Receptors (1)

Many drugs act by binding to specific receptors Protein Macromolecules on & in cell membrane of

— Regulate the function of cell by alle /
- Enzyme activity
- Permeability to ions
- genetic Material in the nucleus.

When a drug acts and produces an effect on tissue it is the result of an interaction b/w the molecule & some part of tissue cells.

In some cases other interaction < Highly specific / None specific

Hence drugs are catagorized into those acting on receptors and others in which receptors are not involved

Which act on receptors ① at at low concentration
② React @ specific receptors
③ Show structure activity relationships
④ Can be antagonized by specific antagonists

Eg: Acetylcholine
adrenaline
Histamine

Which do not act via receptors : ① Act at higher conc
② do not react @ specific receptors,
③ Tend do not show structure activity relation ship
④ Do not have specific antagonists

Eg: Diethyl ether & Halothane
Diuretics like thiazides

Receptor: Macromolecular site on cell where an agonist binds to bring about a change (Response)

Agonist → It has → Affinity → Ability of drug to bind to a receptor
→ Intrinsic activity or efficacy → is the ability of a drug to elicit a response after binding to receptor

Eg: Adrenaline agonist at α, β adrenoreceptors
Morphine at μ opioid receptors

Antagonist: → It a substance that binds to the receptor & prevents the action of agonist on the receptor.

It has → affinity but not intrinsic activity

Eg: **Naloxone** is an antagonist at the opioid receptors
It binds to receptors has no effect by itself but blocks the action of the opioid agonist

Tubocurarine is an antagonist at nicotinic receptors
blocks the receptors & prevents the action of acetyl choline on receptors.

Partial Agonist: ~~binds to receptor~~ has affinity but has less intrinsic activity
Drug Though high in conc will not produce full response which the tissue capable of.
Eg: Pindolol → at β adrenergic Receptors / Pentazocine at μ opioid receptors

Inverse agonist: Some drugs after binding to receptors Produce opposite actions to those produced by agonists
Eg: Diazepam on benzodiazepine Receptors
Produce — Sedation, anxiolysis, Muscle Relaxation & control Convulsions

(3) While the curare agonists. β carbolines bind to same receptors to cause clonical, anxiety like convulsions.

Ligand: A Molecule which binds selectively to specific receptors

Site: ① on Cell membrane
② in cytoplasm
③ on Nucleus

Nature: Proteins

Synthesis: Synthesized by the cells
After their life span they are degraded by cell
& New receptors are synthesized.

Function of Receptor:
- Recognition & binding of the ligand
- Propagation of the message

For this functions the receptors have functional areas
1. Ligand binding site to drug molecule
2. An Effector site → which undergoes change to Propagate the message

Types of Receptors:
1. Ionotropic receptors — Ion channel
2. G-protein coupled Receptor — G-PCR
3. Enzymatic Receptor — Kinase receptor.
4. Nuclear receptor → Regulate gene transcription

(1) Ionotropic receptors: (1) present on cell surface (4)

(2) Binding of agonist opens the channel
↓ allowing

(3) Ions to cross the membrane

(4) They are called "ligand gated ion channels"

(5) Depending upon which ion flows and what voltage changes occur as a consequence depend upon the type of channel.

Thus opening up of Nicotinic Acetyl choline receptor channel → permits Na^+ ions to cross the membrane into cell and cause depolarisation of the membrane.

Gamma amenobutyric acid (GABA) receptor allows Cl^- to permeate ↓ hyperpolarization occur.

Phenobarbitone & benzodiazepines act by modifying the function of receptor channels ↓
opening of K channel allows K^+ to leak out of the cell and there hyperpolarise

The cell membrane Eg: Sulphonylurea receptor.

(5)

(3) G-protein → ① G proteins are bound to inner face of plasma membrane

Type 2 (GPCR) G-Protein coupled Receptor

② When ligand binds to 'G' protein receptor → gets activated

↓

Protein activates Adenylcyclase orphospholipase C

↓

To generate the respective 2nd messengers (2nd messengers are called effector pathways)

↓

G proteins acting through 2nd messengers bring about chain of intracellular changes.

Because they interact with guanine nucleotides called G protein → Guanosine diphosphate/triphosphate

Refers

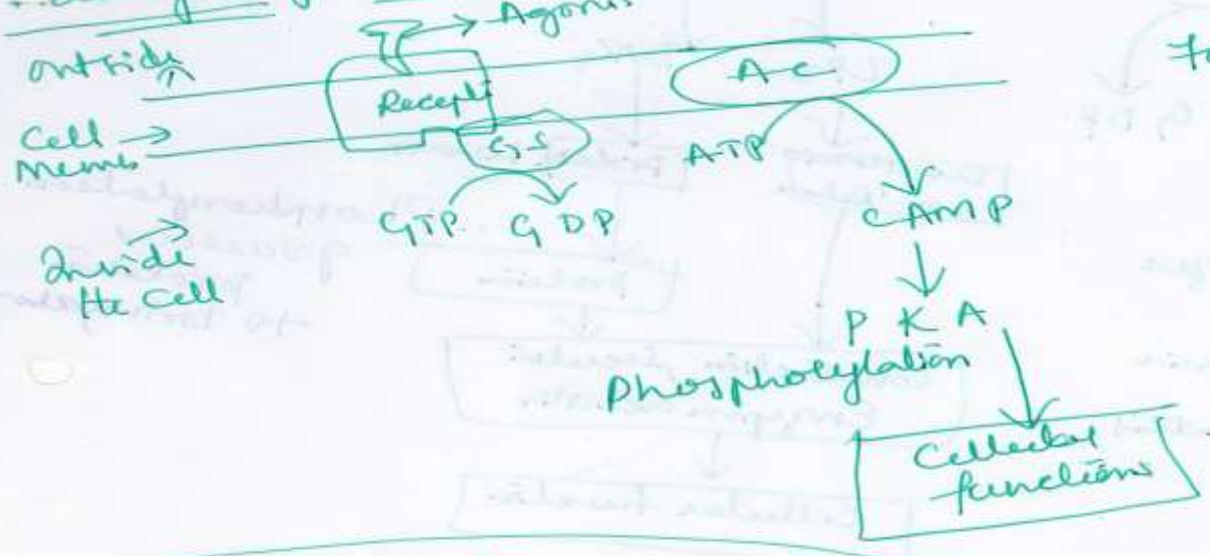
They are → Gs — stimulatory } in action
→ Gi → inhibitory }

Second Messengers Are cAMP, cGMP
IP_3 → Inositol triphosphate
Ca^{++}
DAG → Diacyl glycerol

(6) Effector pathways through which G protein coupled receptors work are

- Adenyl cyclase pathway (cAMP)
- Phospholipase C pathway (PLC) / IP3 – DAG pathway
- Ion channel regulation

∴ Adenyl cyclase pathway :



∴ → Stimulation of Adenyl cyclase

↓

formation ↓ accumulation of cAMP within cell

↓

cAMP acts through protein kinase which phosphorylates various proteins to regulate cell function

- Contraction
- Relaxation
- Hormone synthesis
- Glycogenolysis

cAMP

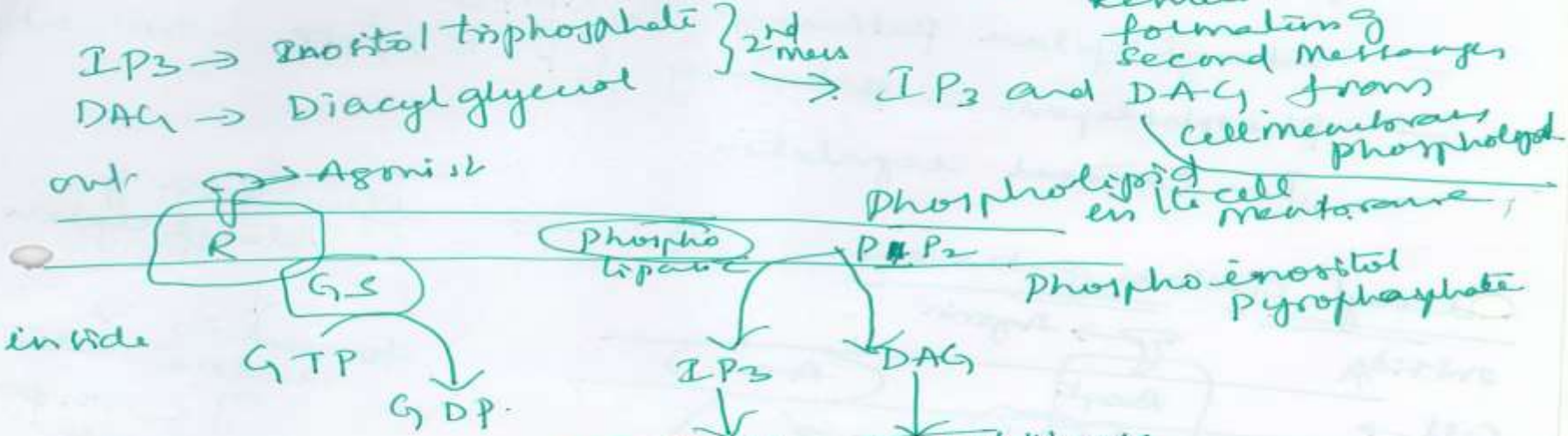
Adenosine Monophosphate from ATP Triphosphate

① Phospholipase pathway : ① Activation of Phospholipase C

↓

Result: formation of second Messengers IP3 and DAG from cell membrane phospholipid

IP3 → Inositol triphosphate } 2nd Messengers
DAG → Diacyl glycerol



② IP3 Mobilizes Ca++ from Sarcoplasmic reticulum and Mitochondria
- Contraction
- Secretion
- Metabolism

③ DAG → Activate protein Kinase which regulate Cell function

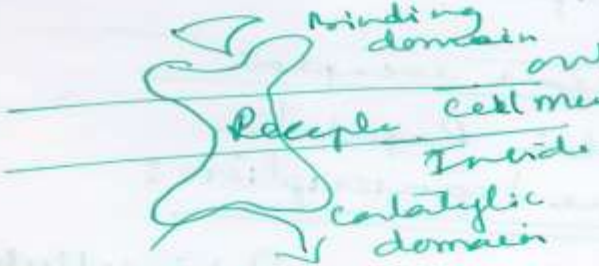
(8) Ion channel regulation

Directly

without help of 2nd messengers

Activated G proteins can directly convey signals to some ion channels causing opening or closing of channels Results Hyperpolarization or depolarization

(3) Enzymatic Receptors : (1) Are Transmembrane proteins with Extracellular site for ligand binding & Intracellular site to carry out catalytic activity



(2) Two sites are linked by a single peptide chain, proteins known as called linked receptors.

(3) Binding of agonist results autophosphorylation of intracellular domain

(4) Triggers phosphorylation of various intracellular proteins resulting characteristic response.

Ex. second subtype of Enzyme linked receptor is JAK-STAT binding receptor

③ Enzyme Receptor when agonist binds Extracellularly
↓
activate intracellular domain
↓
and Mobile JAK (Janus Kinase) molecules are activated
↓
Intern activate STAT
Signal transducers → activation of Transcription
↓
Move to Nucleus & Regulate Transcription

Agonist
↓
Bind Extracellular
↓
Intracellular activation
↓
form dimers
↓
Activate JAK
↓
Activate STAT
↓
Move to nucleus
↓
Regulate transcription

④ Nuclear receptor
Receptor Regulate gene transcription:

① They are Intracellular
② Called Nuclear receptors
③ Binding of agonist
④ activate → receptor
↓
⑤ agonist receptor complex
↓
Moves to Nucleus where interact with DNA to regulate the activity of target Cells
Eg Thyroid Hormone, Vit D & Retinoic

Receptor Regulation

① Desensitization
② Constant antagonist action
③ Prolonged depression of agonist

↓

Result is an ↑ in Number & Sensitivity of Receptors

↓

Called "up regulation"

Type 4

Prolonged use of β adrenergic antagonist like propranolol result in up regulation of β adrenergic receptors

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Continued stimulation of receptors causes desensitization and ↓ se in number of receptors → known as "down regulation" of receptors

(11) Spare Receptors : In an Experiment c adrenaline on Rabbit aortic strips

↓ Shows agonist occupies small percentage of receptors to produce Maximum contraction

Some other Experiment shows that high concentration of agonist can still produce Max response in presence of irreversible antagonist & this was because of presence of spare receptors

Thus possible to stimulate Myocardium even 90% of its cardiac β adrenergic receptors are blocked by an irreversible β blocker.

Silent Receptors : When the agonist binds to receptors but does not produce a response

↓ Presence of such type of silent receptors Explain the phenomenon of Tolerance.

↓ They first bind the drug & the drug is not available for action.

SAR Structural activity relationship

That Means activity of a drug

↓

Related to its chemical structure

Chemical structure of the drug is useful for

I. Synthesis of New compounds with More specific action & few adverse effects

II. Synthesis of competitive antagonists

III. To understand the basic, Chemical groups for Drug action

→ I Synthesis of New compounds:

Drug Substitutes are designed

(1) To ↑ se or ↓ se the duration of action of original drug / to get More potent compounds.

(2) To restrict the drug action to particular system of the body.

3. To reduce adverse effects (reactions) and other disadvantages attributed to available drugs.

I 1. To ↑se/↓se the duration

Eg: procaine is local anaesthetic

↓ when Administered Intravenously

Reduces Cardiac rate & Excitability

↓ but

Rapidly Hydrolized & its action is less transient

Hence structurally similar compound to procaine but resistant to hydrolysis is "procainamide"

↓

Has longer duration of action & Used to treat cardiac arrhythmias

Another Example

Atropine when instilled into Eye

↓

③ Causes Dilatation of Pupil
(i.e Mydriasis)

↓

Paralysis of Ocular Muscles of Accomodation
(i.e cycloplegia).

↓

And this action persists for one week.

Its Substitute Homatropine produces same effect
but its action lasts for 24hrs.

Discussion
Regular Eye Checkups to Examine retina pupils are dilated with help of Mydriatics i.e Homatropine.

I ②. To restrict the drug action to particular systems of the body.

Ex: Chlorpromazine has antipsychotic
— anti cholinergic
— Hypotensive
— Sedative.
} properties. → CNS acti / CNS acti on

By structural Modification of ~~structure~~ of Chlorpromazine
compounds with More potent antipsychotic effect

with negligible sedative & Hypotensive properties can be manufactured.

So that only on one particular system CNS → it acts sparing CNS.

Eg: Trifluoperazine ← Chlorpromazine

I. (3) To Reduce adverse effects
↓
disadvantages

Eg: Nicotinic acid → Deficiency causes Niacen B3 vit causes pellagra.

↓

it produces SideEffects like

- Itching
- flushing of skin
- BP fall

Related compound Nicotinamide has same efficacy against pellagra without above adverse effects.

Similarly Benzyl penicillin → given orally
↓
inactivated by gastric acid

Hence gastric acid resistant penicillins are synthesized to administer orally.

Eg: Phenoxymethyl Penicilline → Penicillinase Resistant
Eg cloxacillin.

II Synthesis of Competitive antagonists

Ex: PABA Para amino benzoic acid

which is essential growth factor for microorganisms

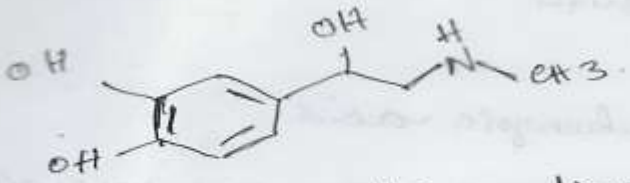
PAS: Para amino salicylic acid competes with PABA

Hence Nonavailability of PABA arrests Multiplication of bacterial growth.

Respiratory depressant action of morphine antagonised by structurally similar compound "Naloxophene"

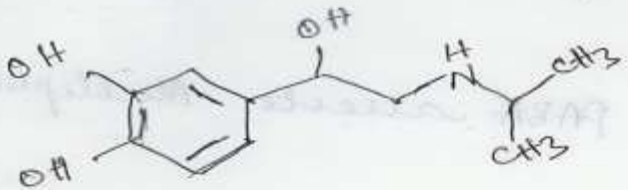
III Understanding of basic chemical groups responsible for drug action:

1. Adrenaline stimulates Both α & β adrenergic receptors.

1. 

→ Stimulates both α & β adrenergic receptors

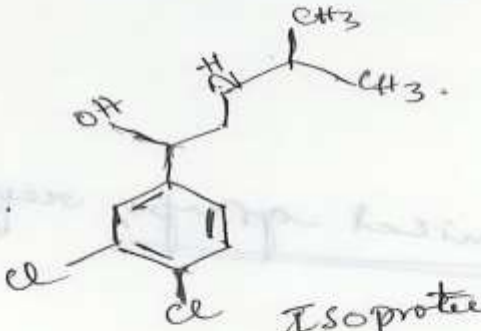
Adrenaline structure

2. 

Isoprenaline → structure : crystalline

Selectivity : Stimulates only β receptors

Bradycardia & Heart blocks

3. 

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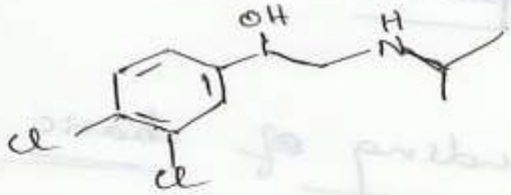
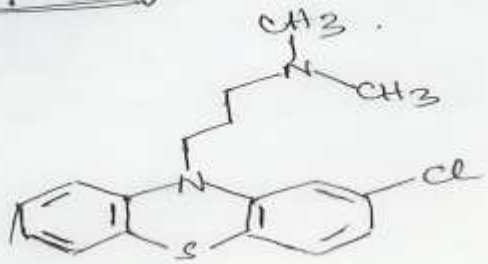


Isoproterenol

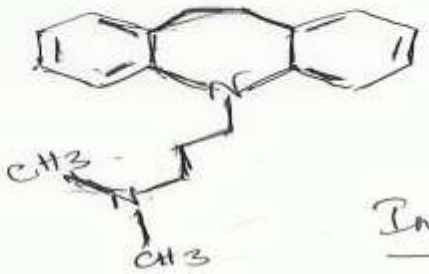
Dichloro Isoproterenol

→ Blocks β adrenergic receptors

Chlorpromazine → Tranquilizer useful in antipsychotic ≫ agitational disorder



Imipramine structurally similar compound is antidepressant used in Mood Elevation.



Imipramine