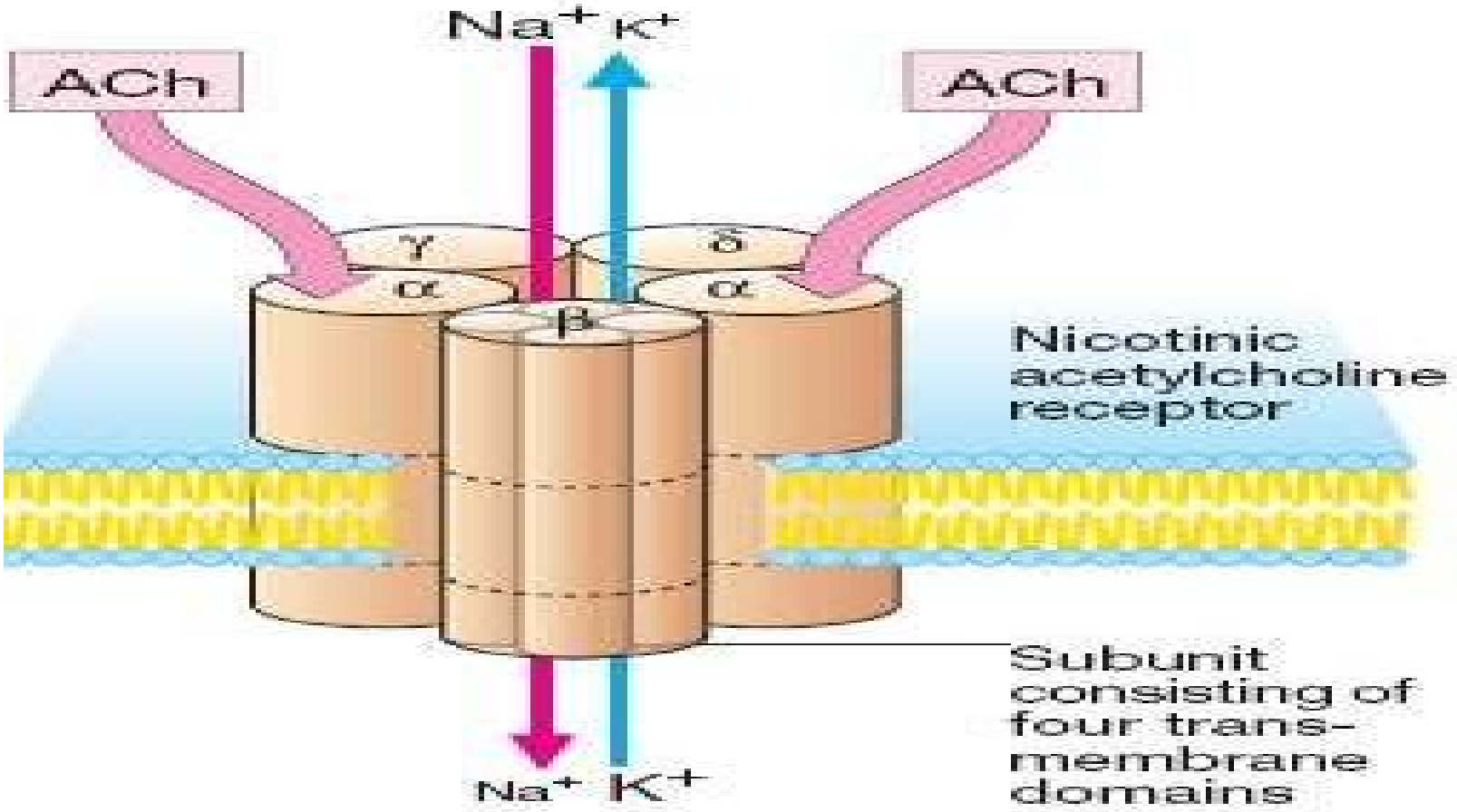
	Ligand gated	G-protein coupled	Enzymatic	Nuclear
Location	Membrane	Membrane	Membrane	Intracellular
Effector	Ion channel	Ion Channel or enzyme	Enzyme	Gene
coupling	Direct	G-protein	Direct	Via DNA
Example	Nicotinic	Muscarinic	Insulin	Steroid , hormone

Signal transduction mechanism

- Ion gated receptors:- Localized on cell membrane and coupled directly toan ion channel.

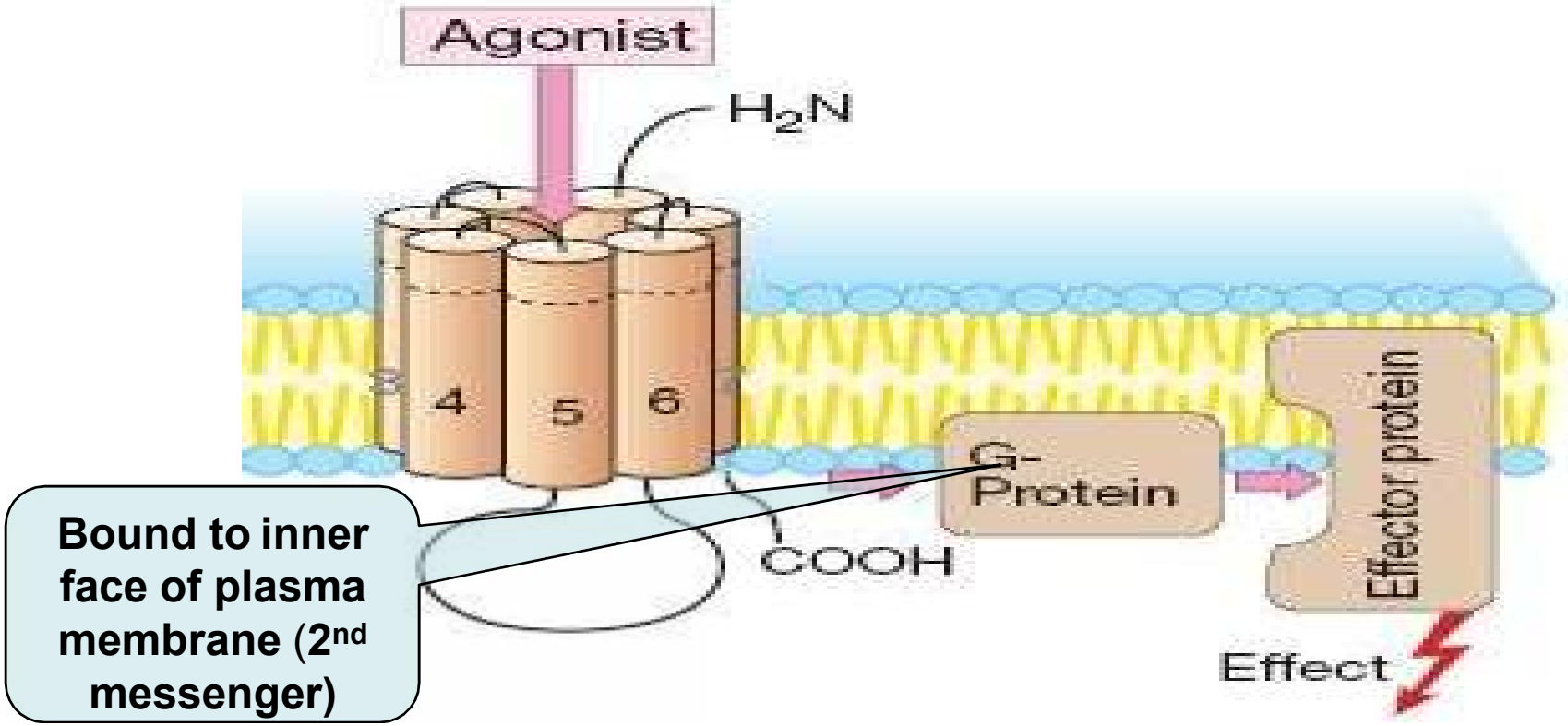


- Ex: Nicotinic cholinergic receptor



G-protein coupled receptors

- Membrane bound, which are coupled to effector system through GTP binding proteins called as G-proteins



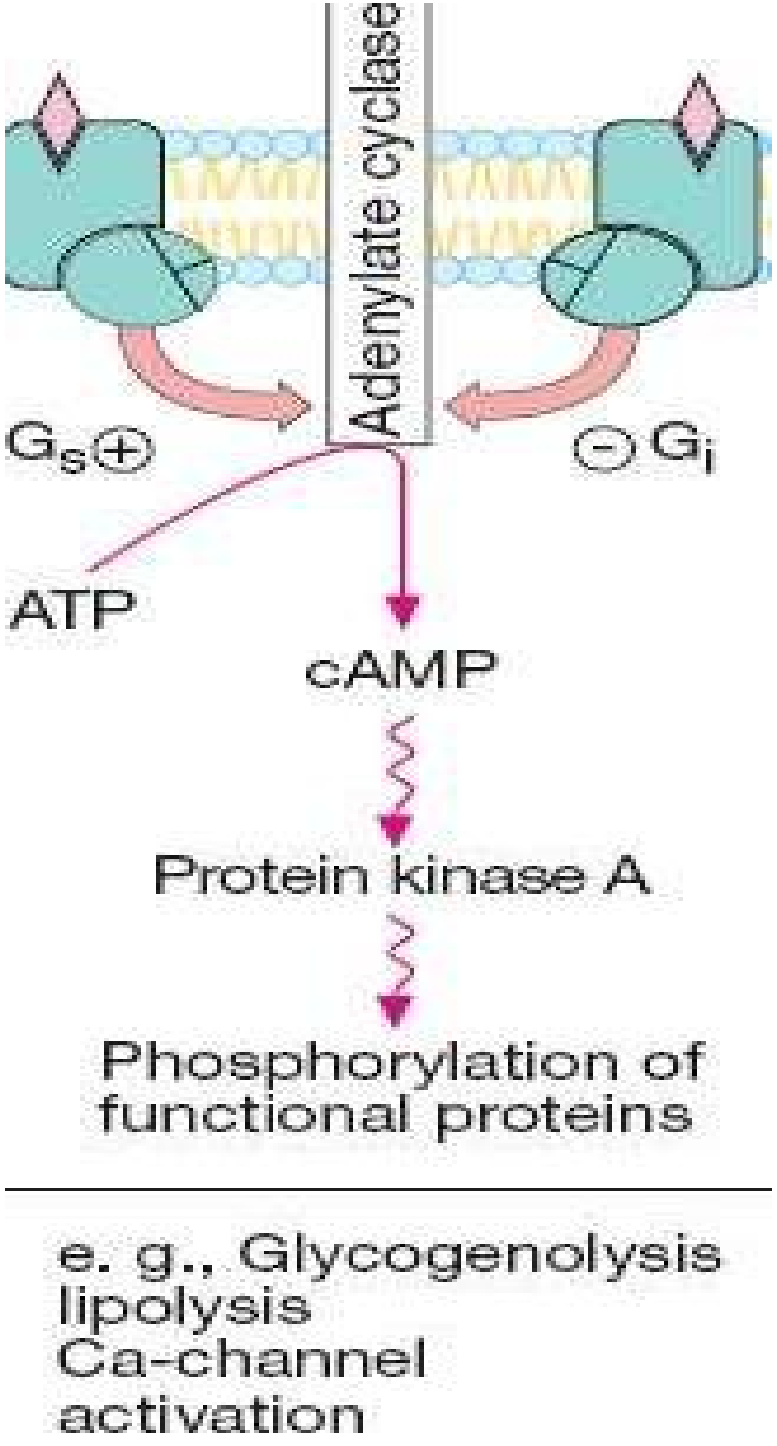
Varieties of G-protein

G-protein	Receptor for	Signaling pathway/ Effector
Gs	ß adrenegic, H,5HT,Glucagon	↑AC— ↑cAMP
$Gi_{1,2,3}$	α_2 adrenergic, Ach,	↓AC— ↓ cAMP, Open K^+
Gq	Ach	Phospholipase-C, IP_3, cytoplasmic Ca^{+2}
Go	Neurotransmitters in brain	Not yet clear

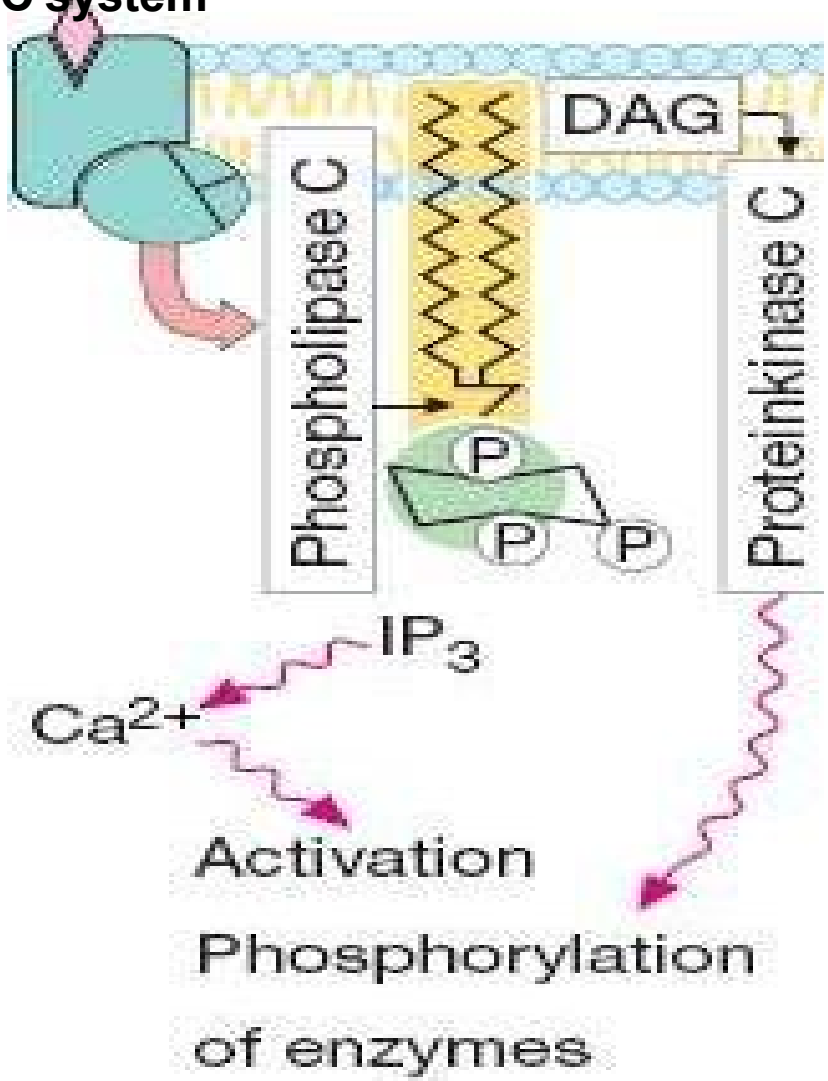
G-protein effector systems

- 1.Adenylase cyclase : **cAMP system**
- 2.Phospholipase –C: **Inositol phosphate system**
- 3. Ion channels

cAMP system


Adenylate cyclase
G_s ⊕
⊖ G_i
ATP
cAMP
Protein kinase A
Phosphorylation of functional proteins
e. g., Glycogenolysis
lipolysis
Ca-channel activation

Phospholipase-C system



e. g., Contraction of smooth muscle, glandular secretion

Ion channel regulation

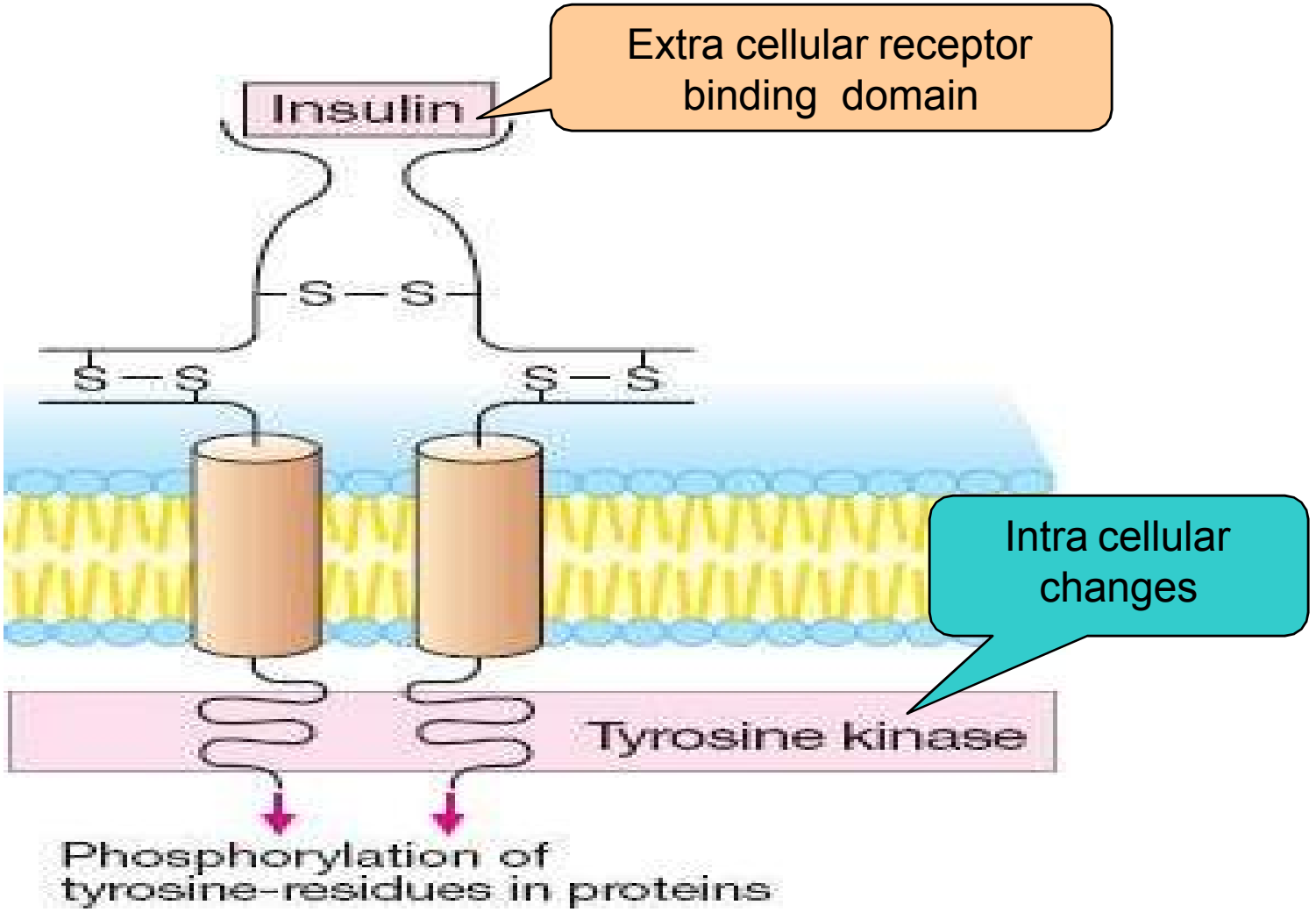
- G-protein coupled receptors can control the functioning of ion channel by don't involving any second messenger
- Ex:- In cardiac muscle

Enzymatic receptors

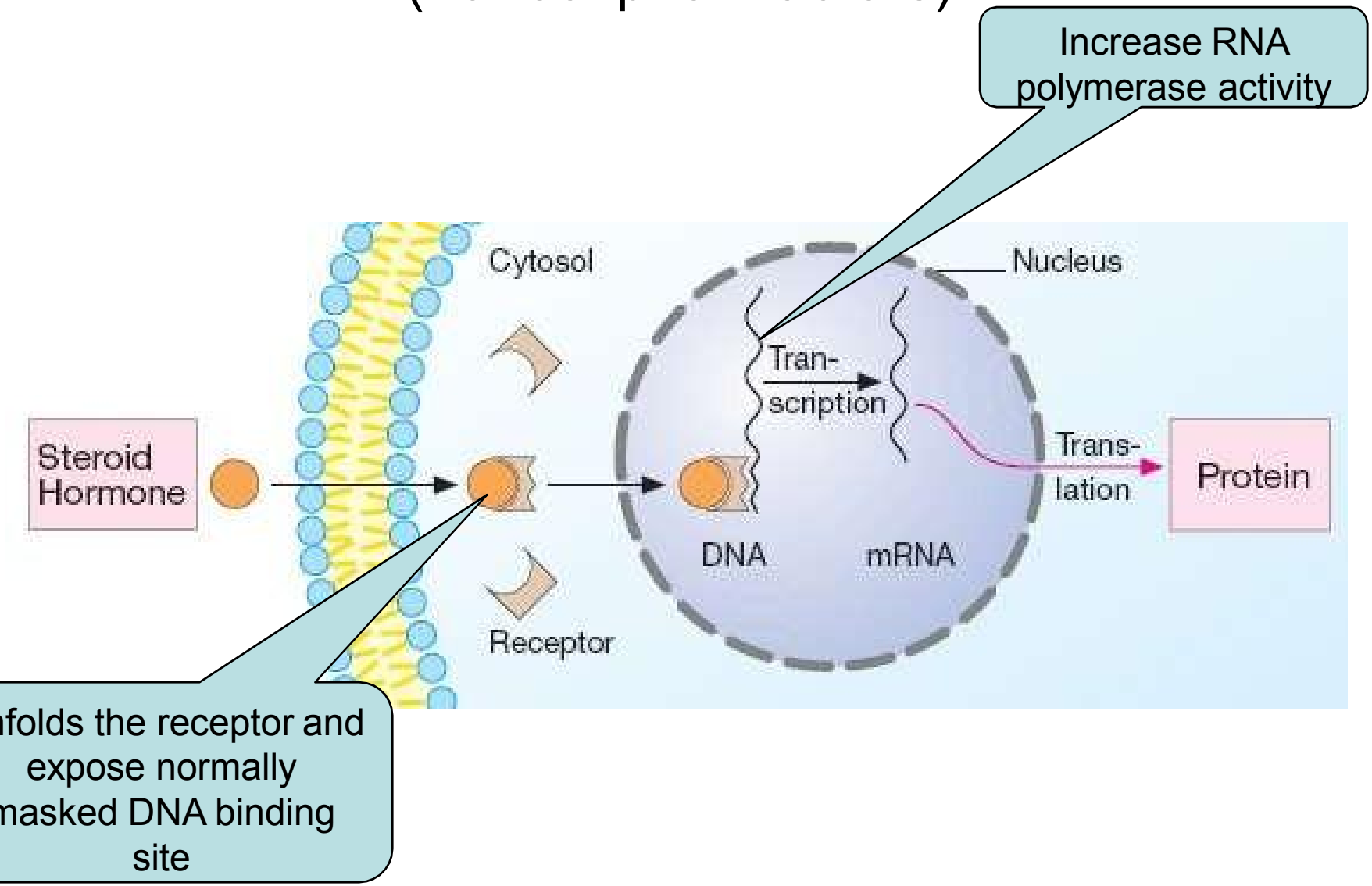
- These receptor are directly linked tyrosine kinase.
- Receptor binding domain present in extra cellular site.
- Produce conformational changes in intra cellular

Ex:- Insulin receptors

Enzymatic receptors



Receptor regulating gene expression (transcription factors)



Receptor regulation theory

- Receptors are in dynamic state.

- The affinity of the response to drugs is not fixed. It alters according to situation.

- Receptor down regulation:

Prolonged use of agonist

↓↓ Receptor number and sensitivity

↓ ↓ Drug effect

Ex: Chronic use of salbutamol down regulates $ß_2$ adrenergic receptors.

- Receptor up regulation:

Prolonged use of antagonist

↓

↑↑ Receptor number and sensitivity

↓

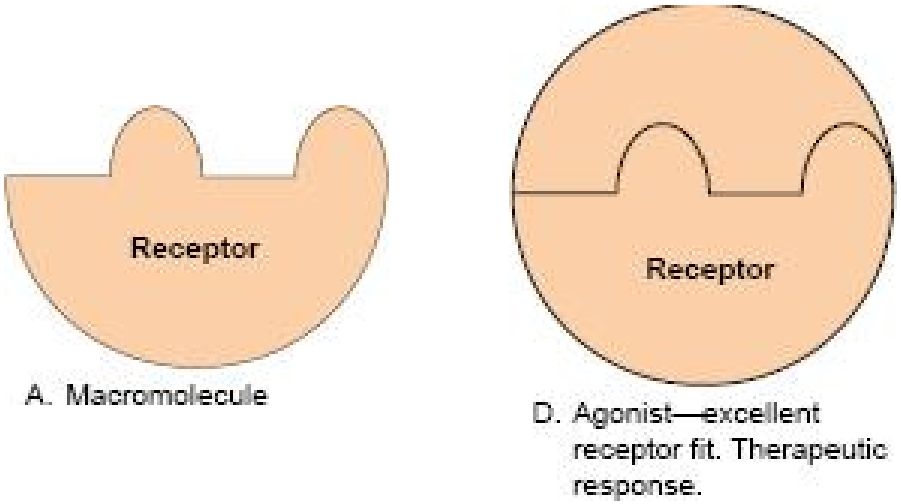
↑↑ Drug effect

- Ex:- propranolol is stopped after prolong use, produce withdrawal symptoms. Rise BP, induce of angina.

Agonist: Both the high affinity as well as intrinsic activity (IA=1)

These drug trigger the maximal biological response or mimic effect of the endogenous substance.

Ex:- Methacholine is a cholinomimetic drug which mimics the effect of Ach on cholinergic receptors.

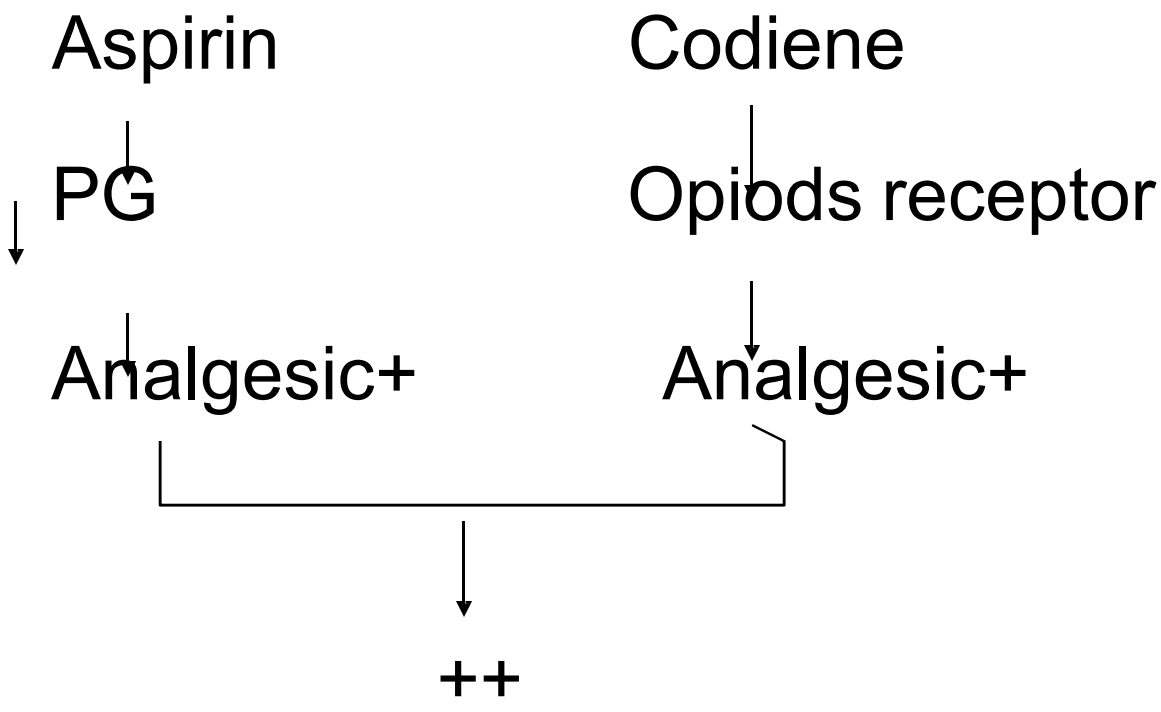


A. Macromolecule

D. Agonist—excellent receptor fit. Therapeutic response.

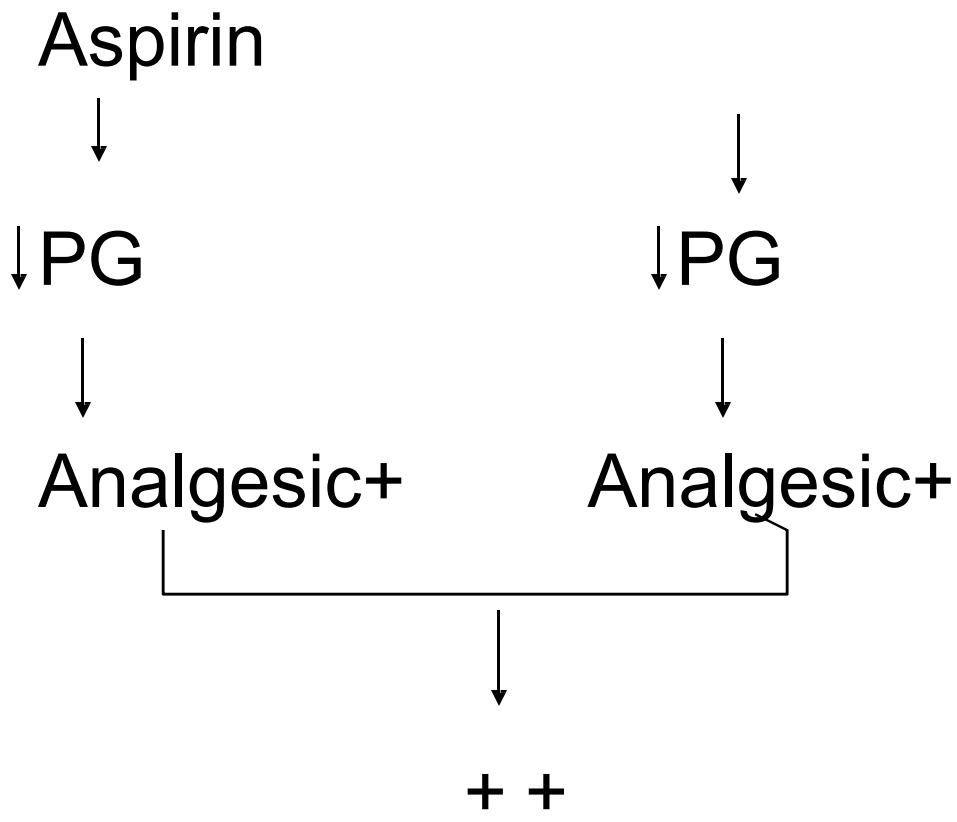
Types of agonism

- Summation :- Two drugs eliciting same response, but with different mechanism and their combined effect is equal to their summation. (1+1=2)



Types of agonism

- Additive: combined effect of two drugs acting by same mechanism



- Synergism (Supra additive):- (1+1=3)

The combined effect of two drug effect is higher than either individual effect.

Ex:-

1.Sulfamethaxazole+ Trimethoprim

2. Levodopa + Carbidopa.

Types of antagonism

Antagonism: Effect of two drugs is less than sum of the effects of the individual drugs.

1. Chemical antagonism

   Ex: -heparin(-ve) protamine +ve, Chelating agents

1. Physiological /Functional antagonism
2. Pharmacokinetic antagonism
3. Pharmacological antagonism
   I. Competitive (Reversible)
   II. Non competitive (Irreversible)

Pharmacokinetic antagonism

- One drug affects the absorption, metabolism or excretion of other drug and reduce their effect.

Ex:-Warfarin in presence of phenobarbitone, warfarin metabolism is increased, it effect is reduced.

Pharmacological antagonism

- Pharmacodynamic antagonism between two drugs acting at same receptors.
- Two important mechanism according to which these antagonists

»1.Reversible(Competitive)

»2.Irreversible(Non)

Reversible antagonism (Competitive antagonism)

- These inhibition is commonly observed with antagonists that bind reversibly to the same receptor site as that of an agonist.

- These type inhibition can be overcome increasing the concentration of agonist

- Ex:- Atropine is a competitive antagonist of Ach.

Irreversible Antagonism

- It occurs when the antagonist dissociates very slow or not at all from the receptors result that no change when the agonist applied.
- Antagonist effect cannot be overcome even after increasing the concentration of agonist

Non receptor mediated action

- All drugs action are not mediated by receptors. Some of drugs may act through chemical action or physical action or other modes.

  - » Chemical action
  - » Physical action (Astringents, sucralfate)
  - » False incorporation (PABA)
  - » Being protoplasmic action (antiseptics)
  - » Formation of antibody (Vaccines)
  - » Targeting specific genetic changes.

Dose

- It is the required amount of drug in weight, volumes, moles or IU to provide a desired effect.
- In clinical it is called as Therapeutic dose
- In experimental purpose it is called as effective dose.
- The therapeutic dose varies from person to person

Single dose:

1. Piperazine (4-5g) is sufficient to eradicate round worm.
2. Single IM dose of 250mg of ceftriaxone to treat gonorrhoea.

Daily dose:

It is the quantity of a drug to be administered in 24hr, all at once or equally divided dose.

1. 10mg of cetrizine (all at once) is sufficient to relive allergic reactions.
2. Erythromycin is 1g per day to be given in 4 equally divided dose (i.e., 250mg every 6 hr)

- Total dose: It is the maximum quantity of the drug that is needed the complete course of the therapy.

Ex:- procaine penicillin →early syphilis is 6 million unit → given as 0.6 million units per day for 10days.

Loading dose:- It is the large dose of drug to be given initially to provide the effective plasma concentration rapidly. The drugs having high Vd of distribution.

Chloroquine in Malaria – 600 mg Stat

300mg after 8 hours

300 mg after 2 days.

Maintenance dose:- Loading dose normally followed by maintenance dose.

- Needed to maintain the steady state plasma concentration attained after giving the loading dose.

Therapeutic index:

- Margin of safety
- Depend upon factor of dose producing desirable effect → dose eliciting toxic effect.

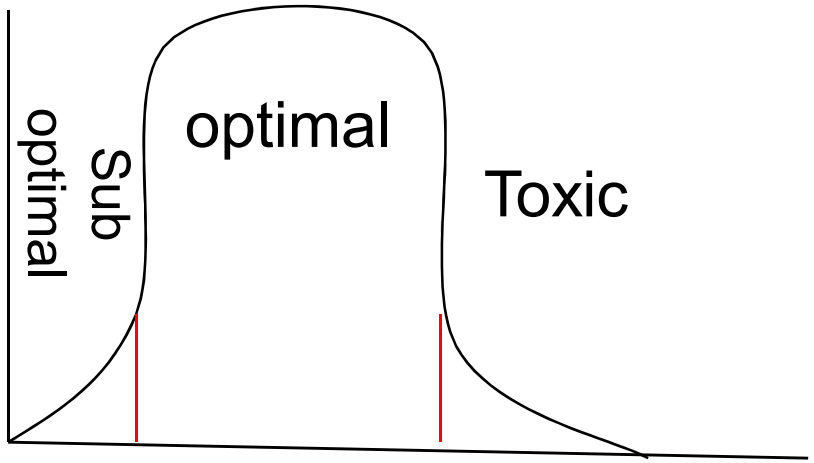
$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}$$

- TI →should be more than one

Therapeutic window:

Optimal therapeutic range of plasma concentrations at which most o the patients experience the desired effect.

Therapeutic range→ Therapeutic window



- Cyclosporine – 100-400ng/ml
- Carbamazapine- 4-10µg/ml
- Digoxin- 0.8-2ng/ml
- Lithium- 0.8-1.4 mEq/L
- Phenotoin – 10-20µg/ml
- Qunindine- 2-6µg/ml

- Tolerance: Increased amount of drug required to produce initial pharmacological response.
- Usually seen with alcohol, morphine, barbiturates, CNS active drugs

- Reverse tolerance:- Same amount drug produces inc pharmacological response.
- Cocaine, amphetamine → rats- inc. motor activity

Types of tolerances

- Innate tolerance: Genetically lack of sensitivity to a drug.

Ex:

- Rabbits tolerate to atropine large doses
- Chinese→ Castor oil
- Negros → Mydriatic action of sympathomimetics
- Eskimos→ high fatty diets

- Acquired tolerances:
- Occurs due to repeated use of drug
  - Pharmacokinetic tolerances
  - Pharmacodynamic tolerance
  - Acute tolerance

Pharmacokinetic tolerances:- Repetitive administration causes decrease their absorption or inc. its own metabolism

Ex: Alcohol → dec. absorption

Barbiturates→ Inc. own metabolism

- Pharmacodynamic tolerance
  - Down regulation of receptors
  - Impairment in signal transduction
  - Ex: Morphine, caffeine, nicotine.
- Acute tolerance: Tachyphylaxis Acute development of tolerance after a rapid and repeated administration of a drug in shorter intervals
- Ex; Ephedrine, tyramine

- Ex: Monday disease.
- Nitroglycerine – Monday , Tuesday workers get headache, after they get tolerances.
- After holiday (Sunday) they get again headache .
- Cross tolerances: Cross tolerance among drugs belonging to same category.
- MORPHIN→HEROIN→ NARCOTIC

FACTORS MODIFYING THE EFFECTS OF DRUGS

- Individuals differ both in the degree and the character of the response that a drug may elicit
- Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions.

- One or more of the following categories of differences among individuals are responsible for the variations in drug response:

  Individuals differ in pharmacokinetic handling of drugs

  Variation in number or state of receptors, coupling proteins or other components of response

  Variation in neurogenic/ hormonal tone or concentrations of specific constituents

- These factors modify drug action either:
  a) Quantitatively
     - The plasma concentration and / or the drug action is increased or decreased
  b) Qualitatively
     - The type of response is altered, eg: drug allergy and idiosyncrasy

- The various factors are:

1. **Body weight/size:**

   It influences the concentration of drug attained at the site of action

   The average adult dose refers to individuals of medium built

- For exceptionally obese or lean individuals and for children dose may be calculated on body weight basis

$$\text{Individual dose} = \frac{\text{BW(kg)}}{70} \text{ x Average adult dose}$$

$$\text{Individual dose} = \frac{\text{BSA(m2)}}{1.7} \text{ x Average adult dose}$$

  - BSA=BW(Kg)0.425 x Height(cm)0.725 x 0.007184

2. **Age:**

Infants and Children:

The dose of drug for children often calculated from the adult dose

$$\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \text{ x adult dose} \ldots\ldots\ldots \text{Y(oung's formula)}$$

$$\text{Child dose} = \frac{\text{Age}}{20} \text{ x adult dose} \ldots\ldots\ldots \text{(Dilling's formula)}$$

- However, infants and children are have important physiological differences
- Higher proportion of water
- Lower plasma protein levels
  - More available drug
- Immature liver/kidneys
  - Liver often metabolizes more slowly
  - Kidneys may excrete more slowly

Elders:

- In elderly, renal function progressively declines (intact nephron loss) and drug doses have to be reduced
- Chronic disease states
- Decreased plasma protein binding
- Slower metabolism
- Slower excretion
- Dietary deficiencies
- Use of multiple medications
- Lack of compliance

3. **Sex:**

- Females have smaller body size, and so require doses of drugs on the lower side of the dose range
- They should not be given uterine stimulants during *menstruation*, quinine during *pregnancy* and sedatives during *lactation*

4. **Pregnancy:**

- Profound physiological changes which may affect drug responses:

  GI motility reduced –delayed absorption of orally administered drugs

  Plasma and ECF volume expands

  Albumin level falls

  Renal blood flow increases markedly

  Hepatic microsomal enzyme induction

5. **Food:**

- Delays gastric emptying, delays absorption (ampicillin)
- Calcium in milk –interferes with absorption of tetracyclines and iron by chelation
- Protein malnutrition

  Loss of BW

  Reduced hepatic metabolizing capacity

  Hypoproteinemia

6. **Species and race:**

- Rabbits resistant to atropine
- Rat & mice are resistant to digitalis
- In humans: blacks require higher Mongols require lower concentrations of atropine and ephedrine to dilate their pupil

7. **Route of drug administration:**

- I.V route dose smaller than oral route
- Magnesium sulfate:

  Orally –purgative

  Parenterally –sedative

  Locally –reduces inflammation

8. **Biorhythm: (Chronopharmacolgy)**

- Hypnotics –taken at night
- Corticosteroid –taken at a single morning dose

9. **Psychological state:**

- Efficacy of drugs can be effected by patients beliefs, attitudes and expectations
- Particularly applicable to centrally acting drugs
- In some patients inert drugs (placebo) may produce beneficial effects equivalent to the drug, and may induce sleep in insomnia

10. **Presence of diseases/pathological states:**

- Drug may aggravate underlying pathology
- Hepatic disease may slow drug metabolism
- Renal disease may slow drug elimination
- Acid/base abnormalities may change drug absorption or elimination
- Severe shock with vasoconstriction delays absorption of drugs from s.c. or i.m
- Drug metabolism in:

  Hyperthyroidism –enhanced

  Hypothyroidism -diminished

11. **Cumulation:**

- Any drug will cumulate in the body if rate of administration is more than the rate of elimination

  Eg: digitalis, heavy metals etc.

12. **Genetic factors:**

- Lack of specific enzymes
- Lower metabolic rate

  Acetylation

  Plasma cholinesterase (Atypical pseudo cholinesterase)

  G-6PD

  Glucuronide conjugation

13. **Tolerance:**

- It means requirement of a higher dose of the drug to produce an effect, which is ordinarily produced by normal therapeutic dose of the drug
- Drug tolerance may be:

  Natural

  Acquired

  Cross tolerance

  Tachyphylaxis (ephedrine, tyramine, nicotine)

  Drug resistance

14. **Other drugs:**

- By interactions in many ways


THANK YOU