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Pharmacology

for Medical Undergraduates



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Foreword
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CHAPTER 4

Pharmacodynamics, Adverse Drug Reactions, Pharmacovigilance and New Drug Approval Process

- Ways Drug Act
- Receptor
- Dose Response Relationship
- Drug Synergism and Antagonism
- Factors that Modify Effects of Drugs
- Drug Interactions
- Adverse Drug Reactions
- General Principles of Treatment of Poisoning Mnemonics (ABCDEFGHI)
- Pharmacovigilance
- New Drug Approval Process and Clinical Trials
- New Drug Application

INTRODUCTION

1. Pharmacodynamics is the study of actions of drugs on the body.
2. It is concerned about the mechanisms of action of the drug, i.e. to know **what drugs do and how they do it.**
3. Drugs produce their effects by interacting with the physiological systems of organisms.
4. Drugs merely modify the rate of functions of various systems.
5. Drugs do not bring about qualitative change.
6. They cannot change basic function of any physiological system.

WAYS DRUG ACT

1. **Stimulation:** It increases in the activity of the specialized cells, e.g. adrenaline stimulates the heart.
2. **Depression:** It decrease in the activity of specialized cells, e.g. quinidine depresses heart, barbiturates depresses the central nervous system (CNS)—some drugs stimulate one system and depresses another, e.g. morphine depresses CNS, but stimulates vagus.
3. **Irritation:** It can occur on all types of tissues, it may result in inflammation, corrosion, necrosis.
4. **Replacement:** It is used when there is deficiency of natural substances such as hormones, metabolites or nutrients, e.g. insulin in diabetes mellitus, iron in anemia, vitamin C in scurvy.
5. **Anti-infective action:** It destroys infective organisms, e.g. penicillins—cytotoxic effect on cancer cells, e.g. anticancer drugs.
6. **Modification of immune status:** For example, vaccines and sera, improve immunity whereas glucocorticoids depress immunity.

Mechanisms of Drug Action

1. Most drugs produce their effects by binding to specific target proteins such as receptors, enzymes or ion channels.
2. Drugs may act on cell membrane inside or outside cell.
3. Some act by complex mechanisms.
4. Action of some drugs is yet to be understood.
5. Some basic mechanisms of drug action:
   a. **Through receptors.**
   b. **Through enzymes and pumps (Fig. 4.1)**.
      i. Inhibition of enzymes, e.g. enalapril inhibits angiotensin-converting enzyme (ACE).
      ii. Inhibition of pumps, e.g. H^+, K^+ adenyltriphosphatase (ATPase) inhibited by omeprazole, Na^+, K^+-ATPase inhibited by digoxin.
      iii. Activation of enzymes, e.g. pralidoxime activates cholinesterases and used in organophosphorus poisoning.
   c. **Through ion channels**, i.e. drugs interfere with movement of ions across specific channels, e.g. calcium channel blockers, potassium channel openers, gamma-aminobutyric acid (GABA) gated chloride channel modulators.
   d. **Physical action**, i.e. drugs act by their physical properties:
      i. Absorption, e.g. activated charcoal in poisoning.
      ii. Mass of drug, e.g. bulk laxatives such as psyllium, bran for relieving constipation.
      iii. Osmotic action, e.g. mannitol (diuretic), magnesium sulfate (purgative).
      iv. Radioactivity, e.g. I^{131} (antithyroid).
      v. Radiopacity, e.g. barium sulfate (as contrast media).

"Only a life lived for others is a life worthwhile." —*Albert Einstein*

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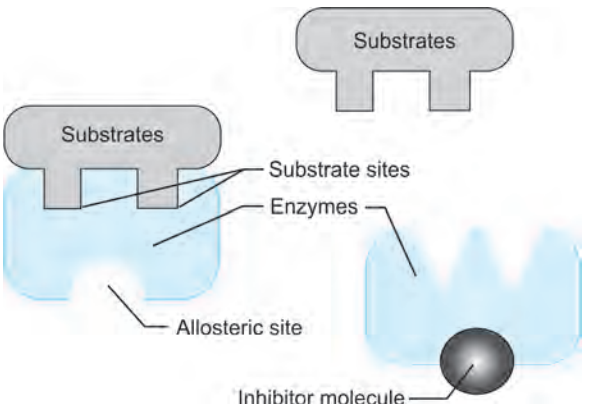


Fig. 4.1: Inhibition of enzymes

e. **Chemical action:**
   i. Antacids—neutralize gastric acid.
   ii. Oxidizing agents—potassium permanganate acts as germicidal.
   iii. Chelating agents—bind heavy metals to make them nontoxic.

f. **Altering metabolic process:** Sulfonamides interfere with bacterial folic acid metabolism.

g. **Placebo effect:**
   i. Latin term means 'I will please'.
   ii. Dummy medicine with no pharmacological activity.
   iii. Uses:
      - Relief of psychomotor symptoms such as anxiety, headache, pain, insomnia, etc.
      - Used in clinical trials in order to minimize bias.
   iv. Factors affecting placebo effect are:
      - *Patient factor:* Patients with neurotic symptoms often respond to placebo
      - *Drug factor:* Placebo response can be affected by the presentation or route of administration of placebo, e.g. colorful tablets and injections give better placebo effect
      - *Doctor factor:* Personality of doctor, motivation way of instruction, doctor-patient relationship, etc.

RECEPTOR

- Langley and Ehrlich put forward a concept of 'receptor substance'
- Clark explained drug action based on drug receptor occupation
- **Definition of receptor:** It is macromolecular site on cell with =which an agonist binds to bring about a change
- **Affinity:** Ability of a drug to bind to a receptor **(Fig. 4.2)**
- **Intrinsic activity/efficacy:** Ability of a drug to elicit a response after binding to the receptor
- **Agonist (Fig. 4.3):**
  – A substance that binds to the receptor and produces a response

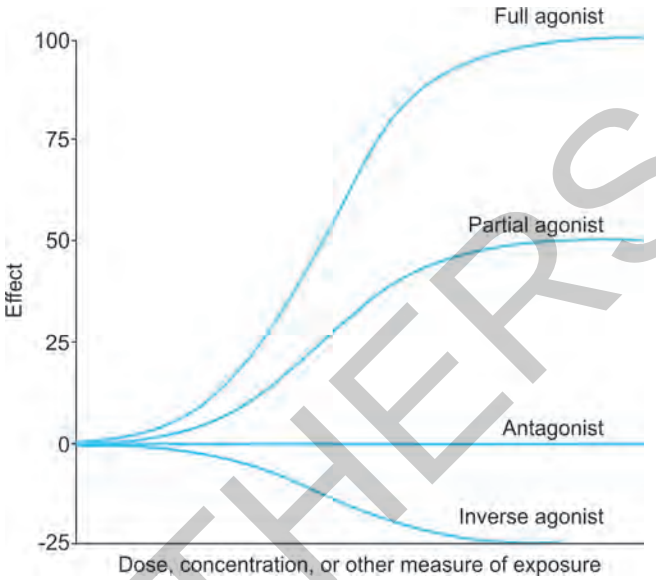


Fig. 4.2: Intrinsic activity of drug

  – It has both affinity and intrinsic activity
  – For example, adrenaline is agonist at α-and β-adrenergic receptors, morphine is an agonist at mu (μ) opioid receptor.
- **Antagonist:** A substance that binds to the receptor and prevents the action of agonist on the receptor:
  – It has affinity, but no intrinsic activity
  – Similar structurally to natural ligand for receptor
  – Hence receptor identifies antagonist as its ligand
  – For example, naloxone is antagonist at μ receptor, binds to receptors, has no effect by itself, but blocks the action of opioid agonist, e.g. morphine
  – For example, tubocurarine blocks and prevents the action of Ach on nicotinic receptors.
- **Partial agonist:**
  – Binds to the receptors, but has low intrinsic activity
  – Occupies receptor, but brings about weak effects
  – Also block action/binding of full agonists
  – Hence they are also called agonist-antagonist
  – For example, pentazocine is a partial agonist at μ-opioid receptors, pindolol is a partial agonist at β-adrenergic receptors.
- **Inverse agonist:**
  – After binding to receptors inverse agonists produce actions opposite to those produce by full agonist
  – For example, carbolines at benzodiazepine receptors (produces anxiety, increased muscle tone and convulsions, whereas diazepam the full agonist causes antianxiety, decreased muscle tone and anticonvulsant effect).
- **Ligand** is a molecule that binds selectively to a specific receptor
- **Spare receptor:**
  – Only a small percentage of receptors are required to produce maximum concentration

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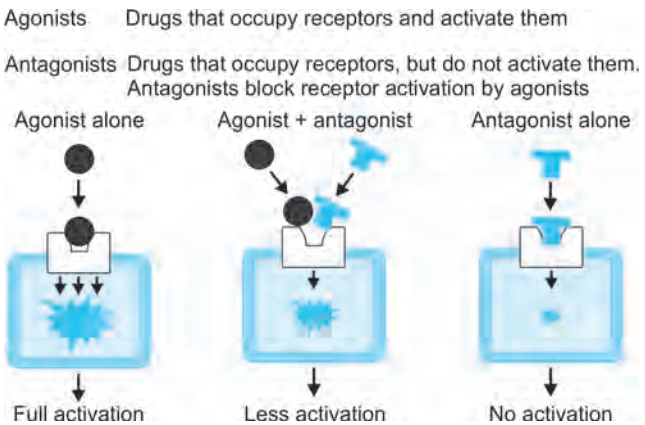


Fig. 4.3: Agonist versus antagonist

  - High concentration of an agonist can still produce maximum response in presence of irreversible antagonist
  - These effects are possible because of spare or 'reserve' receptors.
- **Silent receptors:**
  - Agonist binds to receptors, but does not produce a response
  - This explains the phenomena of tolerance
  - For example, plasma proteins.
- **Site of receptors**—on cell membrane, cytoplasm, nucleus
- **Nature of receptors**—proteins
- **Synthesis and life span of receptors:**
  - Synthesized by cells
  - Definite life span, after which they are degraded by cell and new receptors are synthesized.
- **Functions of receptors:**
  - Recognition and binding of ligand
  - Propagation of message.
- **Receptor domains (areas)** for performing above functions:
  - Ligand binding domain (drug molecule binds to this site)
  - Effector domain (this site undergoes a change to propagate the message).
- **Drug receptor interaction theories:**
  - Lock and key relationship, i.e. drug specifically fits into the particular receptor (lock) similar to a key
  - Rate theory, i.e. magnitude of response depends on rate of agonist—receptor association and dissociation, i.e. rate of receptor binding is more initially, reaches a peak and then there is a decrease
  - Occupation theory, i.e. magnitude of response depends on proportion of receptors occupied by the drug, i.e. response will progressively increase till a steady state is reached
  - Interaction of agonist with receptor changes the receptor
  - This changed receptor conveys signal to effector system
  - The final effect is brought about by effector system through second messengers
  - Agonist is the first messenger
  - Transduction process, which links the binding of receptor and the actual response is called 'coupling'
  - Drug-receptor interaction is explained by 'two-state' model
  - Receptor exists in two states, i.e. resting and activated **(Fig. 4.4)**
  - Drug with greater affinity for activated state will function as full agonist
  - Drug with moderate affinity for activated state will function as partial agonist.
- **Receptor families (Fig. 4.5):**
  - On stimulation of receptor, the time required to elicit the response varies from fraction of a second to hours, or days
  - This difference is because of variation in mechanisms involved in linking the receptor and the effector systems (transduction mechanisms)
  - Based on this, four types or super families of cell surface receptors are identified namely:

    1. Ion channels (ionotropic receptors)

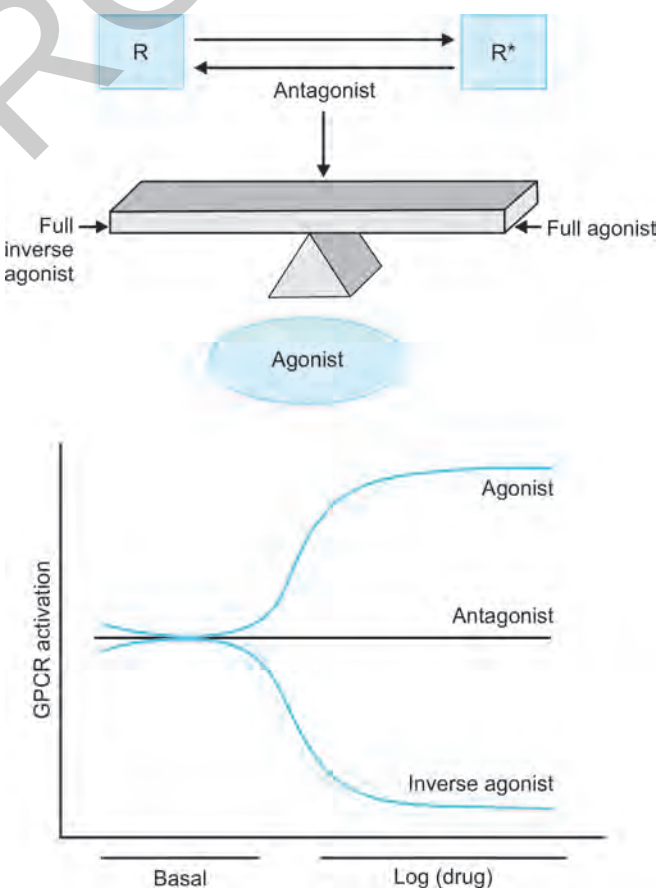


Fig. 4.4: Two state receptor model
Abbreviations: GPCR, G-protein-coupled receptors; R, inactive receptor; R*, active receptor

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2. G-protein-coupled receptor (GPCR/metabotropic receptor)
3. Enzymatic receptor (kinase-linked receptor)
4. Nuclear receptors (transcription factors or receptor that regulate gene transcription).

Receptor Families and their Transduction Mechanisms

1. **Ion channels or ligand-gated ion channels are (Fig. 4.6):**
   a. Proteins present on cell surface.
   b. Binding of agonist opens the channel allowing ions to cross the membrane.
   c. Depolarization/Hyperpolarization occurs depending on ion channels.
   d. For example, nicotinic cholinergic receptors → opens Na^+ channel → depolarization.
   e. For example, benzodiazepines bind to GABA receptor → opens Cl^- channel → hyperpolarization.
   f. For example, nifedipine blocks Ca^{2+} channels.
   g. For example, sulfonylureas blocks Ca^{2+} K^+ channels.
   h. For example, nicorandil opens K^+ channels.
2. **G-protein-coupled receptors (Fig. 4.7):**
   a. These are proteins spanning plasma membrane.
   b. Bound to inner surface of plasma membrane.
   c. Consists of three subunits: α, β and γ.
   d. Gets activated when ligand binds.
   e. This in turn activates adenyl cyclase (AC) or phospholipase C (PLC) to generate respective second messengers.
   f. Second messenger are also called effector pathways.
   g. Second messengers in turn bring about intracellular changes.
   h. Thus G-proteins act as link between receptors and effector systems.
   i. They are called G-proteins because of their interaction with guanine nucleotides, i.e. guanosine-5'-triphosphate (GTP) or guanosine diphosphate (GDP).
   j. They are of different classes, viz. Gs, Gi, Go and G13.
   k. Gs is stimulatory, Gi is inhibitory.
   l. Second messengers are cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), diacylglycerol (DAG) and Ca^{+2}.
   m. Adrenergic receptors and muscarinic cholinergic receptors are examples of GPCR.
   n. Effector pathways through which GPCR work are:
      i. Adenylcyclase/cAMP pathway.
      ii. Phospholipase C (PLC)/Inositol triphosphate and diacylglycerol (IP3-DAG) pathway.
      iii. Ion channel regulation.

- Adenyl cyclase pathway **(Fig. 4.8)**:
  – Stimulation of AC results in formation and accumulation of cAMP within cell
  – cAMP, through protein kinases, which phosphorylate various proteins, regulate cell function

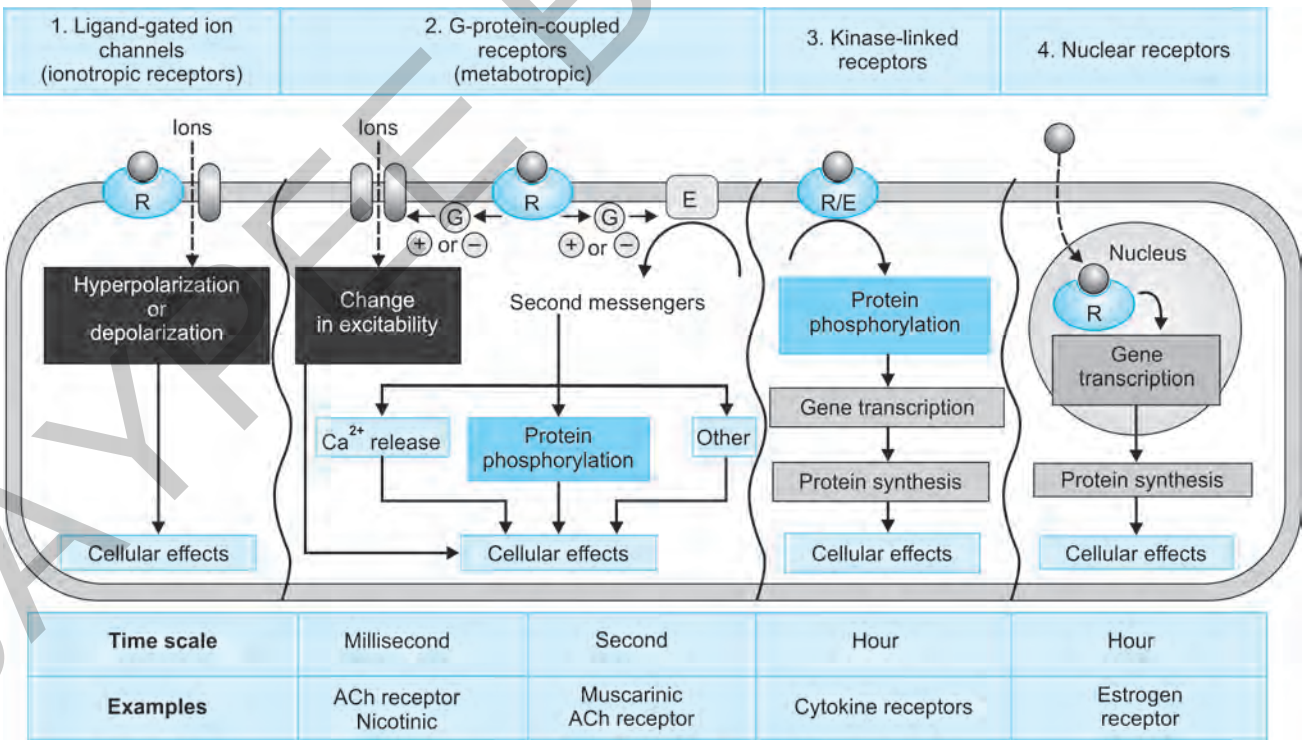


Fig. 4.5: Receptor families
Abbreviation: ACh, acetylcholine

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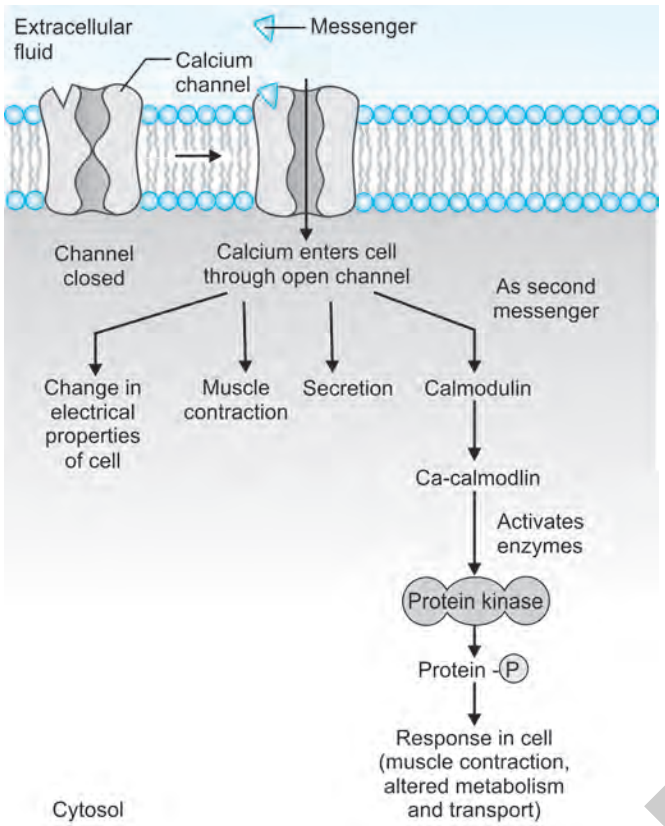


Fig. 4.6: Type 1 ligand-gated ion channels

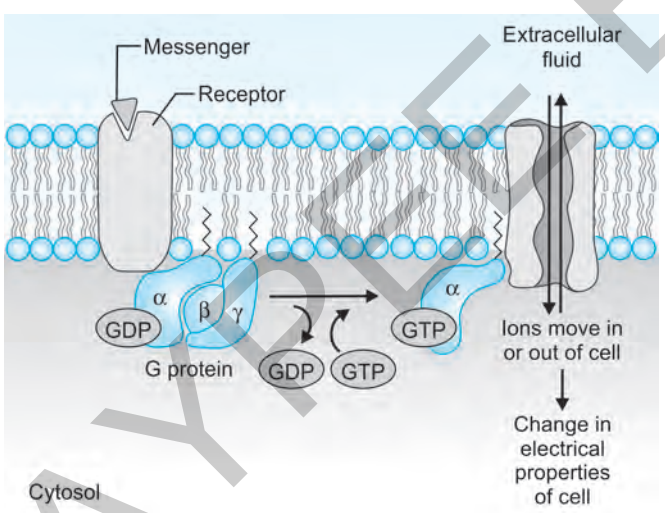


Fig. 4.7: Type 2 G-protein couple receptor
Abbreviations: GDP, guanosine diphosphate; GTP, guanosine-5′-triphosphate

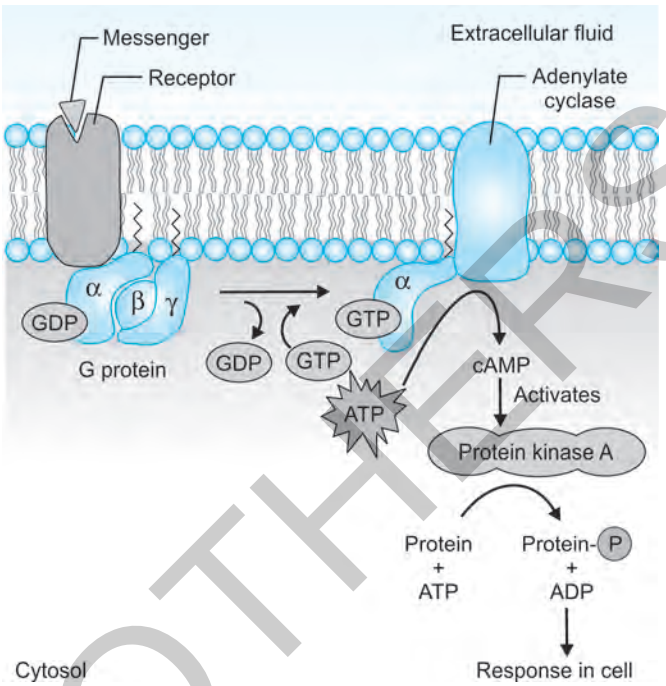


Fig. 4.8: Adenylyl cyclase pathway
Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; GDP, guanosine diphosphate; GTP, guanosine-5-triphosphate

  - Response may be contraction, relaxation, lipolysis or hormone synthesis.
- Phospholipase C/IP3-DAG pathway **(Fig. 4.9)**:
  - Activation of PLC results in formation of second messenger IP3 and DAG from membrane phospholipids
  - IP3 mobilizes Ca^{2+} from intracellular sites
  - Ca^{2+} causes contraction, secretion and metabolism
  - DAG activates protein kinase C, which regulates cell function.
- Ion channel regulation:
  - Activated GPCR directly (without second messengers) opens or closes channels
  - This causes depolarization or hyperpolarization.

3. **Enzymatic receptors (Fig. 4.10)**
   - These are transmembrane proteins:
     a. They have an extracellular domain (site) for ligand binding
     b. Intracellular domain site for catalytic activity
     c. The two domains are linked by single peptide chain
     d. Enzymes are protein kinases and hence called kinase-linked receptors
     e. Binding of agonist to ligand domain causes autophosphorylation of intracellular domain
     f. This in turn trigger phosphorylation of various intracellular proteins, hence cellular response
     g. For example, insulin receptor, growth factor receptors.
   - Second subtype of enzyme-linked receptors is Janus kinase-signal transducer and activator transcription (JAK-STAT) kinase binding receptor:
     a. When agonist binds to extracellular domain it activates intracellular domain (which forms dimers)

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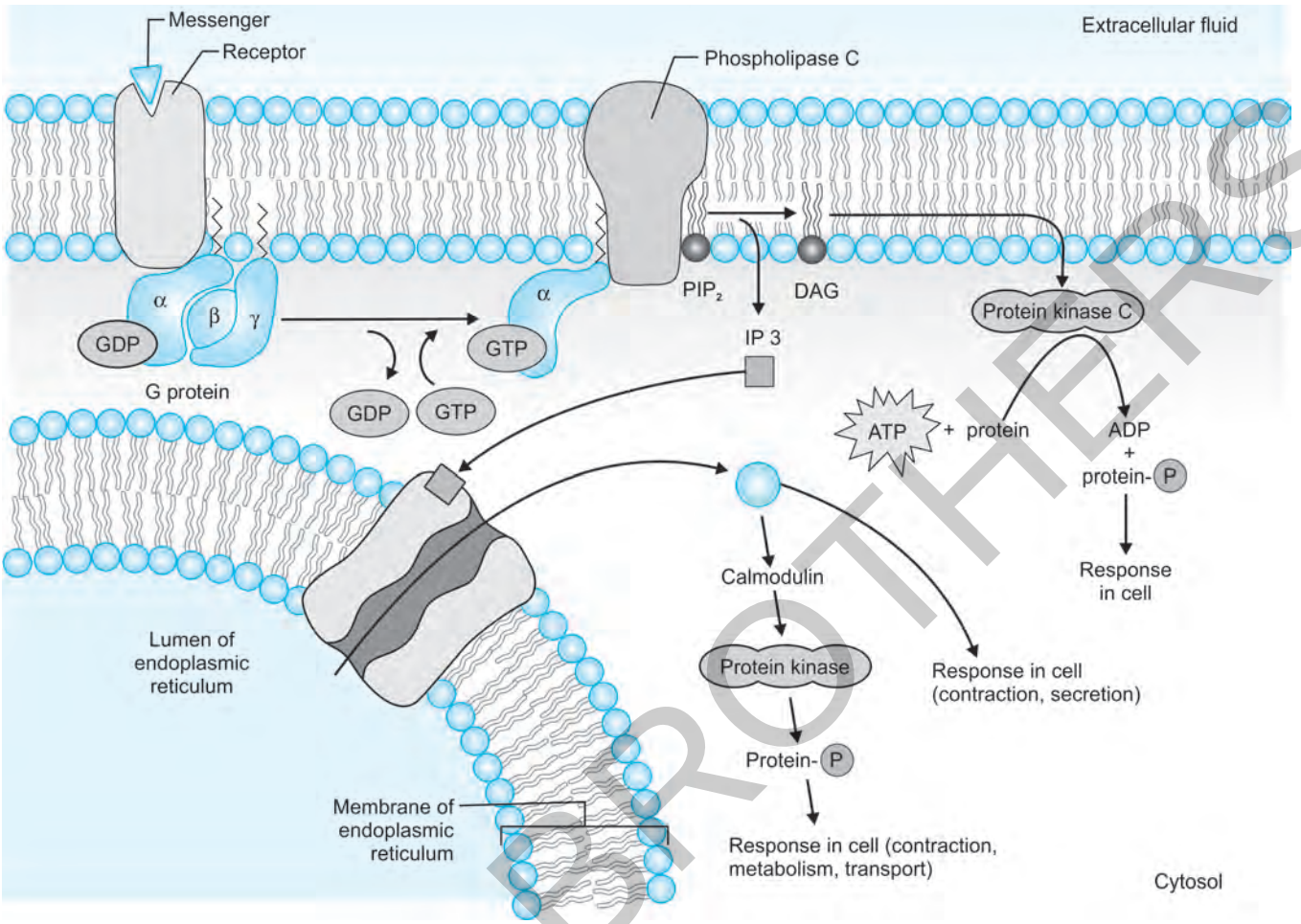


Fig. 4.9: Phospholipase C/Inositol triphosphate and diacylglycerol ($IP3^-$ DAG) pathway
Abbreviations: ADP, adenosine diphosphate; GTP, guanosine-5′-triphosphate

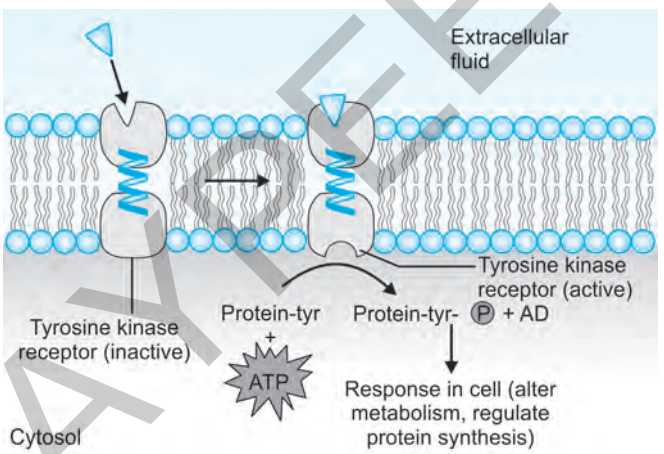


Fig. 4.10: Enzymatic receptors
Abbreviation: ATP, adenosine triphosphate

b. This in turn activates mobile JAK molecules
c. This activates STAT molecules
d. STAT enter nucleus and regulates transcription. For example, interferons, growth hormones.

4. **Nuclear receptor (Fig. 4.11):**
   a. Receptors that regulate gene transcription
   b. These are intracellular proteins in inactive state
   c. They are activated by binding of agonist
   d. Agonist-receptor complementers nucleus → interacts with deoxyribonucleic acid (DNA) → regulates gene transcription → regulate activity of target. For example, receptor for steroid hormones, thyroid hormones, vitamin D, retinoids.

Receptor Regulation

1. Many situation alter the number of receptors (density) and their sensitivity.
2. Denervation/Prolonged deprivation of agonist/constant action of antagonist increased density and sensitivity of receptors. This is called upregulation.
3. Constant use of agonist decrease density and sensitivity of receptors. This is called down regulation.
4. Clinical significance:
   a. Following long-term antagonist, the dose should be tapered to stop it.

"Education is not the learning of facts, but the training of the mind to think." —*Albert Einstein*

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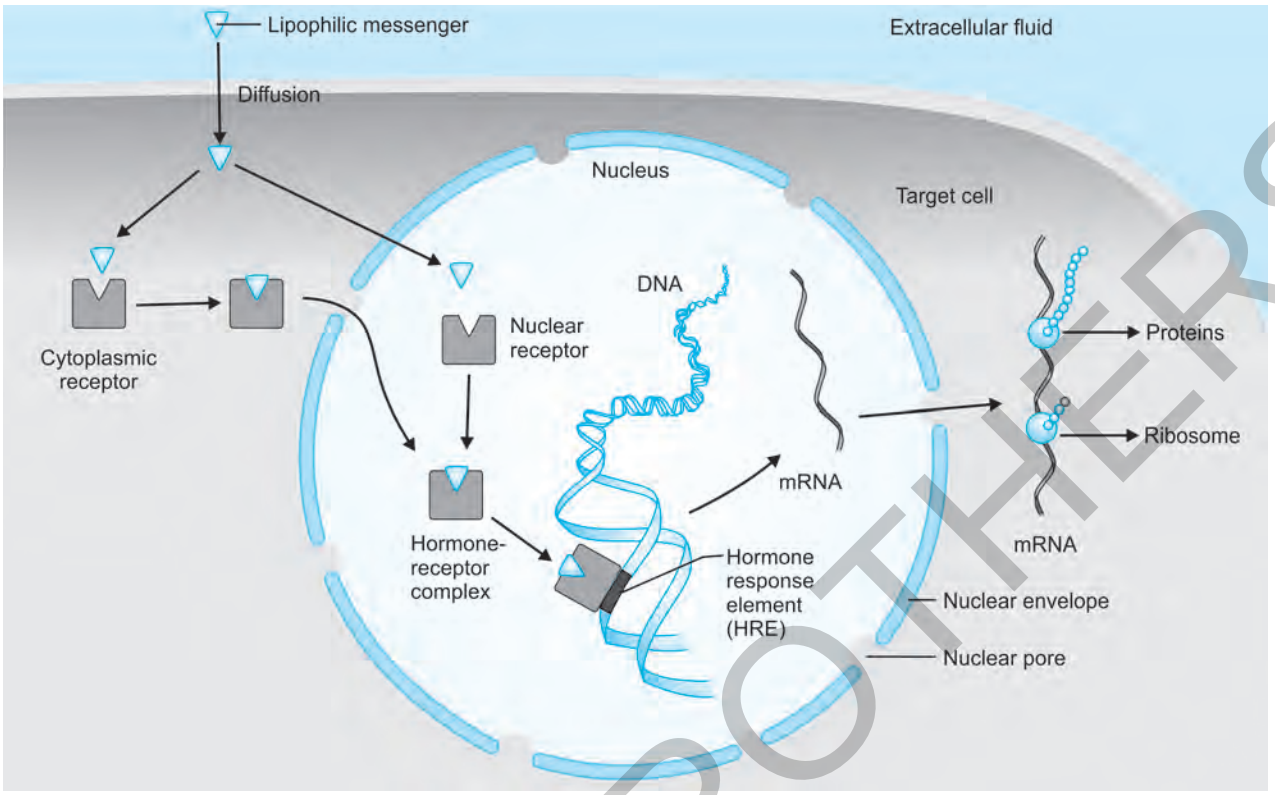


Fig. 4.11: Type four nuclear receptors
Abbreviations: DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid

b. For example, beta blocker propranolol, if suddenly withdrawn can precipitate angina/severe hypertensive crisis due to upregulation of receptors
c. Long-term use of β–agonist such as salbutamol in bronchial asthma can down regulate β2-receptors in respiratory system, leading to decreased therapeutic response.

DOSE RESPONSE RELATIONSHIP

1. Clinical response to the increasing dose of drug is defined by shape of dose-response curve (DRC).
2. Initially the extent of response increases with increase in the dose till the maximum response is reached.
3. The DRC is in a shape of rectangular hyperbola.
4. After maximum effect is obtained further increase in doses does not increase the response.
5. Log DRC is sigmoid shape.
6. Slope of DRC has clinically significance:
   a. Drugs having a steep slope a small increase in dose produces large increase in response, e.g. loop diuretics. Such drugs can cause toxicity, hence dose has to be individualized.
   b. Drugs having a flat DRC an increase in dose, there is little increase in response, e.g. thiazide diuretics. Such drugs are relatively safe, thus a standard dose can be given to most patient.

Drug Potency (Fig. 4.12)

- Amount of drug required to produce a response
- Potency is of little clinical significance
- About 1 mg of drug A produces same effect as 50 mg of drug B, then A is more potent than B.

Drug Efficacy (Fig. 4.13)

- Maximum response that can be produced by a drug
- Efficacy is of great clinical significance
- Drug A produces more response as compared to any dose of drug B, then A is more efficacious than B.

Therapeutic Index

1. Distance between beneficial effect DRC and adverse effect DRC of same drug indicates therapeutic index (TI) or safety margin of drug **(Fig. 4.14)**.
2. *Median lethal dose (LD50):* Dose, which is lethal to 50% of population.
3. *Median effective dose (ED50):* Dose, which produces desired effect in 50% of population.
4. $TI = \frac{LD50}{ED50}$ **(Fig. 4.15)**:
5. Implications of TI
   a. Gives idea about safety of drug.
   b. Higher the TI, safer the drug.

"I can control my destiny, but not my fate. Destiny means there are opportunities to turn right or left, but fate is a one-way street. I believe we all have the choice as to whether we fulfil our destiny, but our fate is sealed."
—Paulo Coelho

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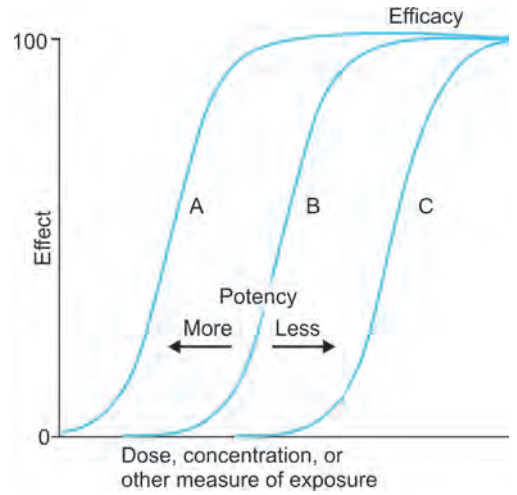


Fig. 4.12: Potency

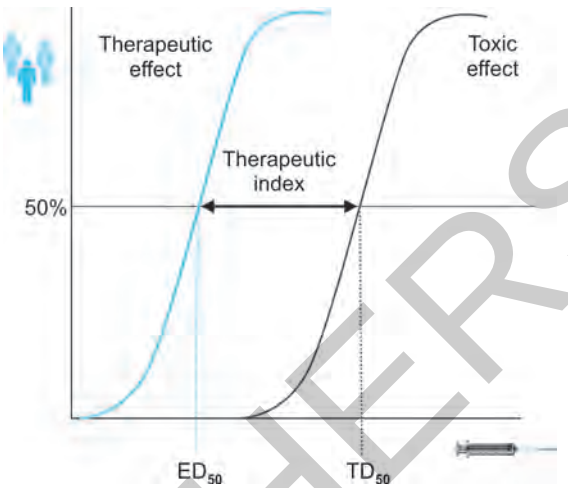


Fig. 4.14: Therapeutic index

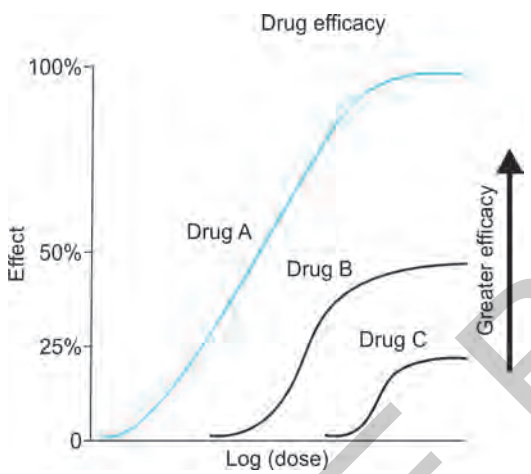


Fig. 4.13: Efficacy

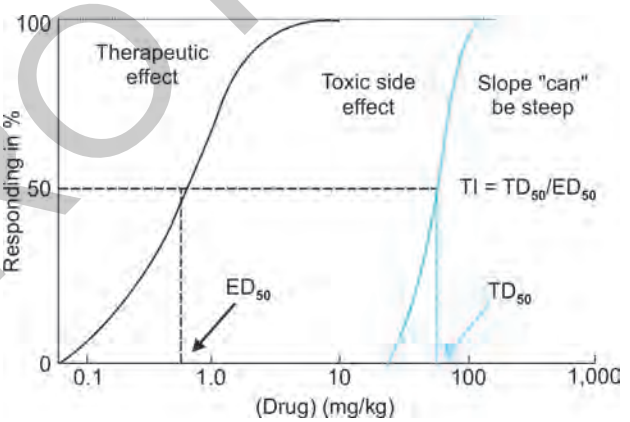


Fig. 4.15: Drug safety–therapeutic index

c. TI more than 1, drug is relatively safe.
d. Drugs with high TI: Penicillin, paracetamol.
e. Drugs with low TI: Digoxin, lithium.
f. TI varies from species to species.

6. Limitations:
   a. Does not consider idiosyncrasy.
   b. Animal cannot be applied to humans.
   c. For humans safety factor is important.

d. Safety factor = $\frac{\text{LD 1}}{\text{ED 99}}$

Therapeutic Window

1. Range of plasma concentration below which drug is ineffective and above which drug is toxic.
2. Hence, it is desirable to have plasma concentration of drugs within the therapeutic window.
3. Thus, drug will have therapeutic effect without significant toxicity.
4. Drugs with narrow therapeutic window, e.g. lithium, digoxin, carbamazepine.
5. Doses of such drugs need to be titrated carefully.

DRUG SYNERGISM AND ANTAGONISM

1. Simultaneous administration of 2 or more drugs can result in additive, synergistic, antagonist effect.
2. **Additive effect (Fig. 4.16):**
   a. Effect of two or more drugs gets added up total effect is equal to the sum of their individual actions.
   b. 2 + 2 = 4.
   c. For example, ephedrine with theophylline in bronchial asthma, nitrous oxide along with ether as general anesthesia.
3. **Synergistic effect (Fig. 4.16):**
   a. Action of one drug is increased by another.
   b. Total effect of two drugs is more than the sum of their individual actions.
   c. 2 + 2 = 5.

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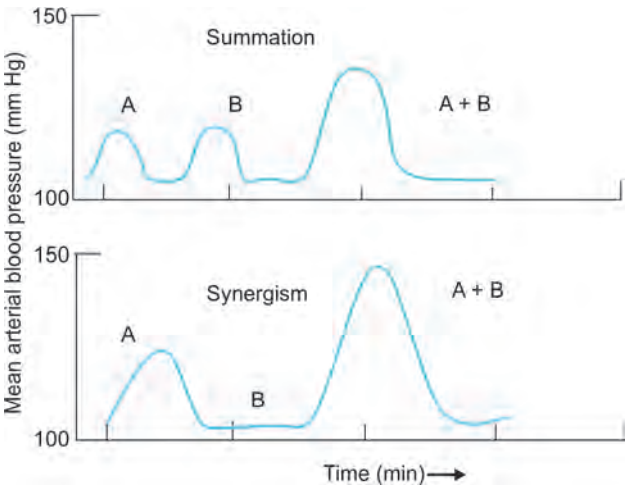


Fig. 4.16: Summation vs synergism

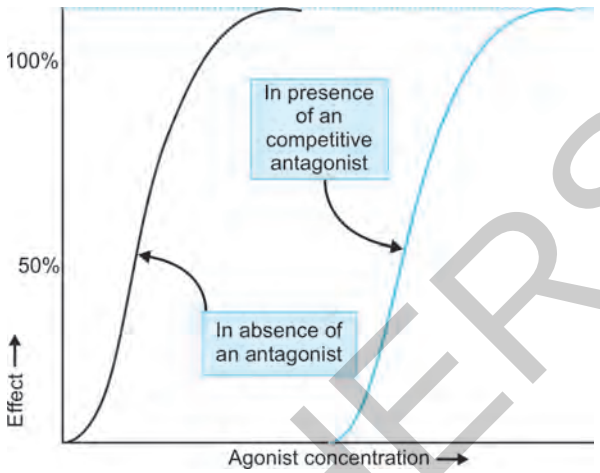


Fig. 4.17: Reversible antagonism

d. Also called 'potentiation' or 'supra-additive effect'.
e. For example, levodopa with carbidopa in parkinsonism, acetylcholine along with physostigmine.

4. **Antagonism**:
   a. One drug inhibiting the action of another.
   b. Types based on mechanism:
      - Chemical antagonism
      - Physiological antagonism
      - Receptor antagonism:
        - Reversible antagonism (competitive)
        - Irreversible antagonism
        - Non-competitive antagonism.
5. **Chemical antagonism:**
   a. Two drugs chemically interact to inactivate the effect.
   b. For example, antacids neutralize gastric acid chelating agents inactivate heavy metals such as lead and mercury.
6. **Physiological antagonism:**
   a. Two drugs act at different sites to produce opposing effects.
   b. For example, insulin and glucagon have opposite effects on blood sugar histamine acts on H1 receptors to produce bronchoconstriction and hypotension these effects are antagonized by adrenaline via adrenergic receptors.
7. **Receptor—level antagonism:**
   a. Antagonist binds to the receptor and inhibits binding of agonist to receptor.
   b. This antagonism is of two types, i.e. reversible or irreversible:
      - **Reversible or competitive antagonism (Fig. 4.17):**
      - Agonist and antagonist compete for same receptor
        - Response to a fixed concentration of agonist is progressively reduced by increasing the dose of antagonist.
        - However, this antagonist can be overcome by increasing the concentration of agonist
        - Same maximum response can be achieved by increasing the dose of agonist
        - Also called surmountable or equilibrium type of antagonism
        - For example, acetylcholine and atropine complete at muscarinic receptors acetylcholine and tubocurarine compete at nicotinic receptors
        - Dose-response curve (DRC) shifts to right in presence of competitive antagonist.
      - **Irreversible antagonism (Fig. 4.18):**
        – Antagonist-binds covalently to receptor
        – Binding is so firm that antagonist cannot dissociate from receptor
        – Thus it blocks action of agonist
        – But blockade cannot be overcome by increasing the concentration of agonist
        – Hence also called irreversible antagonism
        – Duration of action of antagonist is usually long since till new receptors are synthesized the effect of antagonist remains
        – For example, adrenaline and phenoxybenzamine at α-adrenergic receptors
        – Also called non-equilibrium antagonism.
      - **Non-competitive antagonism:**
        – Antagonist acts as a site beyond the receptor and not on the receptor
        – Acts on receptor-effector linkage
        – The DRC – flattening and rightward shift
        – For example, verapamil blocks calcium channels and blocks cardiac stimulant actions of adrenaline and isoprenaline.

"Remember your dreams and fight for them. You must know what you want from life. There is just one thing that makes your dream become impossible: The fear of failure."
—Paulo Coelho

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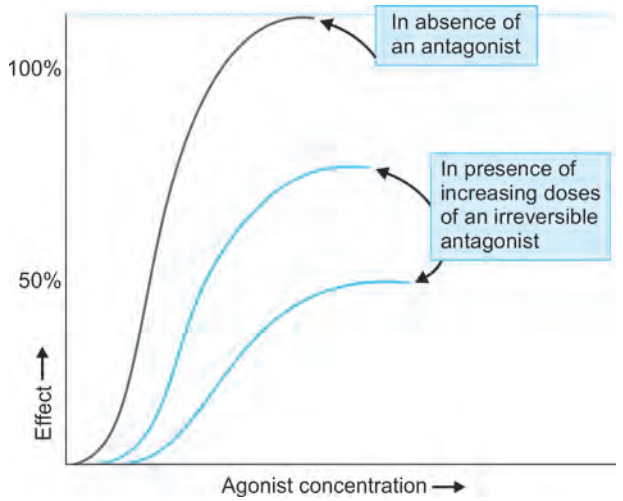


Fig. 4.18: Irreversible antagonism

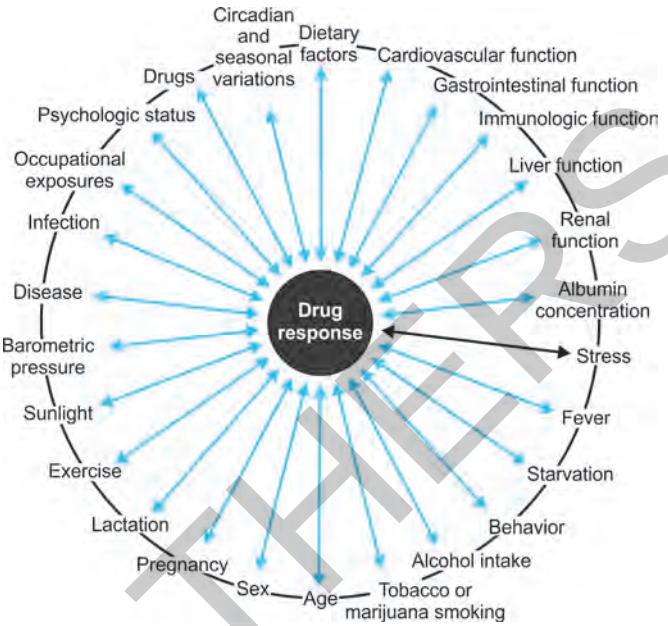


Fig. 4.19: Factors modifying drug effects

FACTORS THAT MODIFY EFFECTS OF DRUGS (Fig. 4.19)

1. Same dose of a drug can produce different degrees of response in different patients.
2. Same dose of a drug can produce different degrees of response in same patient under different circumstances.
3. Factors modifying drug response:

A. Body Weight

1. Recommended dose is generally for medium built persons.
2. For obese and underweight persons the dose has to be calculated individually.
3. Body surface area is a better parameter for more accurate dose calculation.
4. But it is inconvenient hence generally not used:

$$\text{Dose} = \frac{\text{Body weight (kg)} \times \text{Average adult dose}}{70}$$

B. Age

1. Pharmacokinetics of many drugs change with age.
2. Thus, response to drugs varies in extremes of age.
3. In newborn, the liver and kidneys are immature, blood brain barrier is not well formed, gastric acidity is low, intestinal motility is slow, skin is delicate (for topical applications).
4. Hence toxicity can occur at normal dosage, e.g. chloramphenicol causing gray baby syndrome in neonates.
5. Formula to calculate dose in children:

$$\text{Formula} = \frac{\text{Age (years)} \times \text{Adult}}{\text{Age} + 12}$$

6. In adults liver and kidney functions are reduced, hence they are more susceptible to adverse effects, so lower doses are recommended, e.g. nephrotoxicity and ototoxicity due to streptomycin.

C. Sex

1. Hormonal effects and smaller body size may influence drug response in women.
2. Special precautions, while prescribing drugs during pregnancy and lactation.
3. For example, purgative administered during menses, increase menstrual blood flow due to increased pelvic congestion.

D. Species and Race

1. Rabbits are resistant to atropine.
2. Thus extrapolation of results to human becomes difficult.
3. Blacks require higher doses of atropine to produce mydriasis.

E. Diet and Environment

1. Food interferes with absorption of many drugs.
2. For example, calcium present in milk reduces absorption of tetracyclines.
3. Polycyclic hydrocarbons in cigarette smoke increases metabolism of drugs.

F. Route and Time of Administration

Change of route can alter drug response:

1. For example, oral magnesium sulfate is purgative, intravenous (IV) magnesium sulfate causes CNS

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depression (hence used as anticonvulsant during eclampsia of pregnancy), whereas topical magnesium sulfate reduces local edema. Rectal magnesium sulfate reduces intracranial tension.
2. For example, oral/IV N-acetylcysteine is antidote for paracetamol poisoning, whereas inhaled N-acetylcysteine is a mucolytic. Irrigated N-acetylcysteine in urinary bladder counters cystitis caused by cyclophosphamide.
3. Because of diurnal variations timing of drug administration is important.
4. Since glucocorticoids are secreted in morning, exogenous glucocorticoids too are administered in morning.
5. Similarly stains (atorvastatin, etc.) is given in evening/night.
6. Study of such corelation of drug response to circadian rhythm is called '**chronopharmacology'**.

G. Genetic Factors

1. Drug response can vary due to genetic factor.
2. Study of such genetically mediate variations in drug response is called '**pharmacogenetics'**.
3. These differences are mostly due to alterations in drug metabolizing enzyme since metabolizing enzyme production is under genetic control.
4. For example, acetylation of sulfonamide and hydralazine may be fast or slow. Slow acetylators of hydralazine may develop lupus erythematosus.
5. **Atypical pseudocholinesterase:** Succinylcholine in normally metabolized by typical pseudocholinesterase. When it is administered in patients with a typical pseudocholinesterase, they develop prolonged apnea due to persistence of succinylcholine action.
6. Glucose-6-phosphate dehydrogenase (G6PD) deficiency can cause hemolysis when sulfones, primaquine or quinolones are administered.
7. Malignant hyperthermia caused by halothane and succinylcholine.
8. Porphyrias due to administration of barbiturates, griseofulvin and carbamazepine.

H. Dose

1. Generally when dose is increased response increases proportionately till 'maximum' is reached.
2. However, with some drugs increasing the dose beyond maximum may produce opposite effects:
   a. For example, normal doses of neostigmine increase muscle power in myesthenia gravis patients, but high dose can cause muscle paralysis.
   b. For example, physiological doses of vitamin D increases calcification, whereas hypervitaminosis D can lead to decalcification.

I. Diseases

1. *Gastrointestinal diseases:* Drugs are poorly absorbed in malabsorption syndrome.
2. *Liver diseases:*
   a. Decreases drug metabolism.
   b. Decreased protein binding, increase free drug, hence increases toxicity.
3. *Cardiac diseases:*
   a. Decreased function of liver and kidney, therefore decreased tissue perfusion.
   b. Decreased oral absorption, since gastrointestinal tract (GIT) edema.
4. *Renal diseases:*
   a. Increases toxicity, since drug are primarily excreted from kidneys, hence decreases dose.
   b. For example, streptomycin, amphotericin B.
5. *Endocrine diseases:*
   a. Increased toxicity of CNS depression in hypothyroid patients.
   b. Increased urinary retention with anticholinergics and tricyclic antidepressants in patients with prostatic hypertrophy.

J. Repeated Dosing

1. Repeated dosing can lead to:
   a. Cumulation.
   b. Tolerance.
   c. Tachyphylaxis.
      i. *Cumulation:* Drugs, which are slowly excreted cause cumulative toxicity, e.g. digoxin.
      ii. *Tolerance:* Requirement of higher doses to produce a given response, e.g. natural.

- Species/Race shows less sensitivity to a drug.
- For example, rabbits tolerant to atropine blacks tolerant to mydriatics, i.e. acquired.
- Tolerance on repeated administration.
- Initially response is seen, however, later there is unresponsiveness to drug.
- For example, barbiturates, opioids, nitrates.
  - Mechanisms of tolerance.
- **Pharmacokinetic:** Occurs due to changes in absorption, distribution, metabolism and excretion (ADME), which reduces drug concentration. Also called dispositional tolerance, e.g. barbiturates increases metabolism.
- **Pharmacodynamic:** Occurs due to changes in target tissue. Also called functional tolerance. Due to down regulation of receptors, e.g. opioids. Due to compensatory mechanisms, e.g. blunting of antihypertensive response due to salt and water retention:
  - *Cross tolerance:* Tolerance to pharmacologically related drugs, e.g. chronic alcoholics showing tolerance to barbiturates and general anesthetics:

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– *Tachyphylaxis:* Rapid development of tolerance. Also called acute tolerance, e.g. tyramine, ephedrine, amphetamine. It occurs due to depletion of noradrenaline stores from sympathetic nerve ending due to slow dissociation of drug from receptor, hence blocking the receptor.

K. Psychological Factors

- Depends on doctor-patient relationship
- Depends on doctor's confidence
- Are especially important in psychosomatic disorder
- Such patients show response to placebo
- Placebo:
  – Inert dosage with no biological activity
  – Only resembles actual preparation in appearance (dummy medication)
  – Means 'I shall be pleasing' (in Latin)
  – Used in clinical trials to compare new compound
  – Benefits patients with psychosomatic disorders and chronic incurable diseases.

L. Presence of Other Drugs

These are called drug interactions.

DRUG INTERACTIONS

1. Alteration in duration or magnitude of pharmacological actions of one drug by another.
2. Response may be greater or lesser than the sum of their individual effects.
3. Responses may be beneficial or harmful.
4. **Beneficial** drug interactions, e.g. propranolol with hydralazine for hypertension.
5. **Unwanted** drug interactions can cause toxicity, e.g. propranolol with ephedrine increases blood pressure (BP).
6. **In vitro** drug interactions—occurs in the syringe before administration. They could be chemical or physical interaction, e.g. penicillin with gentamicin.
7. **In vivo** drug interactions—occurs within the body. They could either be pharmacokinetic or pharmacodynamic.
8. **Pharmacokinetic drug interactions influencing absorption by:**
   a. Binding drugs, e.g. tetracyclines chelate iron and calcium decreasing absorption.
   b. Altering gastric pH, e.g. antacids increase gastric pH, hence decrease absorption of iron and anticoagulants.
   c. Altering gastrointestinal (GI) motility, e.g. atropine and morphine slows GI motility, thus delays absorption of drugs, purgatives reduce absorption of riboflavin.
9. **Pharmacokinetic drug interactions influencing distribution by:** Competition for plasma protein or tissue binding, which results in displacement interactions, e.g. warfarin displaced by phenylbutazone from protein binding site.
10. **Pharmacokinetic drug interactions influencing metabolism by:**
    a. Hepatic enzyme induction and inhibition, which result in drug interactions, e.g. enzyme inducer such as rifampicin, phenytoin, phenobarbitone and carbamazepine.
    b. Enzyme inhibitors such as cimetidine, ketoconazole, erythromycin, chloramphenicol.
11. **Pharmacokinetic drug interactions influencing excretion by:** Drugs complete for same renal tubular transport system, hence there is prolongation of duration of action, e.g. penicillin and probenecid.
12. **Pharmacodynamics drug interactions:**
    - Drugs acting on same receptors or physiological systems can lead to additive, synergistic or antagonistic effects
    - For example, atropine antagonizes physostigmine
    - Diuretics produce hypokalemia, which potentiates digoxin toxicity
    - Aspirin enhances bleeding risk of anticoagulant warfarin
    - Alcohol enhances sedation produced by antihistaminics.

ADVERSE DRUG REACTIONS (Table 4.1 and Flow chart 4.1)

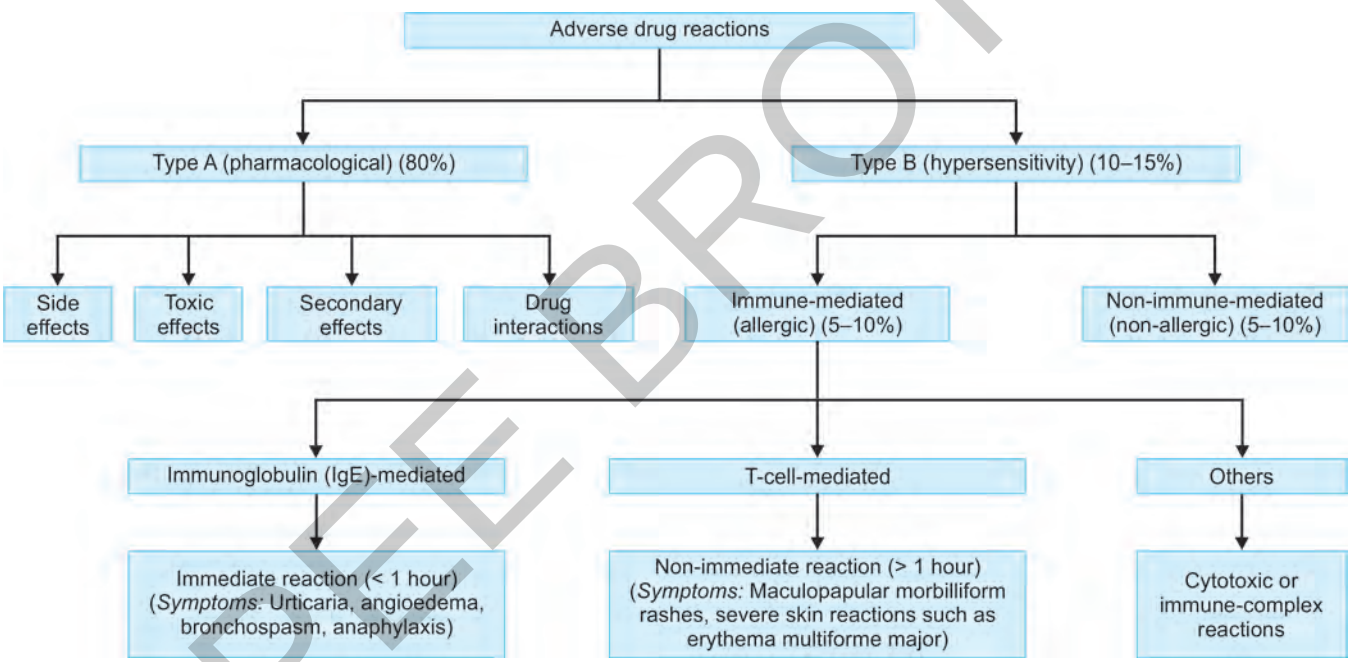
1. "A response to a medicine that is noxious and unintended, and which occurs of doses normally used in man."
2. Undesirable or unwanted effect due to drug administration.
3. **Types:** Dose related or non-dose related.
4. Doses related are:
   Most common
   Predictable.
5. **Side effects:**
   a. Seen with therapeutic doses, e.g. atropine causing dryness of mouth.
6. **Toxic effects:**
   a. Due to overdosing or chronic use, e.g. nephrotoxicity with aminoglycosides, bleeding due to anticoagulants:
      i. Non-dose related.
7. **Hypersensitivity reactions (drug allergy):**
   a. Ag: Ag reaction resulting in release of various mediators.
   b. Classified on basis of immunological mechanism mediating the reaction.
   c. Type I, II, III—humoral (Ab) mediated.
   d. Type IV—cellular (delayed hypersensitivity) mediated.
   e. **Type I hypersensitivity (immediate):**
      i. Rapidly occurring: Immediate.
      ii. Manifestations: Itching, urticoria, hay fever, asthma or even anaphylactic shock.

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Table 4.1: Adverse drug reaction classification

Characteristics	Type A	Type B
Dose dependency	Dose related	Dose relationship is unclearly defined
Frequency of occurrence	Common	Uncommon
Severity of reaction	Variable, but usually mild	Variable, but proportionately more severe
Hot factors	Genetic factors might be important	Department on host factors
Animal models	Usually reproducible in animals	Unknown in animal models
Percentage proportion of adverse drug reaction	80%	20%
Predictable from known pharmacology	Yes	Not usually
First detection (clinical trials)	Phase I–III	Phase IV, occasionally phase III
Clinical burden	High morbidity and low mortality	High morbidity and high mortality

Flow chart 4.1: Types of adverse drug reactions



iii. Ig E-mediated acute allergic reaction to drugs (penicillin, aspirin, etc.) → re-exposure to same drug → Ag: Ab reaction on mast cell surface release of mediators (histamine, 5-HT, PGs, LT's, PAF) → hypotension, bronchoconstriction, angioedema, urticarial

iv. Treatment:
- Treatment promptly as it is medical emergency
- Drug of choice—injection adrenaline (1:1,000) 0.3–0.5 mL IM
- Injection hydrocortisone 100–200 mL IV
- Injection diphenhydramine 25–50 mg IV/1M
- IV fluids.

f. **Type II hypersensitivity (cytotoxic):**
   i. Ab react of complement, which destroys cell-bound antigen.
   ii. Ab (IgG/IgM) reacts with cell-bound → activation of complement → destruction of cells, e.g. blood transfusion reaction, hemolytic anemia due to quinine, cephalosporins, etc.

g. **Type III hypersensitivity (immune complex mediated):**
   i. Ab: Involved are mainly IgG.
   ii. Ab: Complex formed → fix complement → complex

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