Pharmacology

Pharmacokinetics  Pharmacodynamics
Pharmacodynamics vs Pharmacokinetics

What drug does to the body

What body does to the drug

ADME

Absorption

Distribution

Metabolism

Elimination
PHARMACODYNAMICS

Dr. Satyajit, MD
Assistant professor
What the drug does to the body
Deals with

- Mechanism of action
- Organ system effects
- Adverse drug reaction
- Drug-receptor interactions
- Combined drug action
Physiological system

Drug

Effects
Principles of Drug action

- **Stimulation:** \(\uparrow\)ing activity of tissues
- **Depression:** \(\downarrow\)ing activity of tissues
- **Irritation:** Counterirritant
- **Replacement:** Insulin in DM
- **Chemotherapy:** Antibiotics/anticancer drugs
Adrenalin stimulates heart
Quinidine depresses heart
Certain drugs stimulate one type of cell and depress other type of cell

- Ach *stimulates* intestinal smooth muscle but *depress* SA node in heart
IRRITATION

- Non selective, noxious effect
- Applied to less specialized cells (epithelium)
  - Bitters increase salivary and gastric secretion
  - Counterirritants increase blood flow
• Use of natural metabolites, hormones and their congeners in deficiency states
Diabetes

Insulin

glucose does not go into cell

glucose (sugar)

insulin

cell

DIABETES
CYTOTOXIC ACTION

- Selective cytotoxic action for parasites or cancer cells, attenuating them without affecting the host cells
  - Penicillin, Chloroquine, Zidovudine
Mechanisms of drug action

Non receptor mediated

&

Receptor mediated
Non receptor mediated actions

1. Physical action:
   - Mass of drug - Ispaghula husk
   - Adsorptive property - char coal
   - Osmotic activity - Magnesium sulfate
   - Radio activity - $^{131}\text{I}$
   - Oxidising property - KMnO$_4$
HUSK
Ispaghula Husk

Herbal medicinal product for:
Irritable Bowel Syndrome ✓
Constipation ✓
Diarrhoea ✓

100% natural fibre product

200 grams
Powder for Oral Suspension
2. Chemical action

Antacids neutralise gastric HCl
Peptic ulcers may lead to bleeding or perforation, emergency situations.
3. Through enzymes

Stimulation
Pyridoxine acts as co factor for \textit{dopa decarboxylase} activity

Inhibition
Aspirin inhibits \textit{Cyclooxygenase}
4. Through ion channels:

Calcium channel blockers

Sodium channel blockers

Potassium channel openers
5. Altering the metabolic processes

**Sulfonamides** – interfere with bacterial *folic acid synthesis*
6. **Placebo effect**

- Inert substance which is given in the garb of medicine
- Works by psychological rather than pharmacological means
- Often responses equivalent to the active drug
Non receptor mediated actions

- Physical
- Chemical
- Enzymatic
- Ion channel
- Alteration of metabolism
- Placebo
4 major target of drug action

- Enzymes
- Ion channels
- Transporters
- Receptors
Receptor mediated action
What is a receptor???

- Macromolecule or binding site located *on the surface* or *inside the effector cell* that serves to recognise the signal molecule/drug and initiate response to it.

- Itself has *no function*.
Different terminologies

- **Affinity**

Ability of the drug to bind the receptor
• **Intrinsic activity** -

Ability of the drug to elicit a response after binding to a receptor
Agonist

• Has affinity + IA

An agent which activates the receptor to produce an effect similar to that of physiological signal molecule drenaline on β receptor
Antagonist

- Affinity + No I.A.

Agent which *prevents* the action of an *agonist* on a receptor and subsequent response.

Does not have any effect of its own.

*Propranolol on β receptor*
Partial agonist

Affinity + sub maximal I.A.

Binds to receptor but sub maximal response

Eg: Nalorphine
**Inverse agonist**

Affinity+ I.A with negative sign

- **GABA Receptor**
- **Agonist**
- **Inverse agonist**
- **Anti convulsant**
- **Convulsions**

**Eg:** β-Carboline
Ligand

- Any molecule which attaches selectively to particular receptors or site

- Only indicates affinity or binding without regard to functional change

- Agonists or competitive agonists are ligands of same receptors
Functions of Receptors

- Recognition & binding of the ligand
- Propagation & integration of the message/signal
Dose - Response relationship
Dose - response relationship

- *Dose - plasma concentration* (Pk study)
- *Plasma concentration- response* (*in Vitro*)
Dose response curve

Rectangular hyperbola
• Intensity of the response increases with dose
• Dose response curve is *rectangular hyperbola*
• Drug-receptor interaction obeys the *Law of mass action*

\[ E = \frac{E_{\text{max}} \times [D]}{K_D + [D]} \]

- \( E \) = Observed effect at dose D
- \( E_{\text{max}} \) = Maximal response
- \( K_D \) = dissociation constant
Log dose response curve

Sigmoid curve
• Linear relationship between log dose and response is seen in intermediate (30-70%)

Advantages of plotting a LDRC
- Wide range of drug doses can be easily displayed
- Comparison between agonist and antagonist becomes easier
Fig. 1–2. A dose–response curve obtained in one patient relating the dose of aspirin ingested to the percentage of headache pain relieved. (A) A linear plot: the abscissa (dose in milligrams) has a linear scale. (B) A semilog plot: the abscissa (dose in milligrams) has a logarithmic scale.
A. An experiment was performed on 100 subjects and the effective dose to produce a quantal response was determined for each individual. The number of subjects who required each dose is plotted, giving a lognormal frequency distribution (bars with diagonal lines). The stippled bars demonstrate that the normal frequency distribution, when summated, yields the cumulative frequency distribution—a sigmoidal curve that is a quantal dose-effect curve.
Potency

*Amount of the drug* required to elicit a response
Relative Potency

Analgesia

Dose

- hydromorphone
- morphine
- codeine
- aspirin
Efficacy

It is the *maximum effect* of the drug.
Potency: Drug A > Drug B > Drug C
SELECTIVITY
• **DRCs** for different effects of a drug may be different

• Extent of separation of **DRCs** of a drug for different effects is a measure of its selectivity
A – Salbutamol – bronchodilatation
B – Isoprenaline – bronchodilatation
C – Isoprenaline – cardiac stimulation
D – Salbutamol – cardiac stimulation
Therapeutic Index
The gap between the *therapeutic effect* and the *adverse effect* DRC defines the *safety margin* or *therapeutic index* of a drug.
Therapeutic index

Mnemonic : T I L E

Indicates - safety margin of a drug

Therapeutic index = $\frac{LD_{50}}{ED_{50}}$
• What should be the value of TI??

• Is it $< 1$ or $> 1$?

• If $< 1$, what do you mean?
• If $> 1$, what do you mean?

**Drugs should have TI $> 1$**
• TI is irrelevant in clinical set up

• In clinical trials, defined as TD_{50} / ED_{50}

• So defined by *therapeutic range*
Therapeutic Window

- Certain drugs - optimal therapeutic effect is exerted only over a narrow range of plasma concentration.
- Below and above it, beneficial effects are suboptimal.

- **Clonidine** - anti hypertensive effect - 0.2 - 2 ng/ml
  - BP may rise above 2 ng/ml

- **TCAs** exert maximum effect 50-150 ng/ml
Figure 2: The concept of a therapeutic window

- **Toxic**: Concentration levels too high, exceeding the MTC.
- **Effective**: Concentration levels within the Therapeutic Range, optimal for treatment.
- **Ineffective**: Concentration levels not high enough to achieve therapeutic effects.
Combined effect of Drugs
When two or more drugs are given simultaneously or in quick succession, they may be *indifferent* or exhibit *synergism* or *antagonism*.

May be **PK** or **PD** interactions.
Synergism

- **Syn** – together
- **Ergon** – work
- They may act in same direction
- One may be inactive, but enhances others action
• Additive

• **Supraadditive** (Potentiation)
1. **Additive:**

Effect of combination is equal to the individual effect of components

Effect of drugs $A+B =$

Effect of drug $A$ + Effect of drug $B$
• Aspirin + Paracetamol – analgesic/antipyretic

• Nitric oxide + Halothane – General anesthetic
Potentiation

**Supra additive:**
Effect of combination is greater than the individual effects of components

\[
\text{Effect of drug A+B} > \text{Effect of drug A + effect of drug B}
\]

- Levodopa + Carbidopa – Inhibition of peripheral metabolism
- Sulfamethoxazole + Trimethoprim – sequential blockade
Antagonism
One drug *decreases* or *inhibits* the action of other

1. **Physical Antagonism**
   - Charcoal (adsorbs alkaloids)
   - Used in Rx of alkaloidal poisonings

2. **Chemical antagonism**
   - Two drugs react chemically – inactive product
   - Antacids in the Rx of peptic ulcer
3. Physiological antagonism:

Two drugs act on different receptors or by different mechanisms, but have opposite effects on same physiological function.

- Histamine & Adrenaline in anaphylactic shock
- Glucagon and insulin on blood glucose level
Receptor antagonism
• One drug (antagonist) blocks the receptor action of other (agonist)

• *Receptor antagonists are selective*  
  (anticholinergic will block the contraction of smooth muscles by cholinergic agonists only not by histamine)
- Competitive antagonism
- Noncompetitive antagonism
Competitive antagonism

Agonist & Antagonist have
- **Same** chemical structure
- **Same** receptor
- **Same** binding site

• Action overcome by ↑ing agonist concentration
  *(surmountable* antagonism)*
• Potency affected
- **ACh & Atropine** at Muscarinic receptor

- This principle is used in the treatment of *Insecticide (fertiliser) poisoning*
Competitive Antagonist

Agonist

Agonist + Competitive Antagonist
Non competitive antagonism

Agonist & antagonist have

- Different chemical structure
- Same receptor
- Different binding site

Cannot be overcome by ↑ing agonist concentration (unsurmountable antagonism)

- **Efficacy** ↓ed
- Eg: Diazepam & Bicuculine at GABA receptor
Non-Competitive Antagonists

- Agonist
- Agonist + Non-Competitive Antagonist
Non equilibrium type / Irreversible antagonism

- Antagonist forms strong *covalent bonds*
- Bind to the same site of receptor, but dissociates very slowly
- Flattens as well as rightward shift of DRC

Adrenaline & Phenoxybenzamine on alpha receptors
So far we discussed......
• Therapeutic index
• Therapeutic range
• Combined drug effect
• Antagonism
Action-Effect sequence
Drug Action

Initial combination of the drug with its receptor resulting in *conformational changes* in the receptor.
Drug effect

Ultimate change in the biological function brought about as a consequence of drug action, through a series of intermediate steps (Transducers)
Receptor

- Two functions
  - *Recognition* of specific ligand
  - *Transduction* of signal into response

- So it has
  - *Ligand binding domain*
  - *Effector domain* - undergoes conformational changes
Transducer mechanism
1. Ion channel linked
2. G protein linked
3. Enzyme linked
4. Nuclear (gene) linked
Ligand Gated Ion Channel Receptor
Signal molecule (ligand) binds to the ion-channel protein in the plasma membrane. This leads to the channel opening, allowing ions to flow through. The change in ion concentration triggers cellular responses. The ligand then dissociates from the protein, and the channel closes.
Ion channel receptors

- *Nicotinic* receptor - Na\(^+\) ion
- \(\text{GABA}_A\) receptor - Cl\(^-\) ion
G protein-linked receptors

EXTRACELLULAR FLUID

Plasma membrane

CYTOSOL

Signal-binding site

Segment that interacts with G proteins

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GPCR

- G-protein coupled receptor

- Receptors are linked to the effector (enzyme/channel) through one or more GTP-activated proteins
Structure of GP

- Single polypeptide chain threaded back and forth resulting in 7 transmembrane helices
- There’s a G protein attached to the cytoplasmic side of the membrane (functions as a switch)
3 extracellular loops and 3 intracellular loops

Agonists bind to extracellular face
G protein bind to the cytosolic site
Remember just 3 types of G proteins

- $G_\text{s}$: Adenylate cyclase stimulation
- $G_\text{i}$: Adenylate cyclase inhibition
- $G_\text{q}$: Phospholipase-C activation
3 major effector pathways for GPCR

- Adenylyl cyclase: cAMP pathway
- Phospholipase C: IP$_3$ -DAG pathway
- Channel regulation
Effector pathways

1. **Adenylyl cyclase: stimulation**
   \[ \uparrow \text{cAMP} \rightarrow \text{cAMP dependent protein kinase} \]
   - \(\uparrow\) contraction, impulse generation (Heart)
   - Relaxation - Smooth muscle
   - Glycogenolysis
   - Lipolysis
2. Phospho lipase C: stimulation

\[
\text{PIP2} \quad \text{↓} \\
\text{IP}_3 \quad \text{↓} \\
\text{Mobilisation of Ca}^{2+} \\
\]

\[
\text{DAG} \quad \text{↓} \\
\text{Activates PKC} \\
\]
Functions Of Gq activation:

• Contraction
• Secretion/transmitter release
• Neuronal excitability
Enzyme linked receptors

Intrinsic tyrosine protein kinase receptor: On binding the peptide hormone to the extracellular domains, the monomeric receptors move laterally in the membrane and form dimers. Dimerization activates tyrosine-protein kinase (t-Pr-K) activity of the intracellular domains so that they phosphorylate tyrosine (t) residues on each other, as well as on several SH2 domain substrate proteins (SH2-Pr). The phosphorylated substrate proteins then perform downstream signaling function.
Receptor regulating gene expression
Answer • • •
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| **Inverse agonist**      | Has affinity and intrinsic activity  
                           | In opposite direction to that of agonist |
| **Partial agonist**      | Has affinity and submaximal intrinsic activity |
## Match the following

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Tick All the appropriate answers.

1. $\beta$ subunit of G-protein coupled receptor has intrinsic GTPase action.
2. An agonist binds with GPCR and then only changes in ion channel occur.
3. Whereas in an ionotropic receptor, agonist directly binds with the ion channel and cause effects.
4. Therapeutic Index is a measurement of Safety.
5. Competitive antagonist shifts DRC to right.
Short note on GPCR
1. They form the largest family of receptors.
2. They are cell membrane bound receptors which are coupled to effector (enzymes/ion channels) through GTP binding proteins known as G-proteins.
3. Guanosine proteins have seven $\alpha$ helices.
4. GPCR is a trimer, having $\alpha, \beta$ & $\gamma$ subunits.
6. Eg: Muscarinic receptor, $\alpha, \beta$ adrenergic receptor.
7. There are 3 main varieties of G-proteins.
8. Gs & Gi act on Adenylate Cyclase enzyme.
10. In inactive state GDP is bound to $\alpha$ subunit of $\alpha\beta\gamma$ trimer.
11. When agonist binds, receptor activation occurs, GDP dissociates from $\alpha$ subunit, GTP-GDP exchange occurs.
12. GTP- $\alpha$ subunit dissociates from $\beta$ & $\gamma$ subunits.
13. $\alpha$-GTP activate target cells.
14. GTPase activity of $\alpha$ subunit hydrolyses GTP to GDP and reunites with $\beta$ & $\gamma$ subunits. This completes a cycle.
Next Class is On

- Measurement of drug effects
- Factors Modifying drug Action
- Learn and come for the class.
- Thank You For Your Patience.
Factors affecting drug action

- Body weight:
Individual dose = $\text{BW(Kg)} \times \text{average adult} \quad 70 \quad \text{dose}

Individual Dose = $\text{BSA} \times \text{average adult} \quad 1.7 \quad \text{dose}$
• Age:
Kernicterus

Jaundice

Yellowing of eyes

Yellowing of skin

Excess bilirubin in blood

Kernicterus

Bilirubin moves from bloodstream into brain tissue
Young’s formula:

\[
\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{Adult dose}
\]

Dilling’s formula:

\[
\text{Child dose} = \frac{\text{Age}}{20} \times \text{Adult dose}
\]
Sex
Ketoconazole, Metoclopramide -
gynecomastia
Species & Race

• Resistant to atropine
• Sensitive to curare
• β blockers - less effective
• Higher concn of atropine as mydriatic
Psychological Factor
Psychological Factor
Diet & Environment

- Food-

-
Genetic Factors

- Malignant hyperthermia- Halothane
- SCh apnoea- SCh
Diseases

- Prodrug - should not be given
- drugs having high metabolism-
- BA - increased
• Aminoglycosides, Digoxin - Dose Reduction
• Vancomycin, Cyclosporine - Avoid
• Achlorhydria- Reduces aspirin absorption
Cumulation

- Chloroquine- Retinal damage
Tolerance

• **Natural:**
  Species or individual is inherently less sensitive to the drug.
  eg: Black races are tolerant to mydriatics.
  Rabbits are tolerant to atropine.

• **Acquired:**
  Repeated use of a drug in an individual who was initially responsive.
Eg: Tolerance – analgesic & euphoric action of morphine

- **Cross tolerance:**
  Development of tolerance to pharmacologically related drugs.

Eg: Alcoholics are generally tolerant to General anaesthetics.
• **Tachyphylaxis**: (Rapid development of tolerance)

Doses repeated in quick succession results in marked reduction in response.

Eg: Ephedrine, Tyramine, Nicotine
13. Drug resistance:

- ???
Summary

- most drugs act through receptors
- there are 4 common signal transduction methods
- the interaction between drug and receptor can be described mathematically and graphically
- agonists have both affinity and intrinsic activity.
- antagonists have affinity only
- antagonists can be competitive or non-competitive when mixed with agonists
- agonists desensitize receptors.
- antagonists sensitize receptors.
THANK YOU