Lecture notes on Pharmacology

For Nursing students

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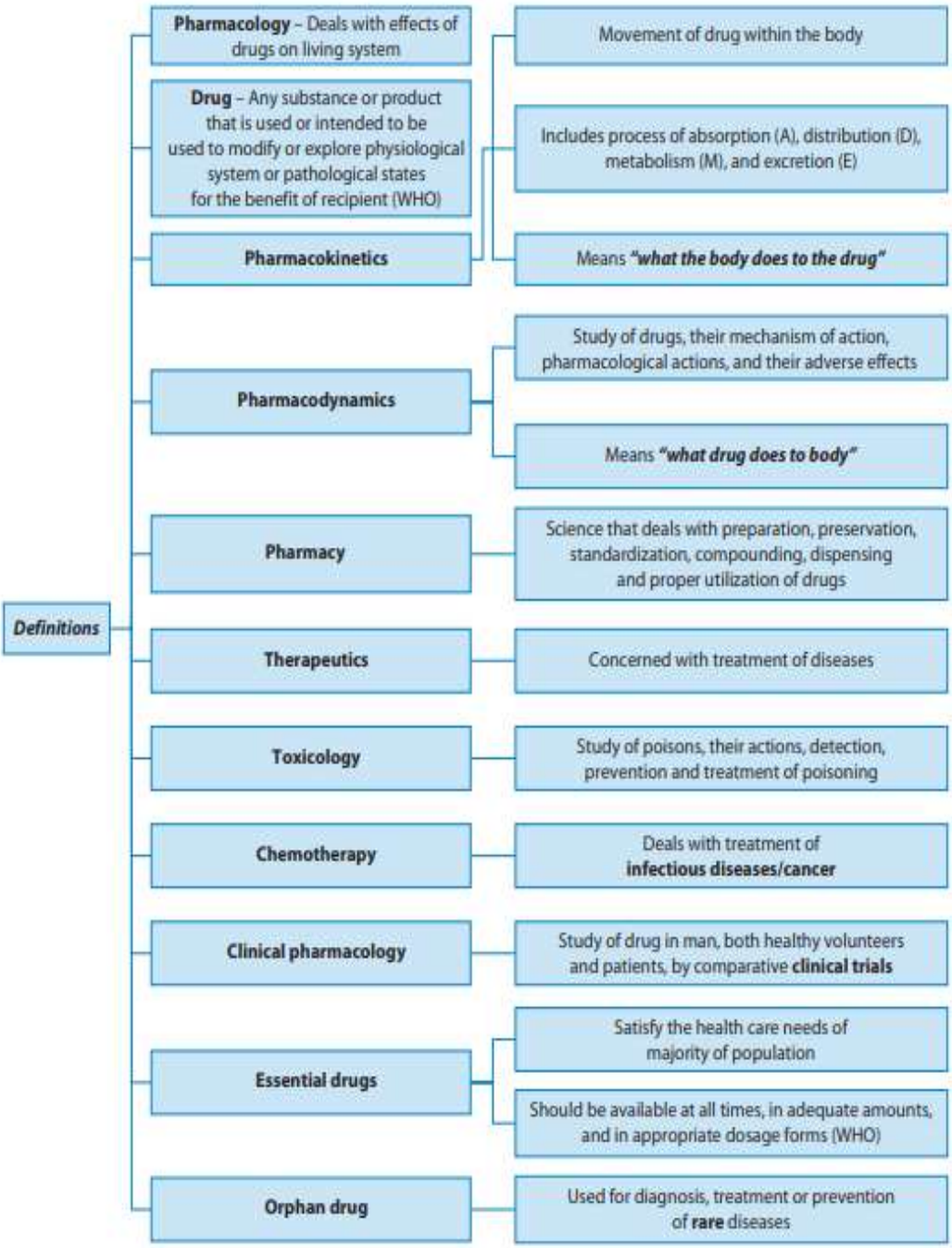
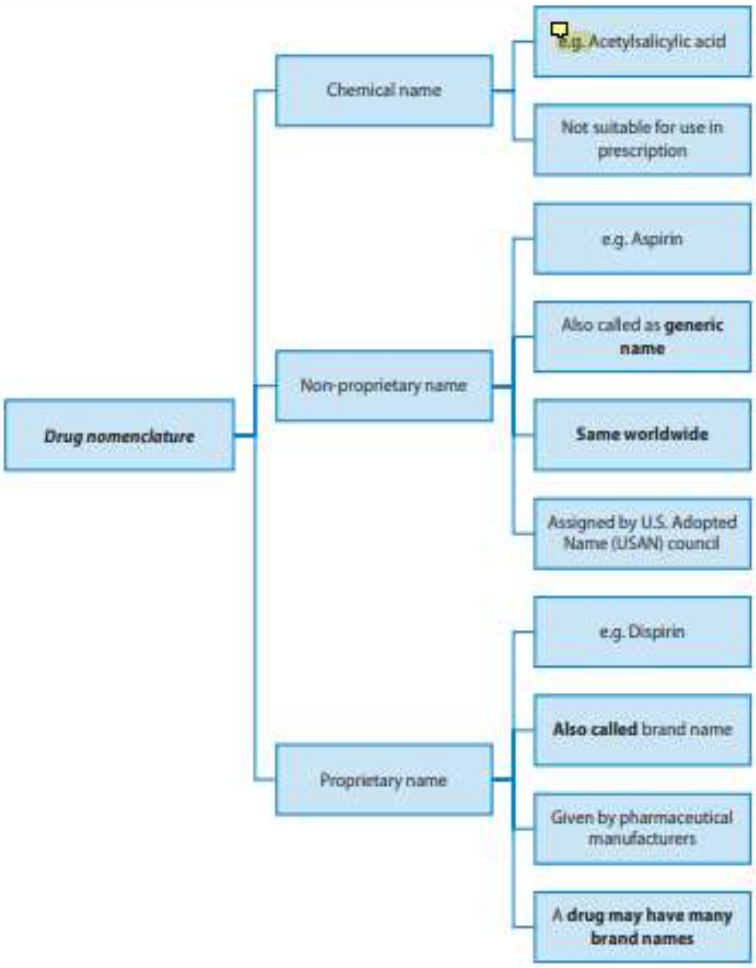
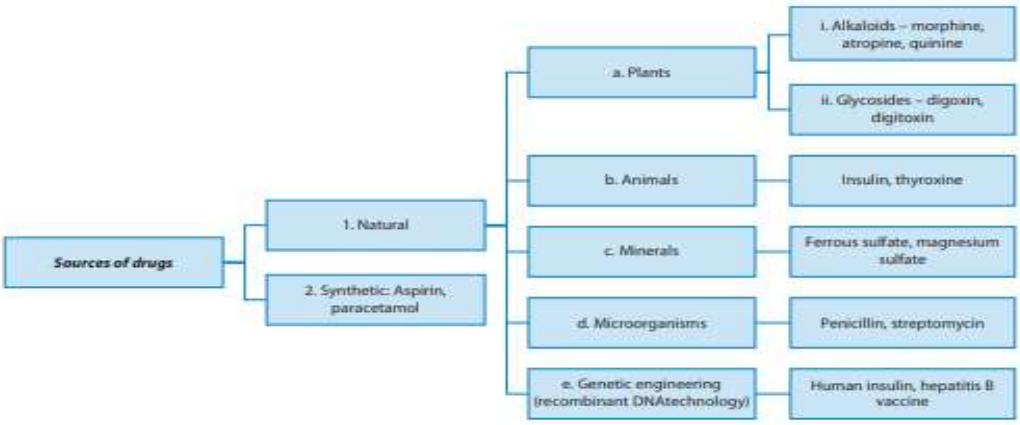

Definitions
Pharmacology – Deals with effects of drugs on living system
Drug – Any substance or product that is used or intended to be used to modify or explore physiological system or pathological states for the benefit of recipient (WHO)
Pharmacokinetics
Movement of drug within the body
Includes process of absorption (A), distribution (D), metabolism (M), and excretion (E)
Means "what the body does to the drug"
Pharmacodynamics
Study of drugs, their mechanism of action, pharmacological actions, and their adverse effects
Means "what drug does to body"
Pharmacy
Science that deals with preparation, preservation, standardization, compounding, dispensing and proper utilization of drugs
Therapeutics
Concerned with treatment of diseases
Toxicology
Study of poisons, their actions, detection, prevention and treatment of poisoning
Chemotherapy
Deals with treatment of infectious diseases/cancer
Clinical pharmacology
Study of drug in man, both healthy volunteers and patients, by comparative clinical trials
Essential drugs
Satisfy the health care needs of majority of population
Should be available at all times, in adequate amounts, and in appropriate dosage forms (WHO)
Orphan drug
Used for diagnosis, treatment or prevention of rare diseases

1.2 DRUG NOMENCLATURE

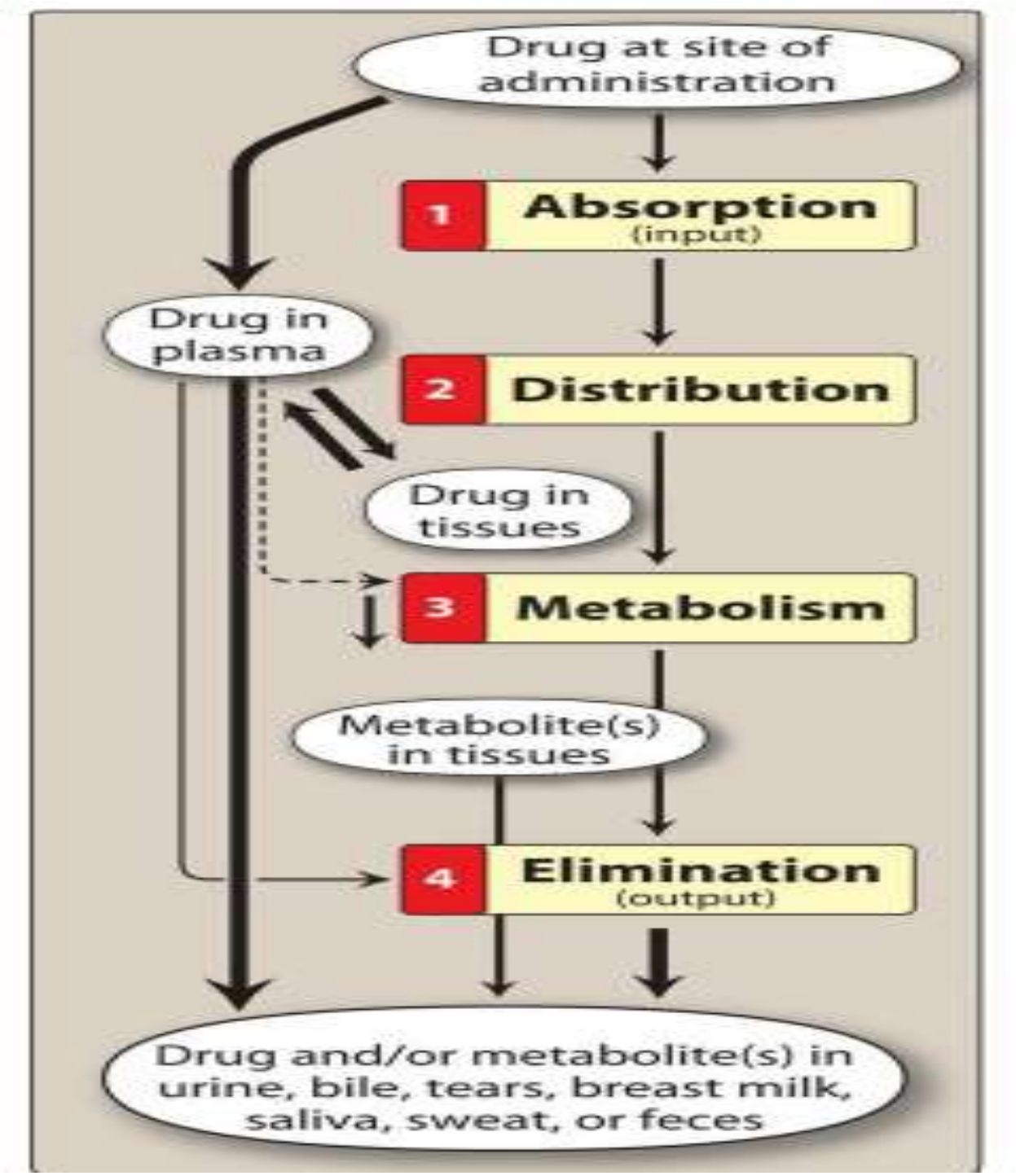


1.3 SOURCES OF DRUGS



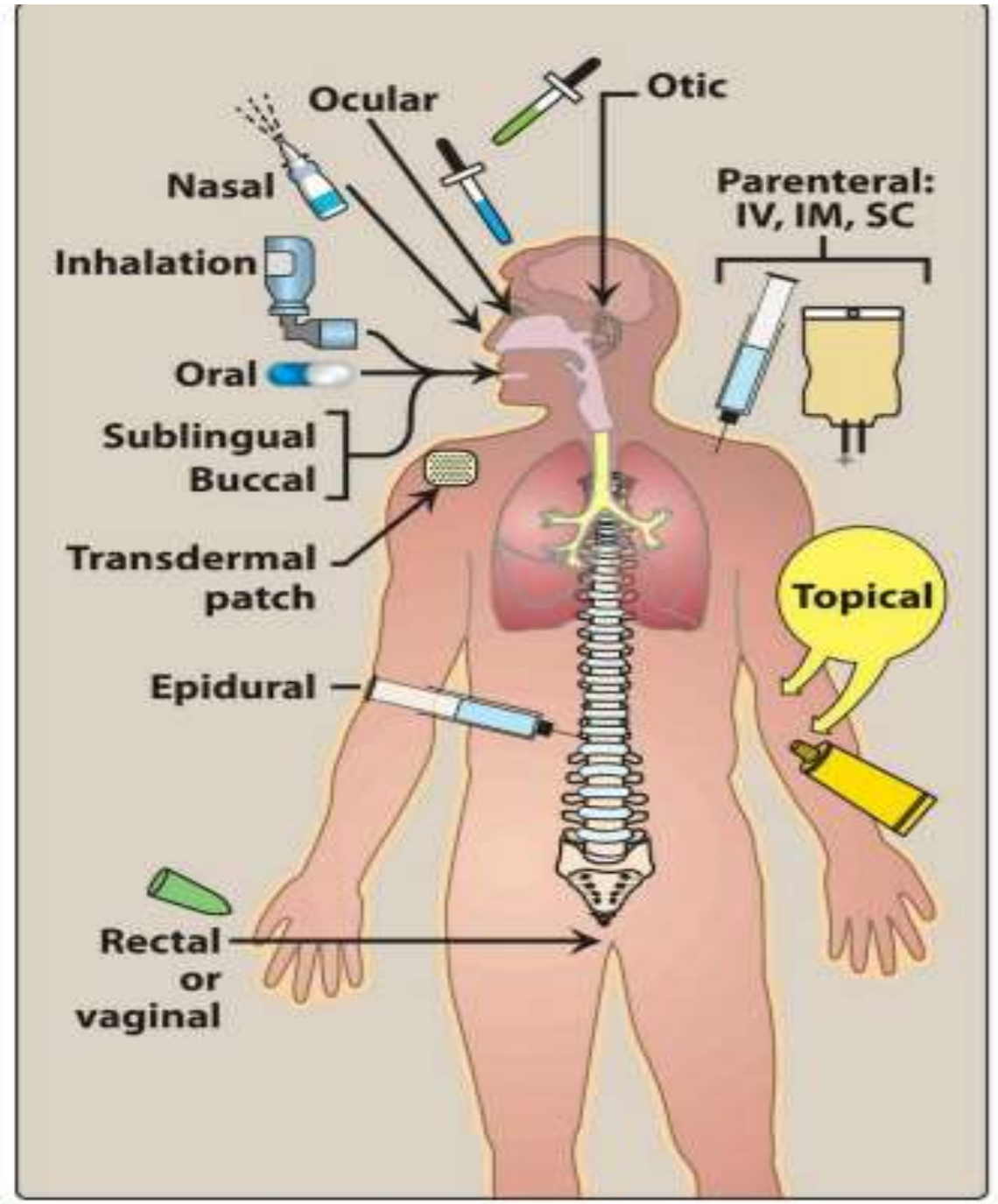
Pharmacokinetics refers to what the body does to a drug, whereas **pharmacodynamics** describes what the drug does to the body.

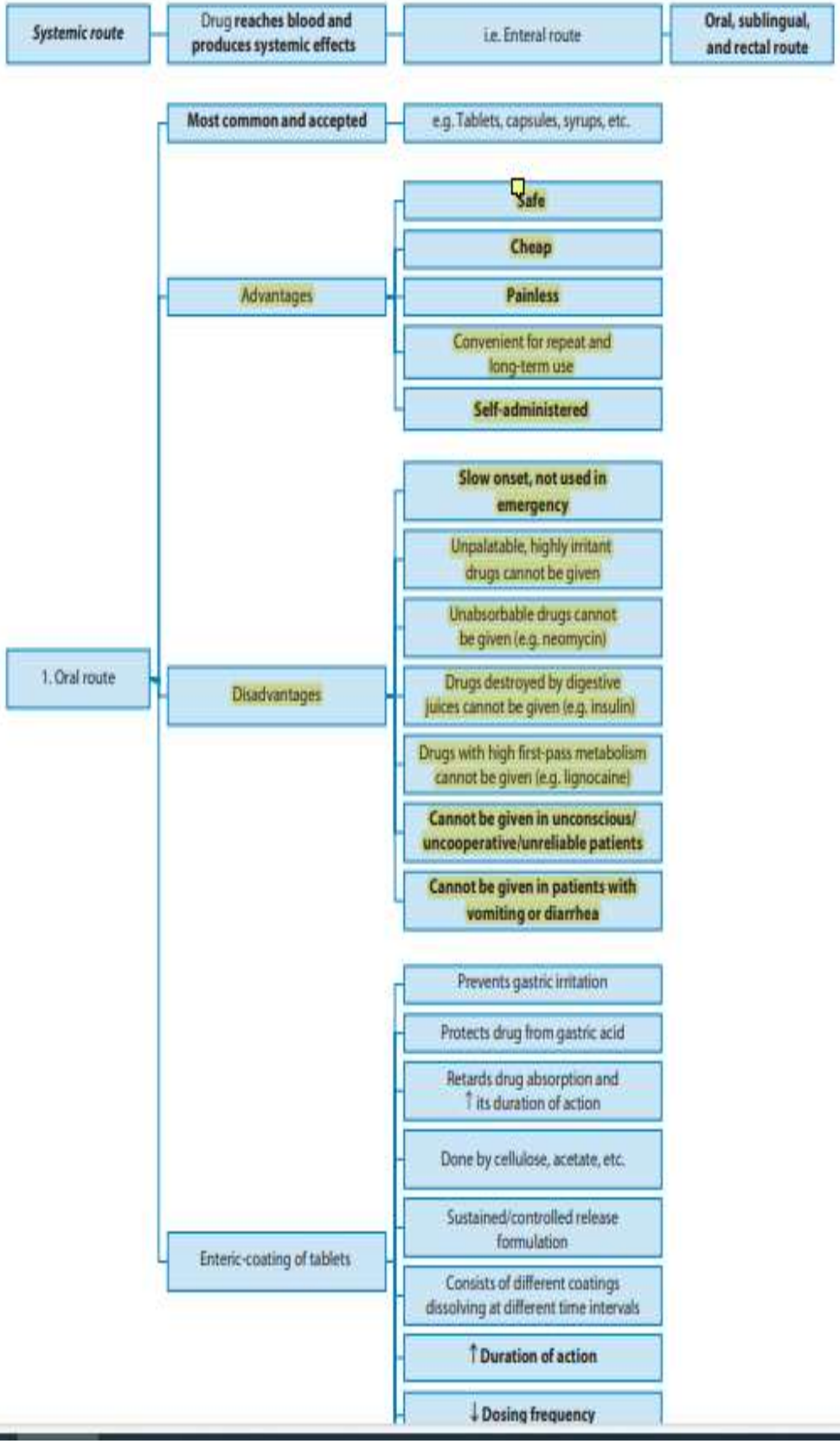
Four pharmacokinetic properties determine the onset, intensity, and duration of drug action:

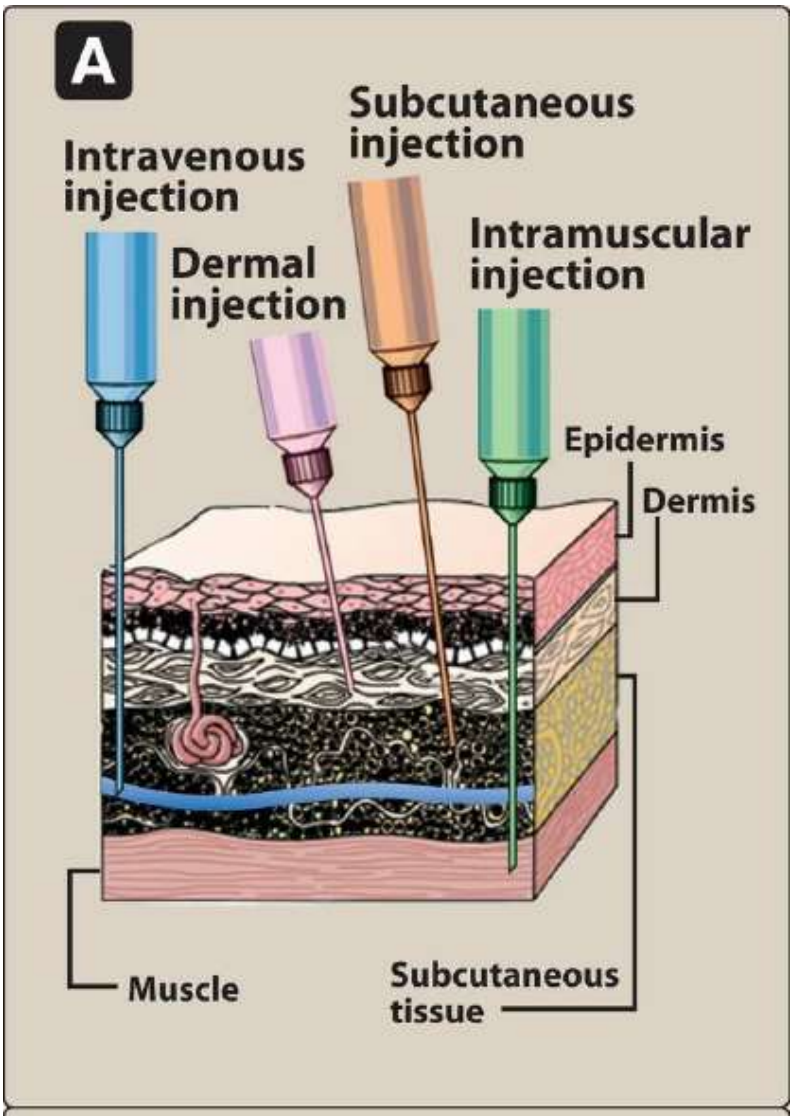


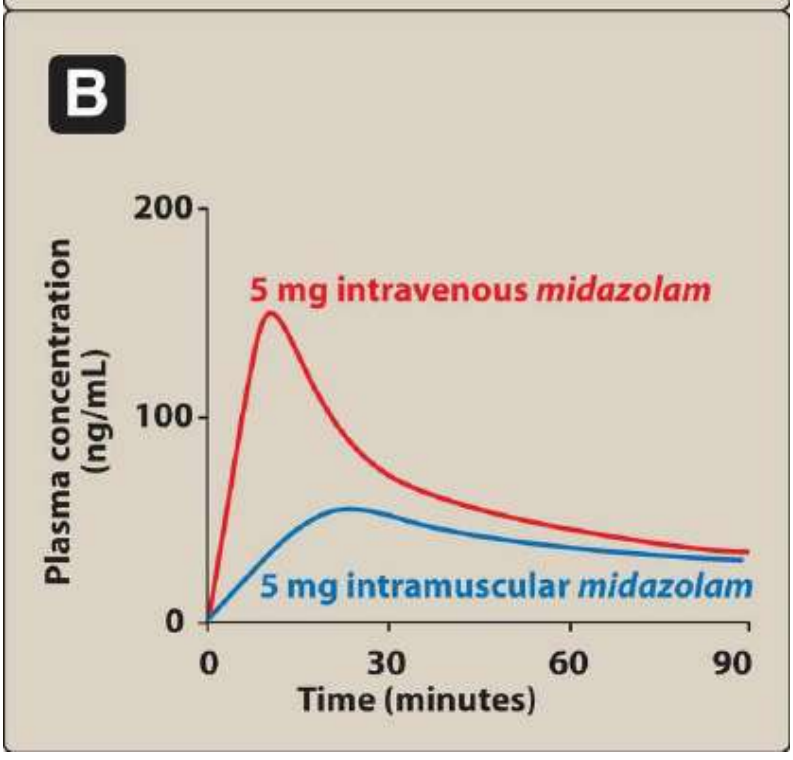
Routes of Drug Administration

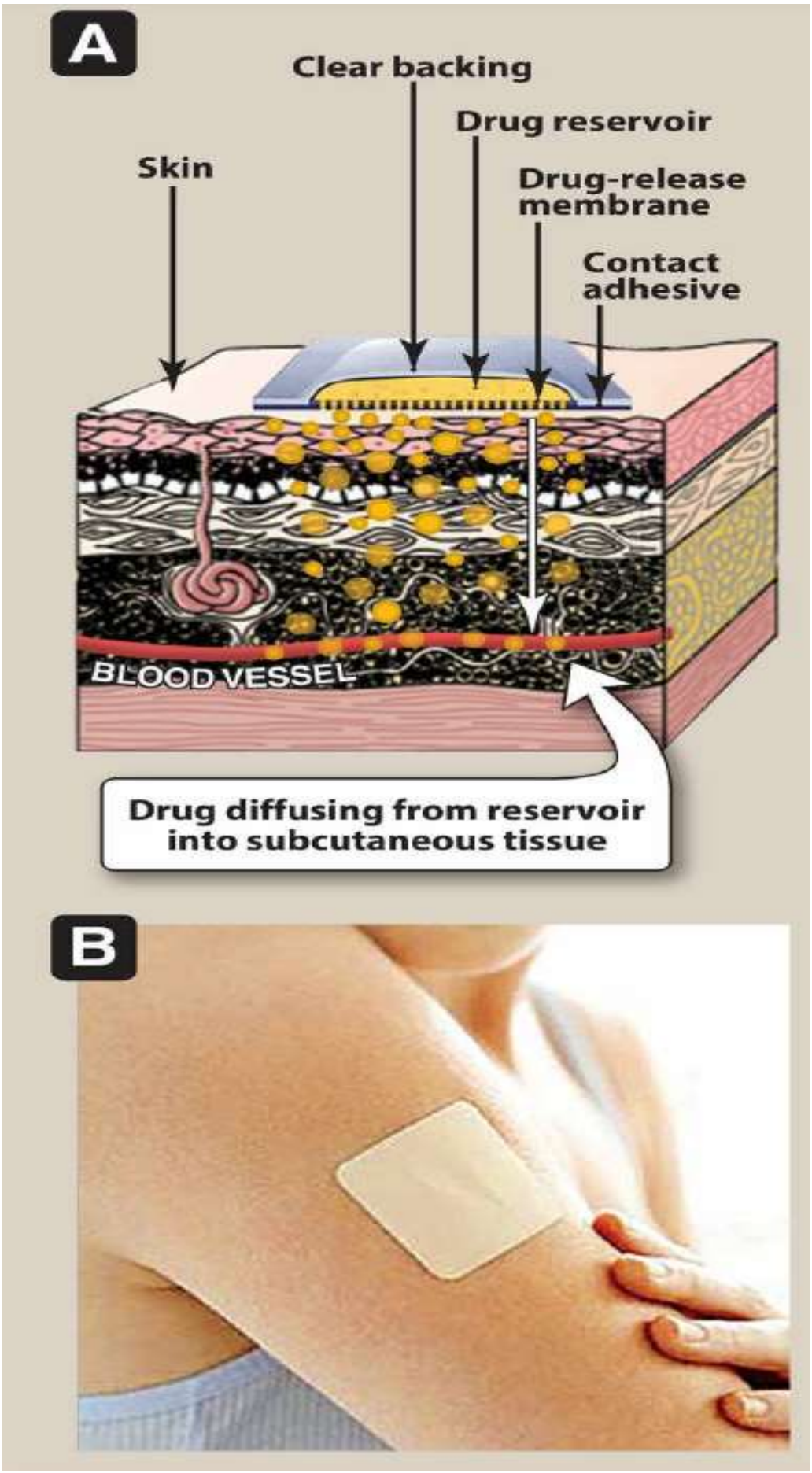
The route of administration is determined by properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical, among others.



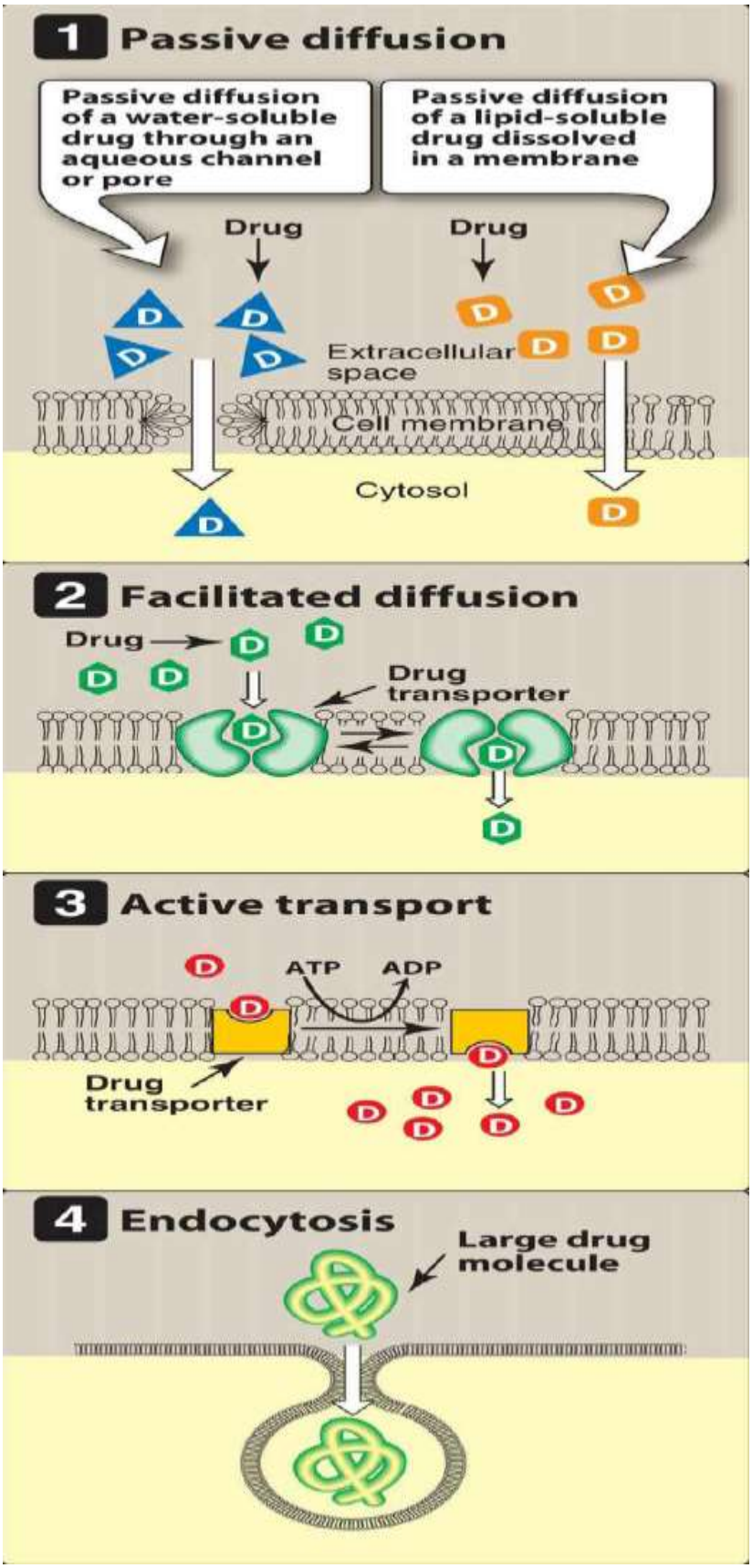

Systemic route
Drug reaches blood and produces systemic effects
i.e. Enteral route
Oral, sublingual, and rectal route
1. Oral route
Most common and accepted
e.g. Tablets, capsules, syrups, etc.
Advantages
Safe
Cheap
Painless
Convenient for repeat and long-term use
Self-administered
Disadvantages
Slow onset, not used in emergency
Unpalatable, highly irritant drugs cannot be given
Unabsorbable drugs cannot be given (e.g. neomycin)
Drugs destroyed by digestive juices cannot be given (e.g. insulin)
Drugs with high first-pass metabolism cannot be given (e.g. lignocaine)
Cannot be given in unconscious/ uncooperative/unreliable patients
Cannot be given in patients with vomiting or diarrhea
Enteric-coating of tablets
Prevents gastric irritation
Protects drug from gastric acid
Retards drug absorption and ↑ its duration of action
Done by cellulose, acetate, etc.
Sustained/controlled release formulation
Consists of different coatings dissolving at different time intervals
↑ Duration of action
↓ Dosing frequency

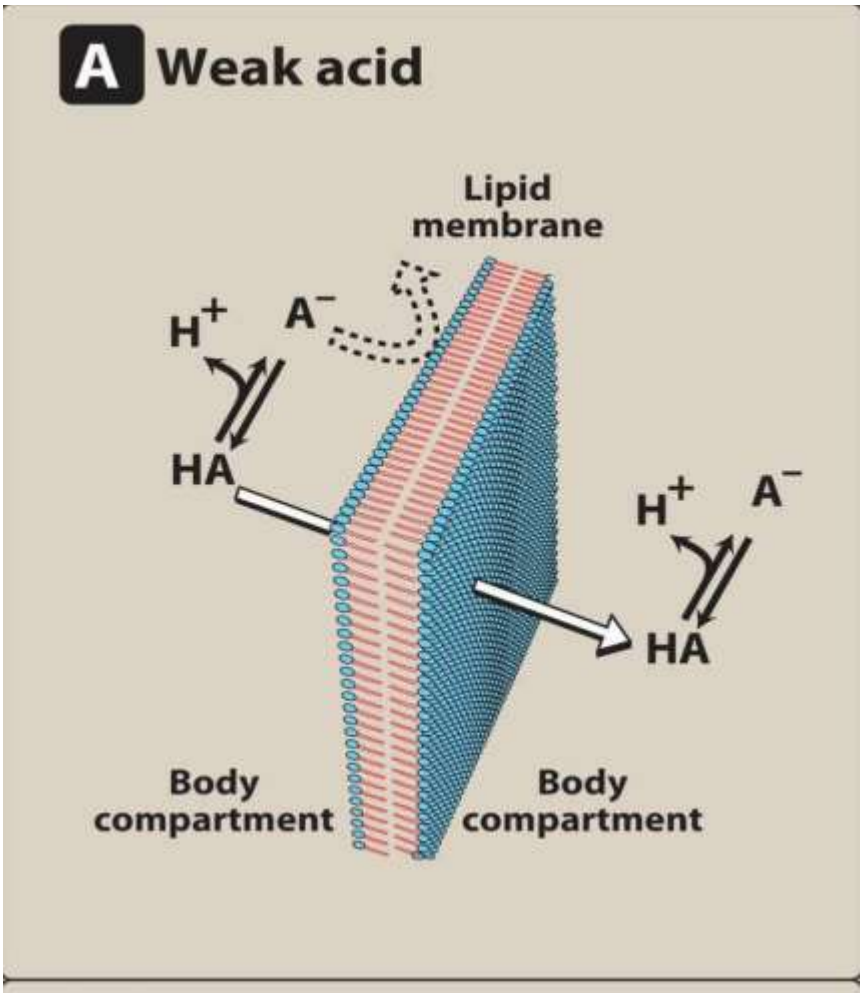

A
Intravenous injection
Subcutaneous injection
Dermal injection
Intramuscular injection
Epidermis
Dermis
Muscle
Subcutaneous tissue

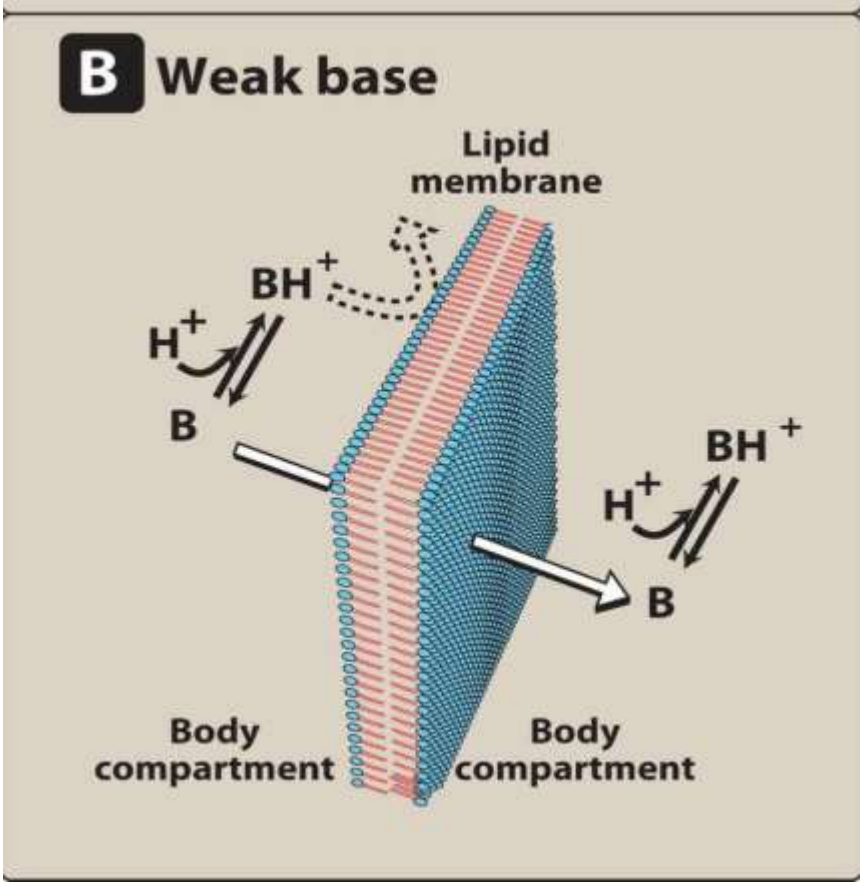

B
Plasma concentration (ng/mL)
200
100
0
5 mg intravenous midazolam
5 mg intramuscular midazolam
0
30
60
90
Time (minutes)


A
Clear backing
Drug reservoir
Skin
Drug-release membrane
Contact adhesive
BLOOD VESSEL
Drug diffusing from reservoir into subcutaneous tissue
B

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* tablets • *Amoxicillin* suspension
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed	• *Nitroglycerin* • *Buprenorphine*
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	• *Haloperidol* • *Depot medroxy-progesterone*
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes	• *Epinephrine* • *Insulin* • *Heparin*
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs; lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers	• *Albuterol* • *Fluticasone*
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intravaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream • *Timolol* eye drops
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route	• *Bisacodyl* • *Promethazine*

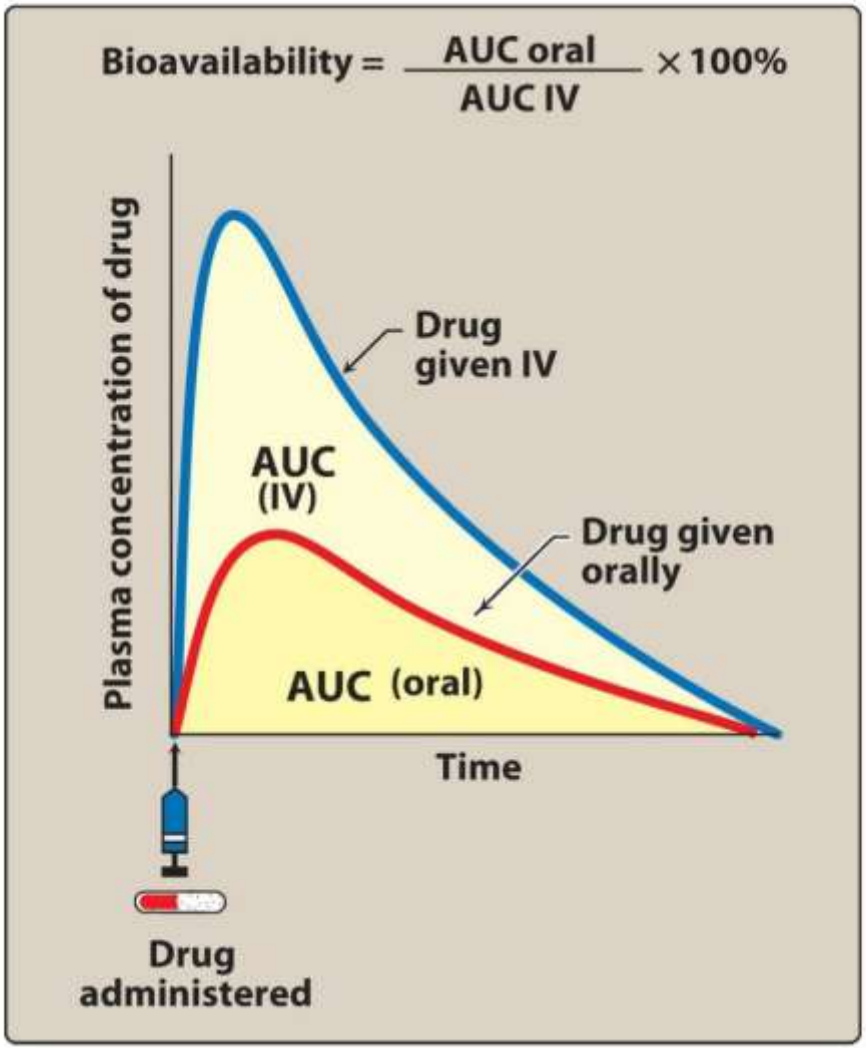

1 Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
Extracellular space
Cell membrane
Cytosol
2 Facilitated diffusion
Drug
Drug transporter
3 Active transport
ATP
ADP
Drug transporter
4 Endocytosis
Large drug molecule

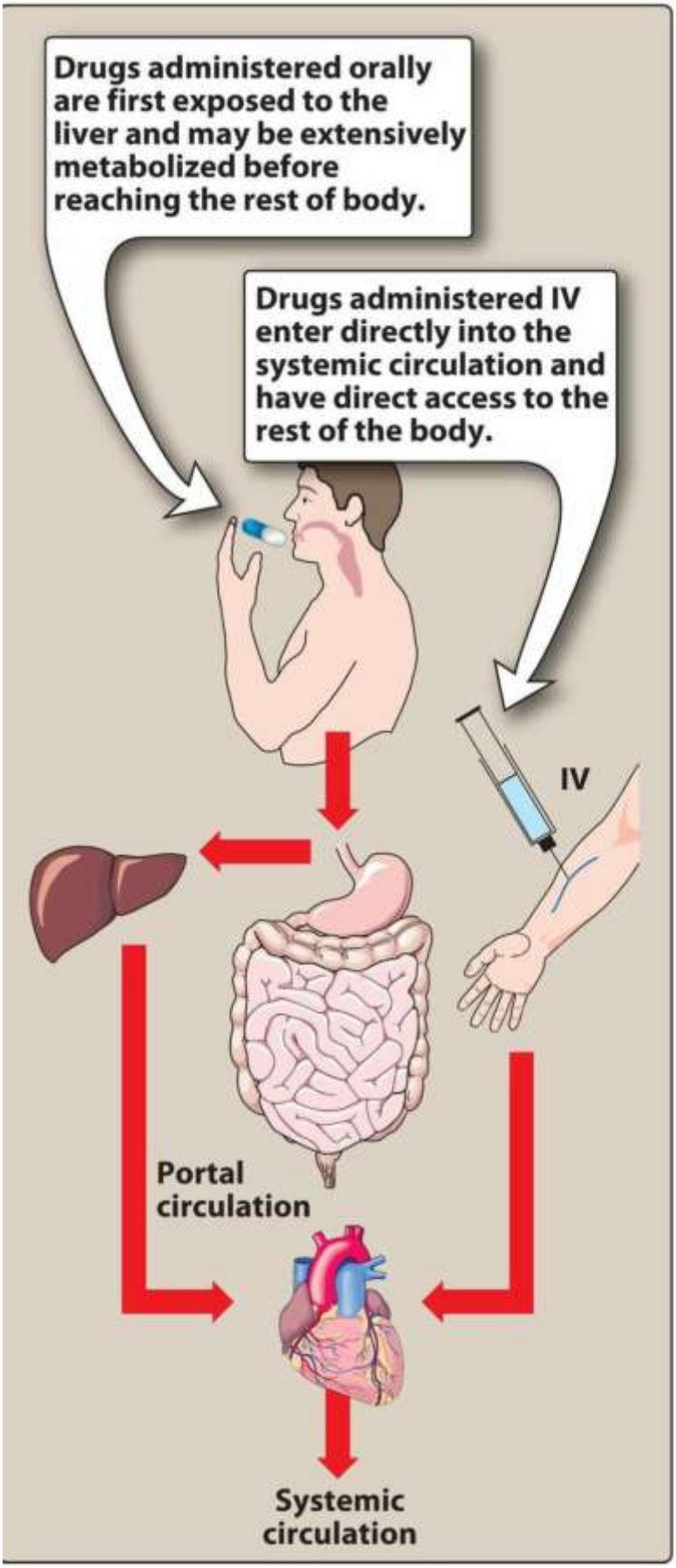

A Weak acid
Lipid membrane
H+
A−
HA
H+
A−
HA
Body compartment
Body compartment


B Weak base
Lipid membrane
BH+
H+
B
BH+
H+
B
Body compartment
Body compartment

Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration.





First-pass metabolism can occur with orally administered drugs.

Binding of drugs to plasma proteins and tissues

1. **Binding to plasma proteins**: Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows transfer out of the vascularcompartment. Albumin is the major drug-binding protein, and it may act as a drug reservoir. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. **Binding to tissue proteins:** Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood.

Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of cyclophosphamide, can cause hemorrhagic cystitis because it accumulates in the bladder.)

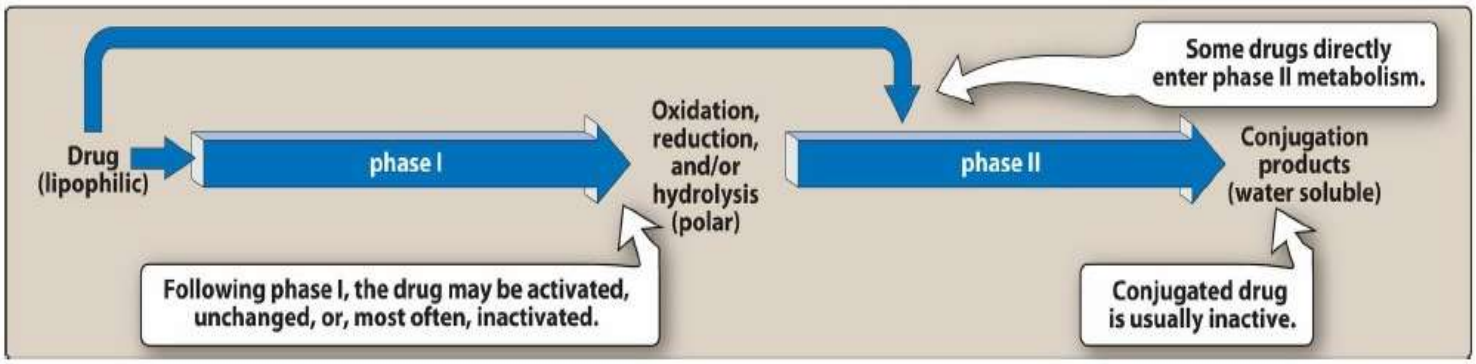
Volume of distribution

The apparent volume of distribution, Vd, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

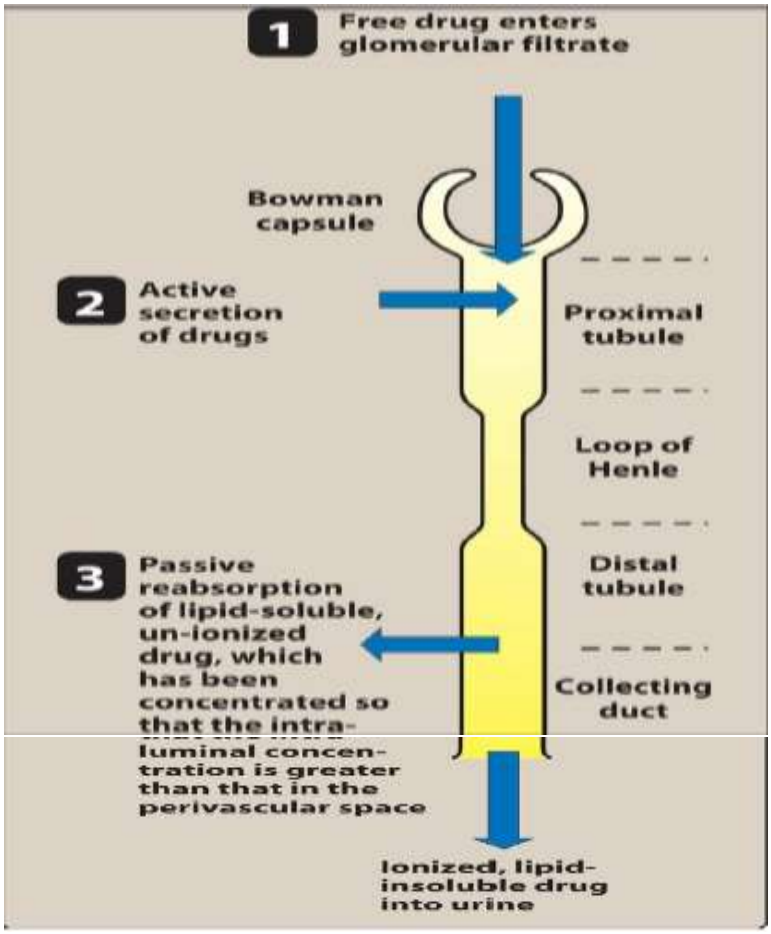
Reactions of drug metabolism

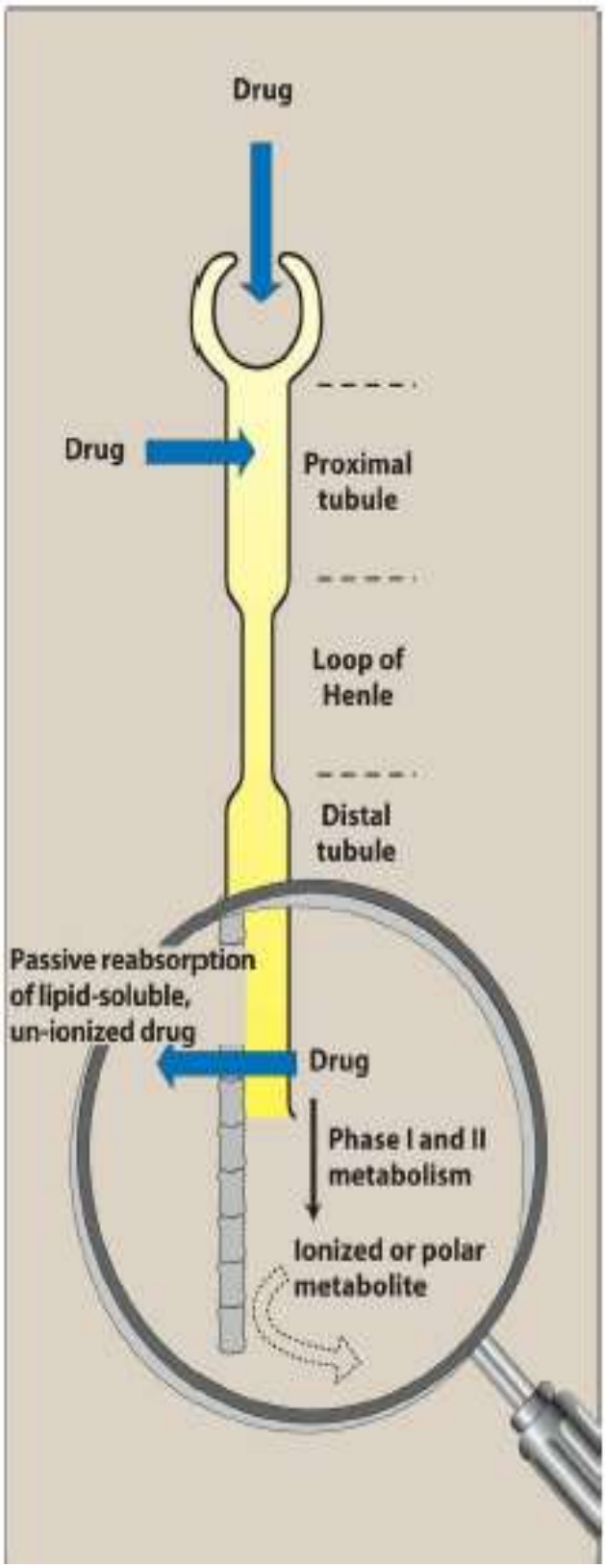
The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic)substances in the liver via two general sets of reactions, called phase I and phase II.



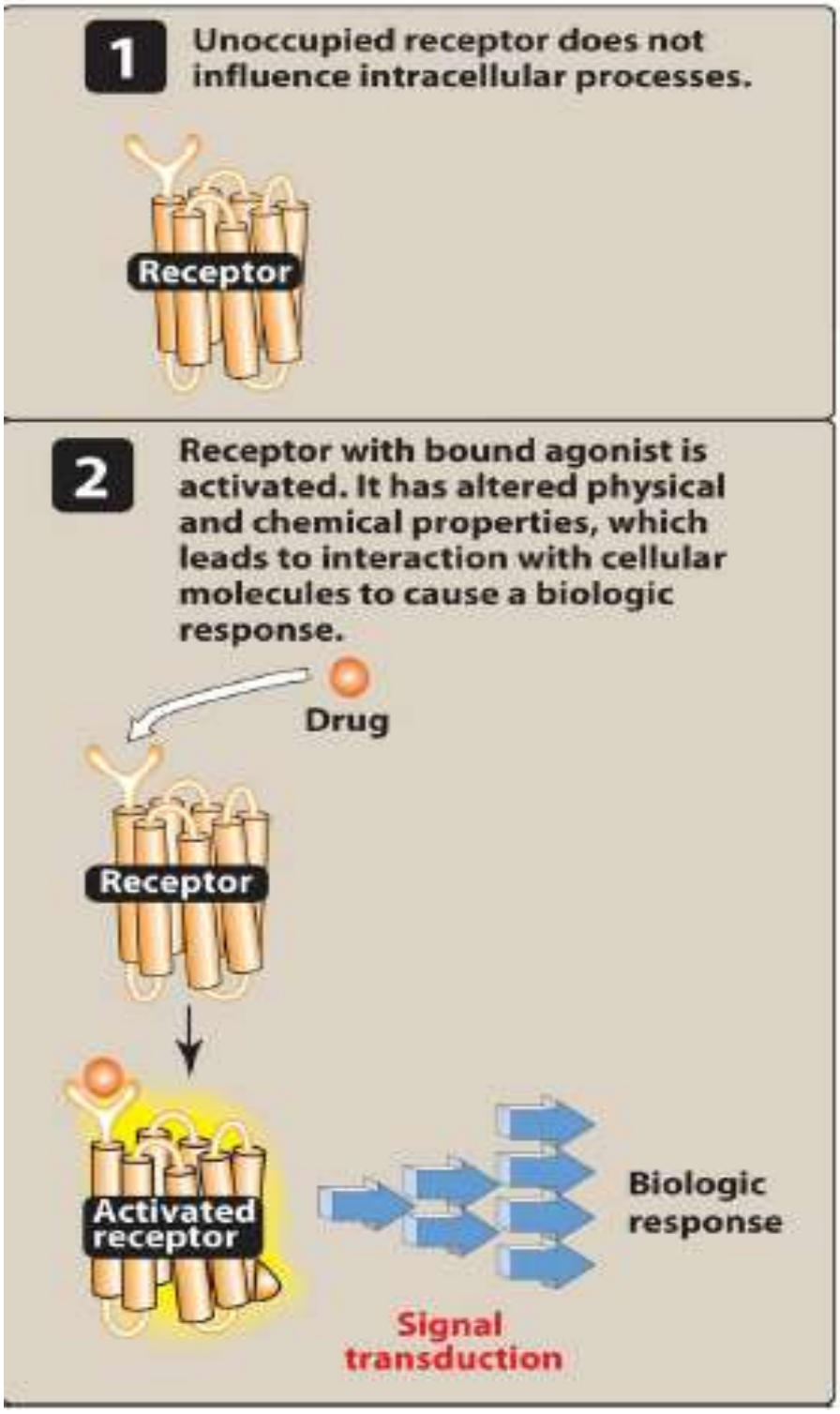
The biotransformation of drugs.

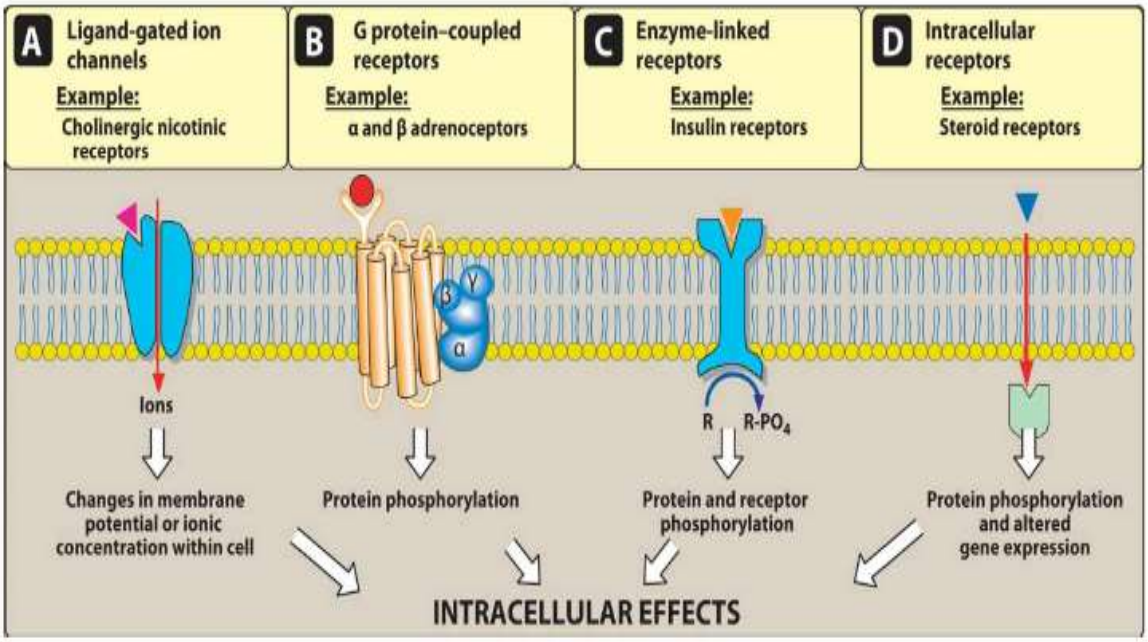
Drug excretion

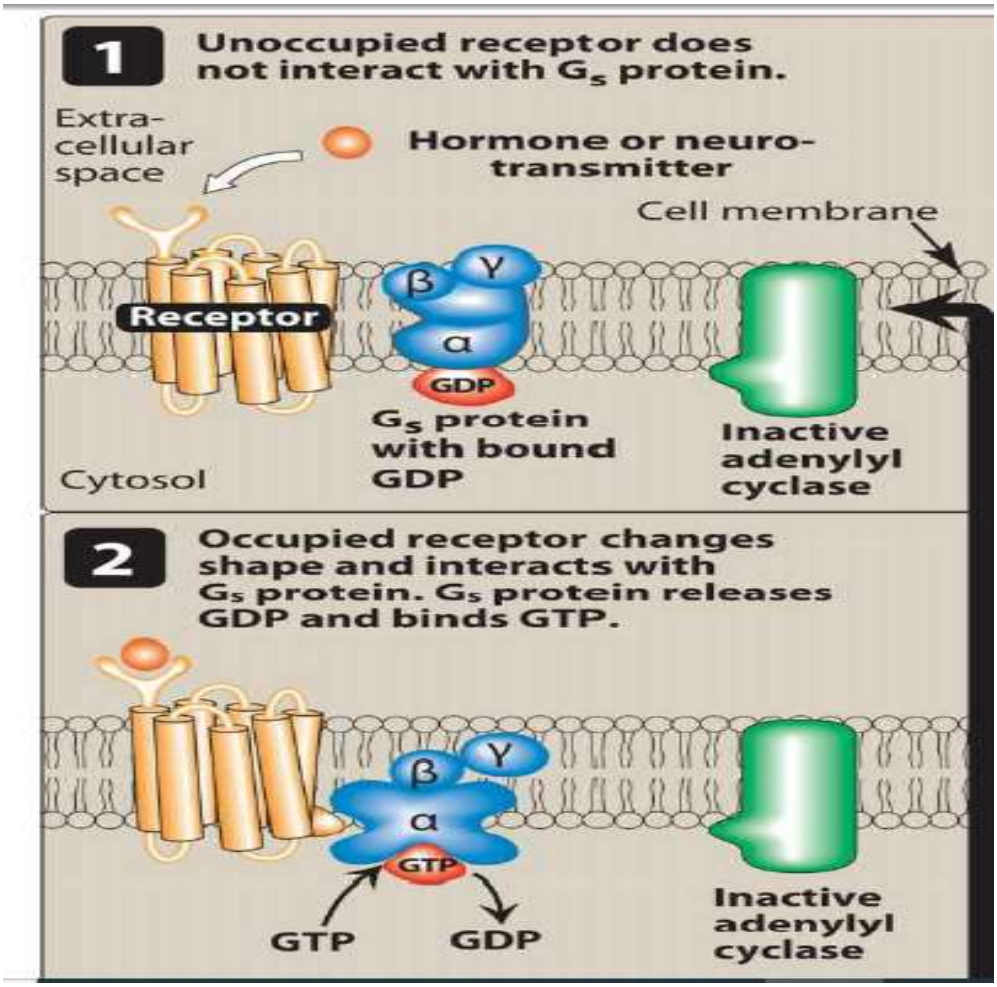


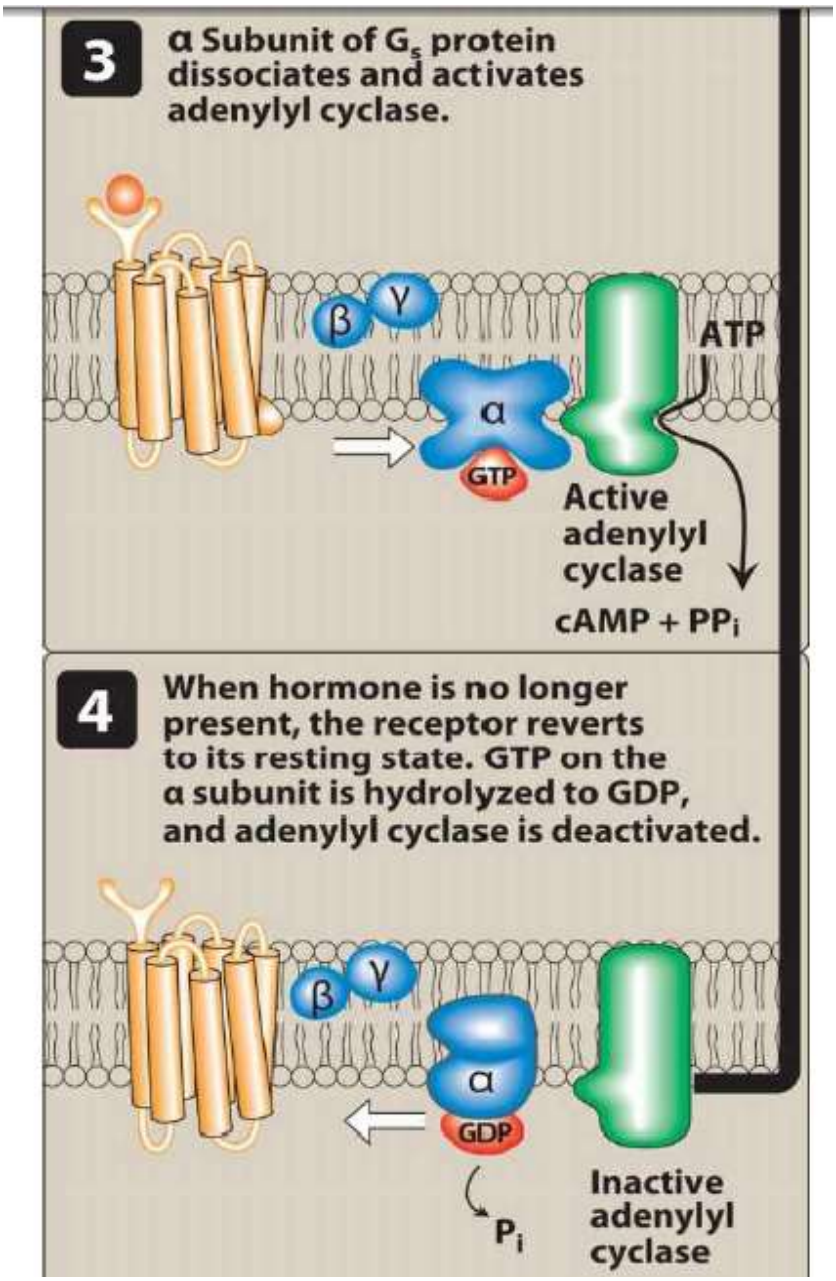

Drug
Drug
Proximal tubule
Loop of Henle
Distal tubule
Passive reabsorption of lipid-soluble, un-ionized drug
Drug
Phase I and II metabolism
Ionized or polar metabolite

Pharmaco-dynamics

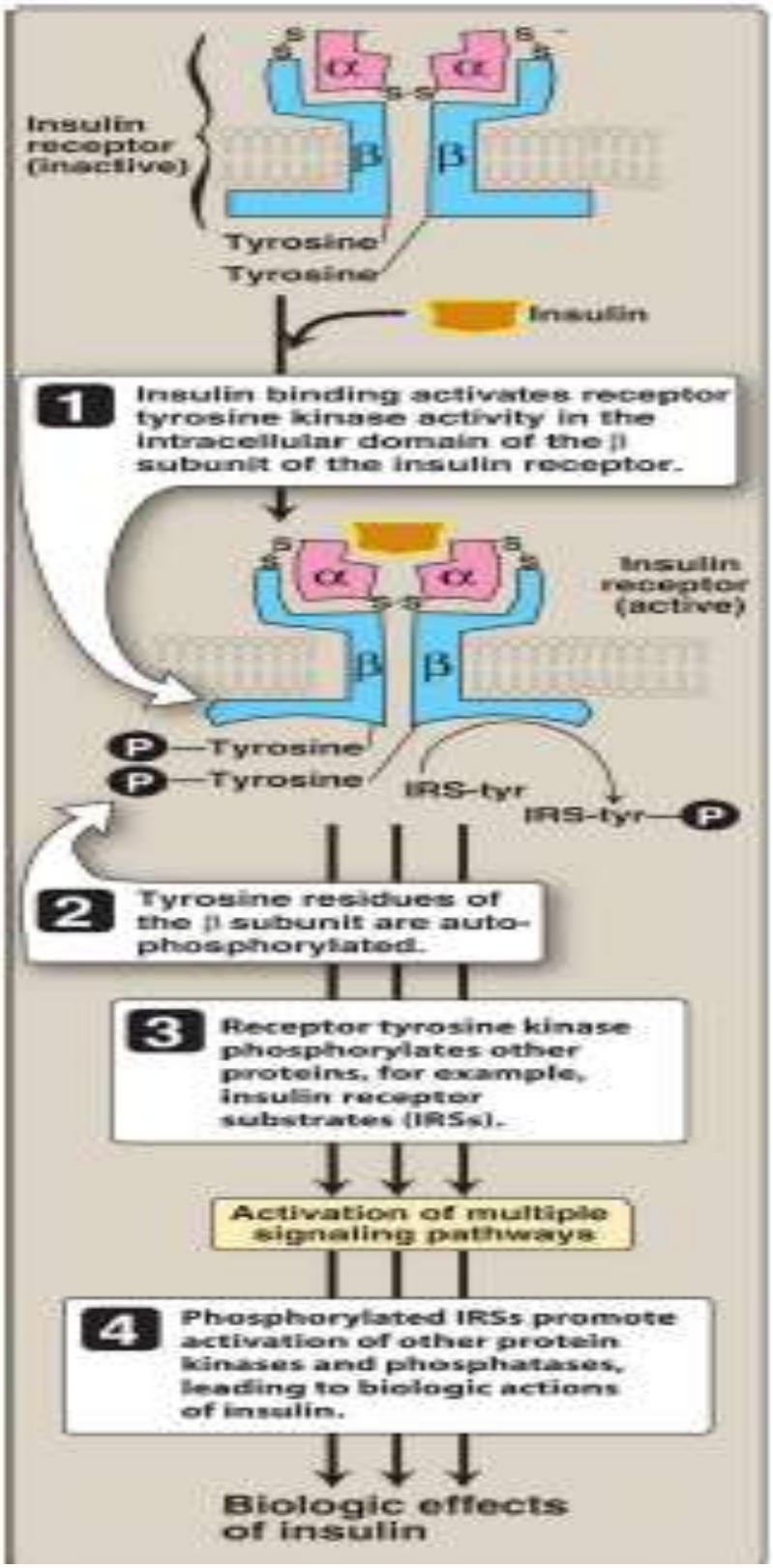



A Ligand-gated ion channels
Example:
Cholinergic nicotinic receptors
B G protein–coupled receptors
Example:
α and β adrenoceptors
C Enzyme-linked receptors
Example:
Insulin receptors
D Intracellular receptors
Example:
Steroid receptors
Ions
β
γ
α
R
R-PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

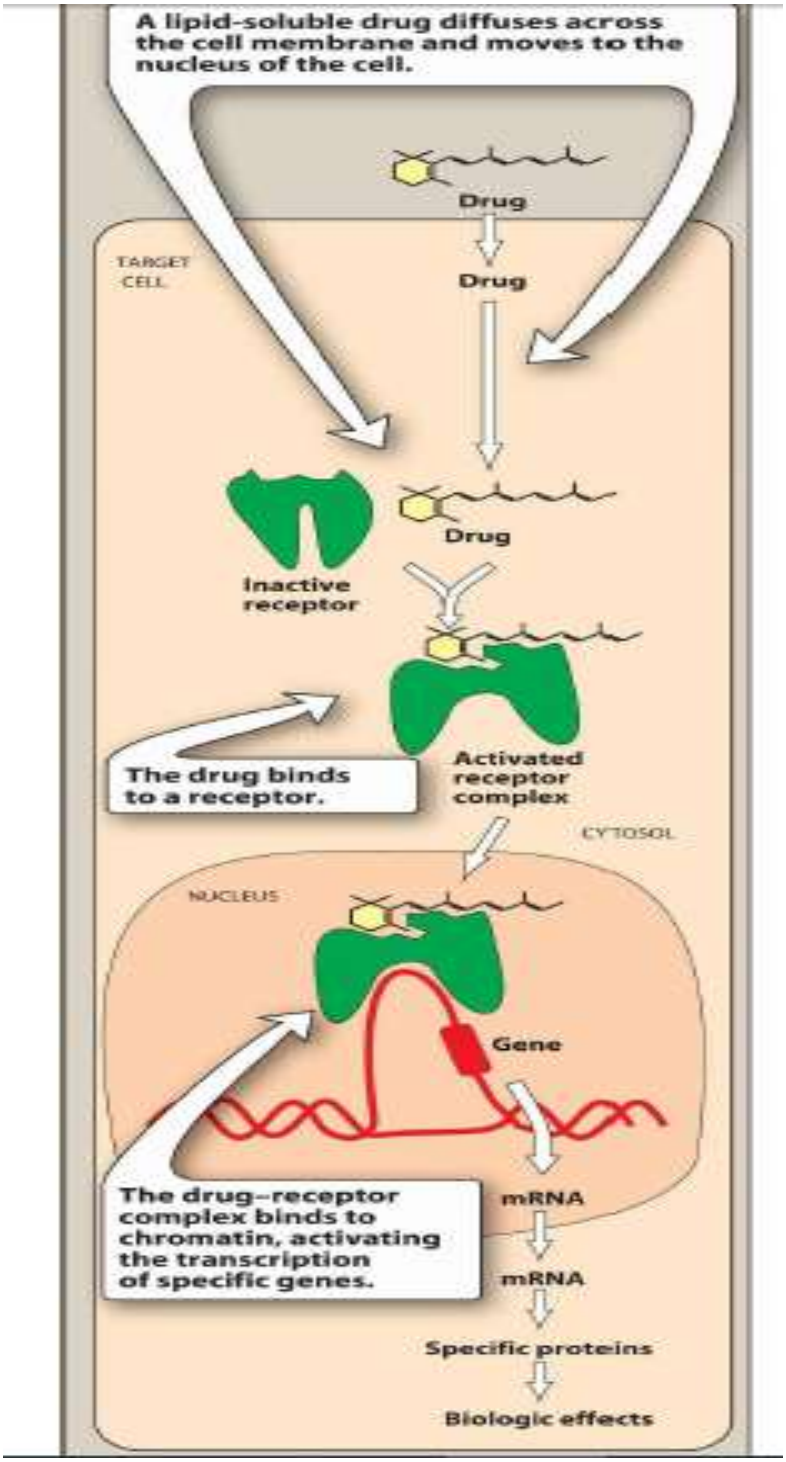

1
Unoccupied receptor does not interact with Gs protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
Gs protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with Gs protein. Gs protein releases GDP and binds GTP.
β
γ
α
GTP
GTP
GDP
Inactive adenylyl cyclase



G- Protein coupled receptors

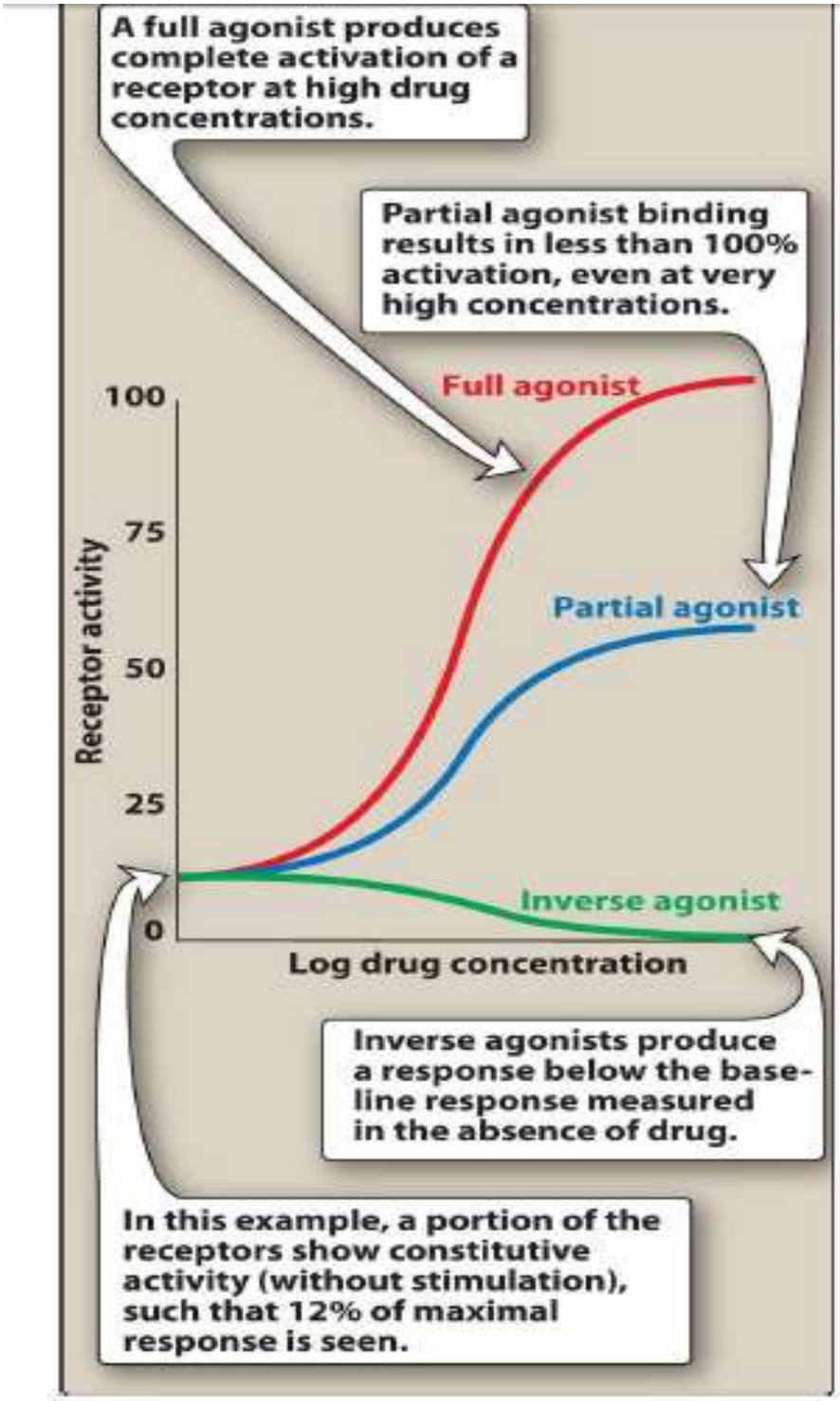


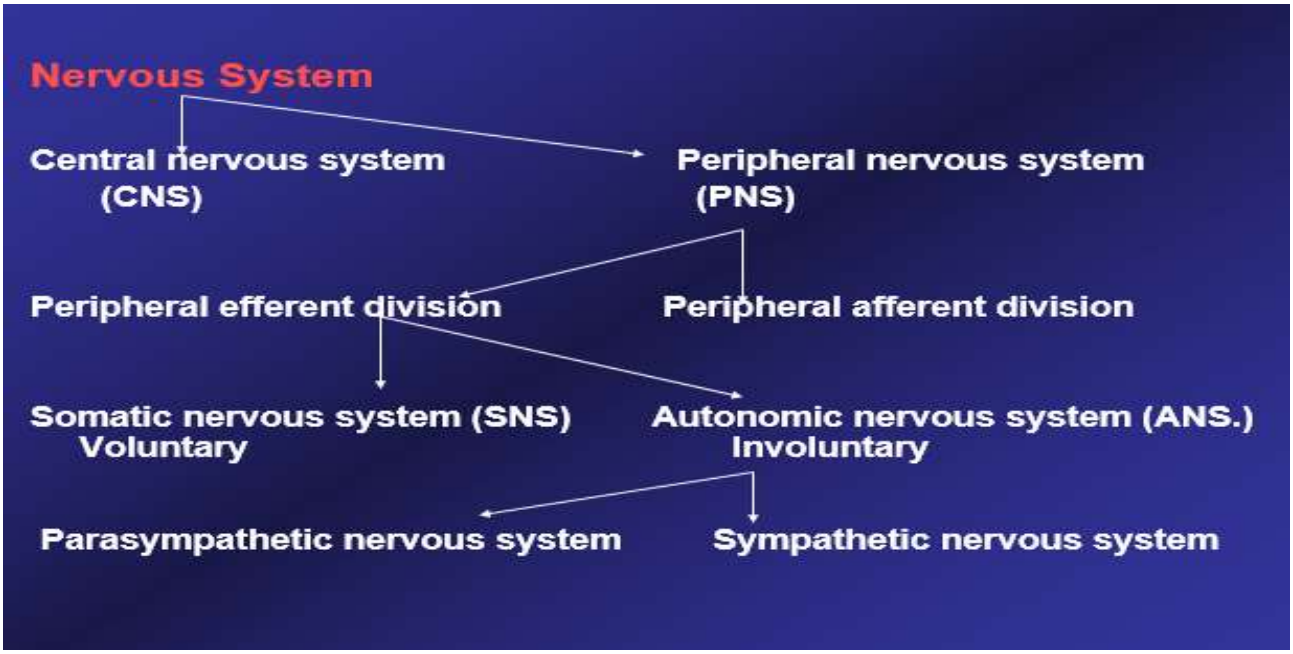
Tyrosine kinase linked receptors



Intracellular receptors

Agonist-Antagonist-Partial Agonist



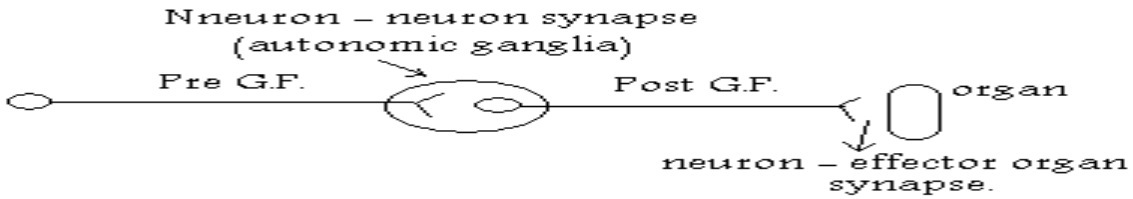


Difference	ANF	SNF
Supply	All body structure except skeletal muscles	Only skeletal muscles
Ganglia	Interrupted by a ganglia which divides the fiber into: pre- and postganglionic fibers.	No ganglia but direct supply from the CNS to the skeletal muscles.
Function	Involuntary –or- automatic control (not under conscious control).	Voluntary i.e. under conscious control.
Denervation	Change the function of organs but they show some degree of activity.	Completely paralyze the muscle.

Types of synapses in ANS:

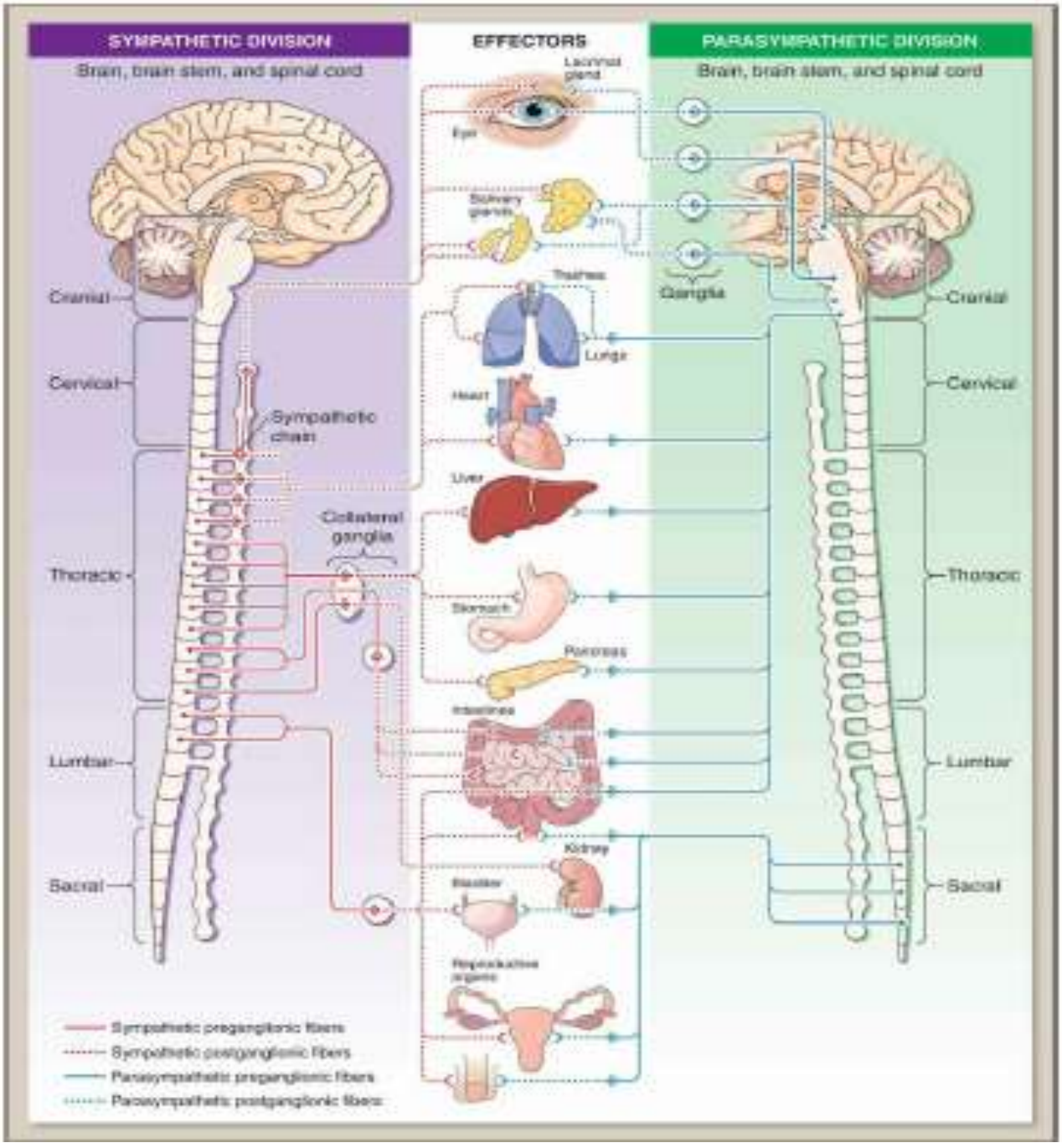
1) Neuron-neuron synapse, between the pre- and postganglionic fiber (Ganglia).

2) Neuron-effector organ synapse, (nerve end of postganglionic fiber and the organ).



Difference	Sympathetic	Parasympathetic
Origin	All thoracic and upper three Lumbar	III, VII, IX, and X cranial nerves and 2nd , 3rd and 4th of sacral
Ganglion	Ganglia are closed to spinal cord (shorter pre-ganglion and longer post-ganglion fibers).	Ganglia are away from spinal cord usually embedded in supplied organ (longer pre-ganglion and shorter post-ganglion fibers).

Physiological function	**Not essential for life .It acts mainly under stress and emergency condition.**	**Essential for life, it regulates vital function as digestion ….. etc.**
chemical mediator	**Generally nor epinephrine (NEP)**	**Generally acetylcholine (A Ch)**

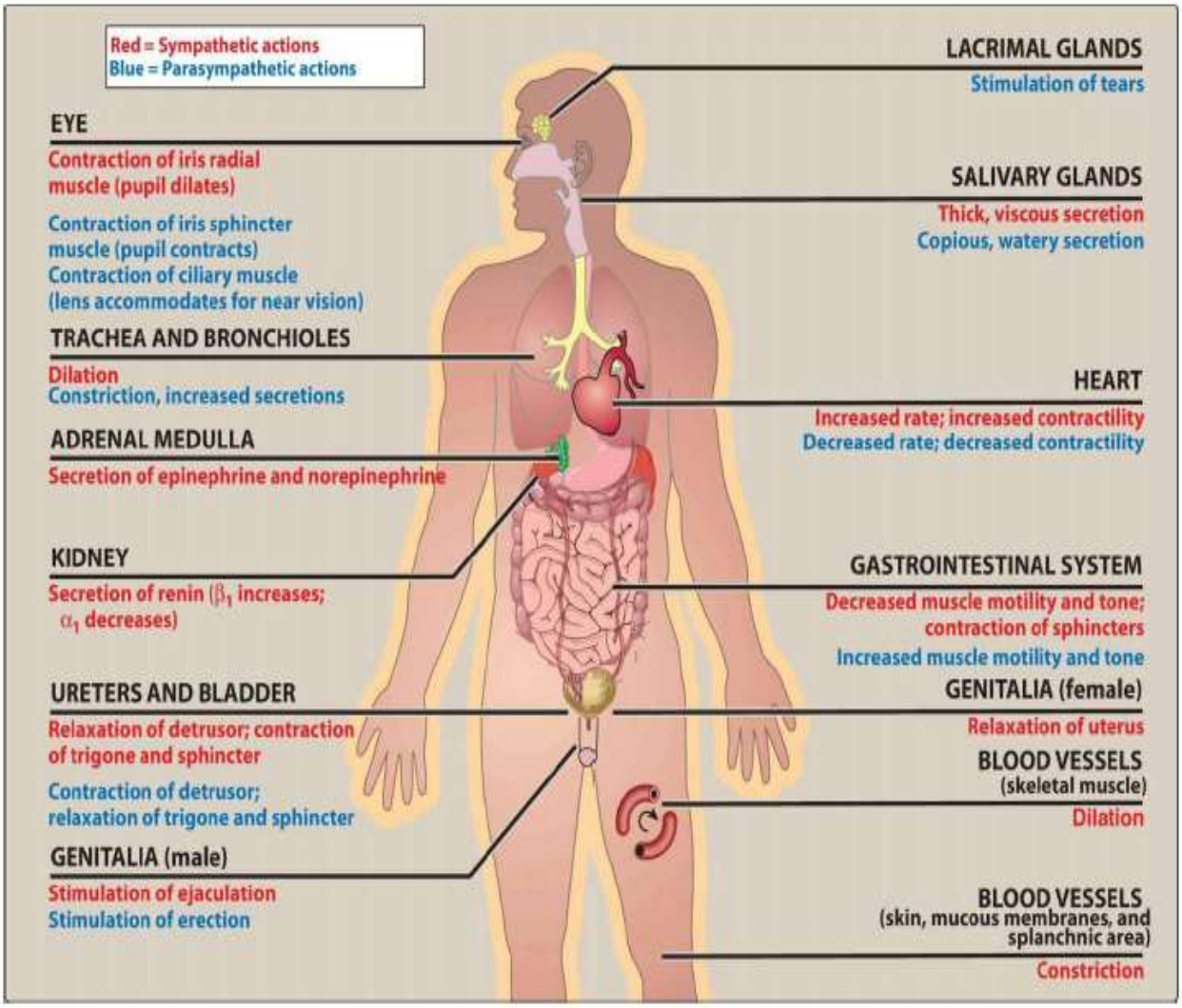


Types of the autonomic nerve fibers:-

According to the type of chemical mediator, the ANF. are classified into

1- *Cholinergic* nerve fibers A Ch as chemical mediator

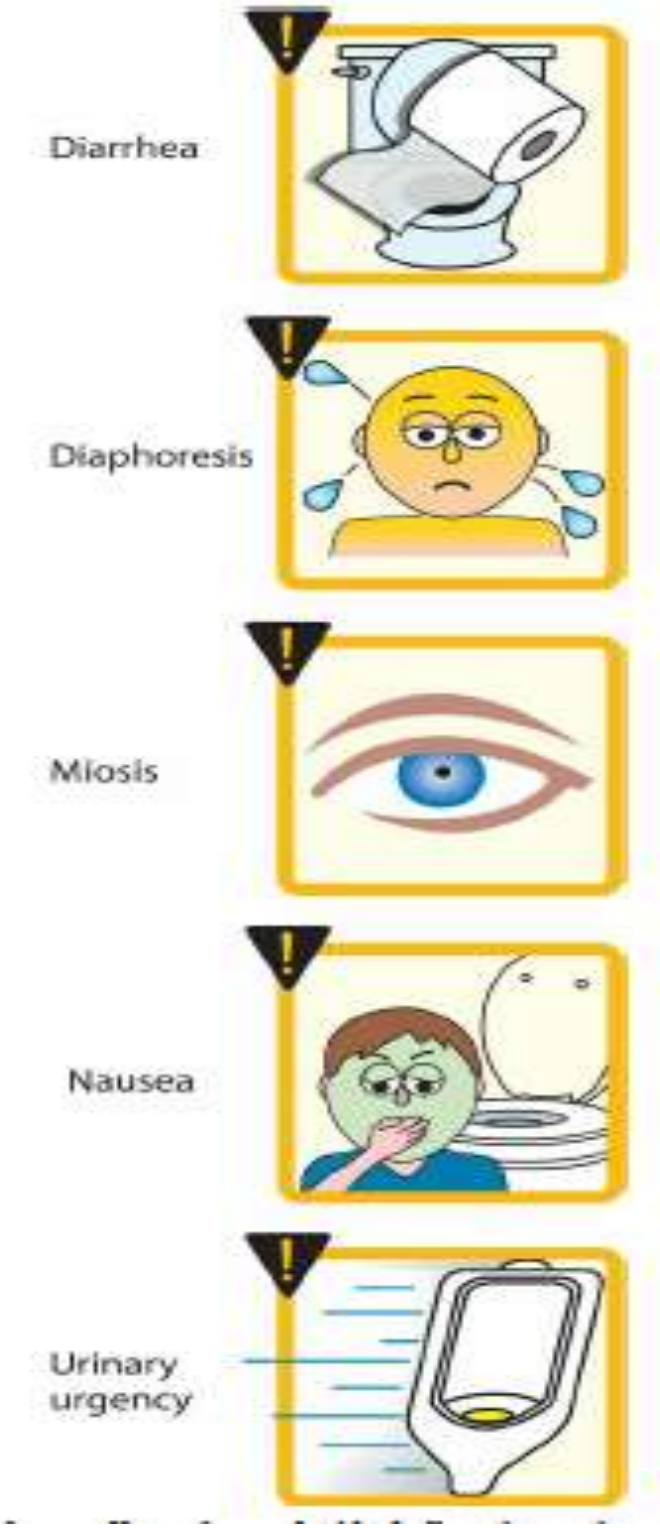
2- *Adrenergic* nerve fibers NEP as chemical mediator.



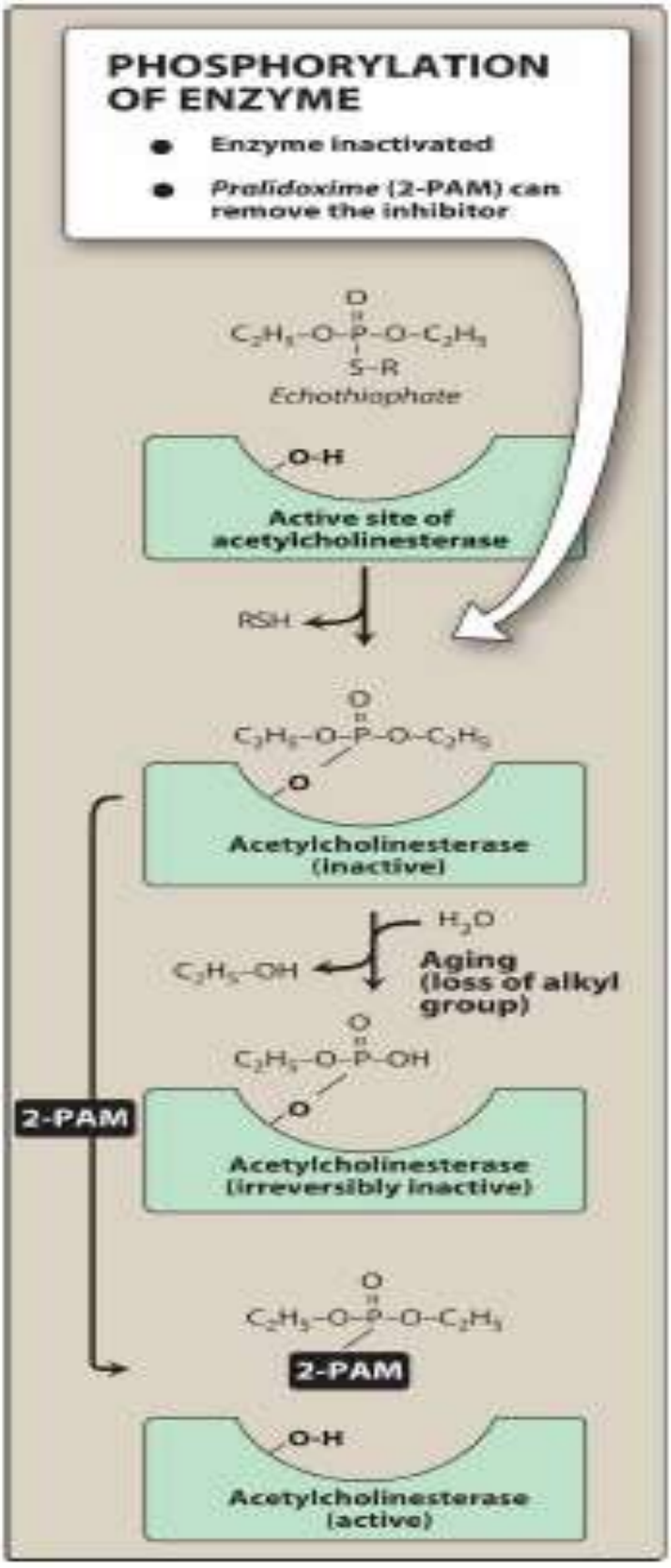
Difference	M1-Receptors	M2-Receptors	M3-Receptors
Location	Gastric parietal cells - CNS.	- Myocardium - Smooth muscles	Smooth muscles - Exocrine glands
Agonists	ACh Methacholine Carbachol	ACh Methacholine Carbachol	ACh, Methacholine Carbachol
Antagonists	Atropine and Pirenzepine	Atropine	Atropine

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

	Physostigmine (Eserine)	Neostigmine (Prostigmine)
Nature	Natural Tertiary ammonium	Synthetic Quaternary ammonium
Kinetics	1- Well absorbed orally. 2- Passes BBB. 3-Rapid metabolism by ChE. 4- Short duration	1- Irregular oral absorption. 2- Does not pass BBB. 3-Slow metabolism by ChE. 4- Long duration.
Dynamics	1-Stimulate M&N receptors. 2- Specific on eye. 3- CNS stimulant.	1- Stimulate M&N receptors. 2- Specific on GIT and UB. 3- Direct Sk.M stimulant.
Uses	1- Eye drops: a- Glaucoma. b- To counteract mydriatics. 2- IV in atropine poisoning. 3- Alzheimer disease.	1- Myasthenia gravis. 2- Curare poisoning. 3- Paralytic lleus. 4- Urine retention
Toxicity	1- Exaggerated ACh-like actions. 2- CNS convulsions	1- Exaggerated ACh-like action. 2- No convulsions in CNS.
Management	1- Atropine. 2- Anticonvulsants.	1- Atropine only.



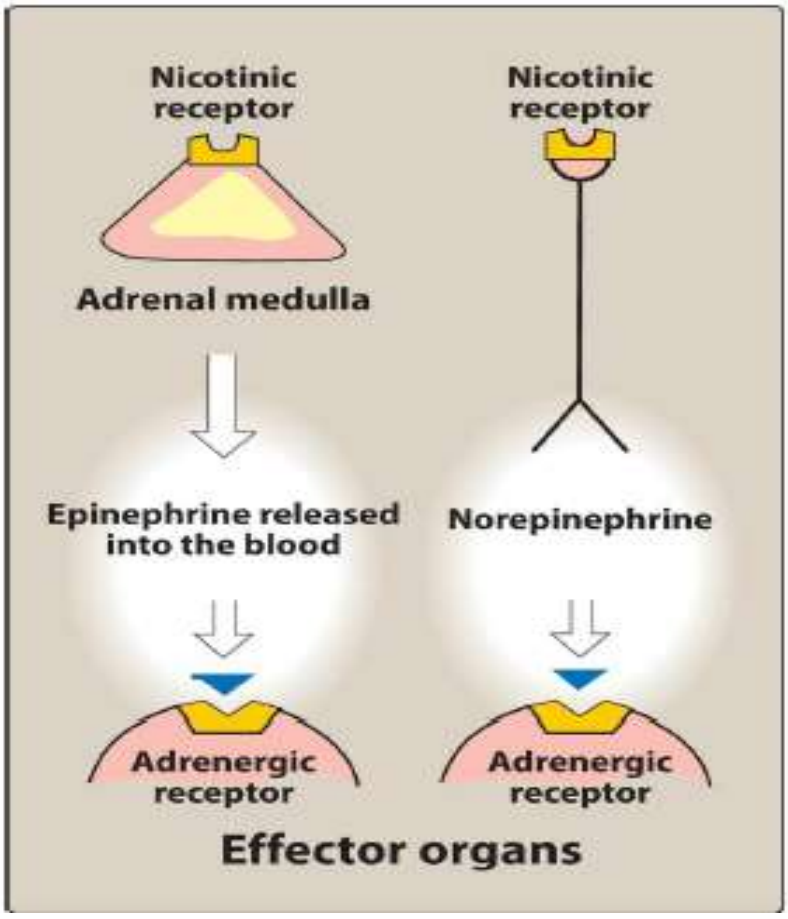
Adverse effects of Cholinergic agonists

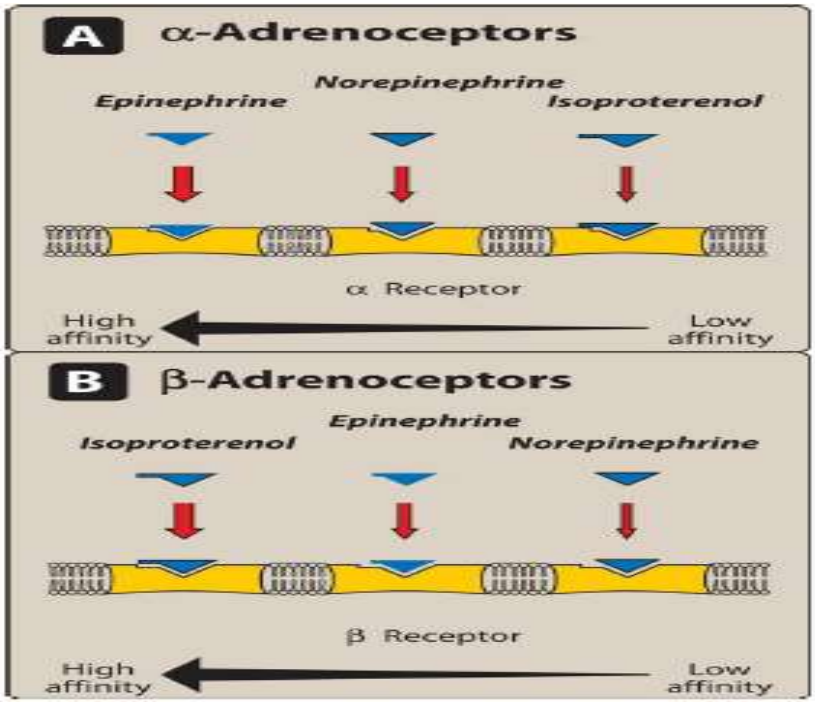

PHOSPHORYLATION OF ENZYME
Enzyme inactivated
Pralidoxime (2-PAM) can remove the inhibitor
Echothiophate
O-H
Active site of acetylcholinesterase
RSH
Acetylcholinesterase (inactive)
Aging (loss of alkyl group)
2-PAM
Acetylcholinesterase (irreversibly inactive)
2-PAM
O-H
Acetylcholinesterase (active)

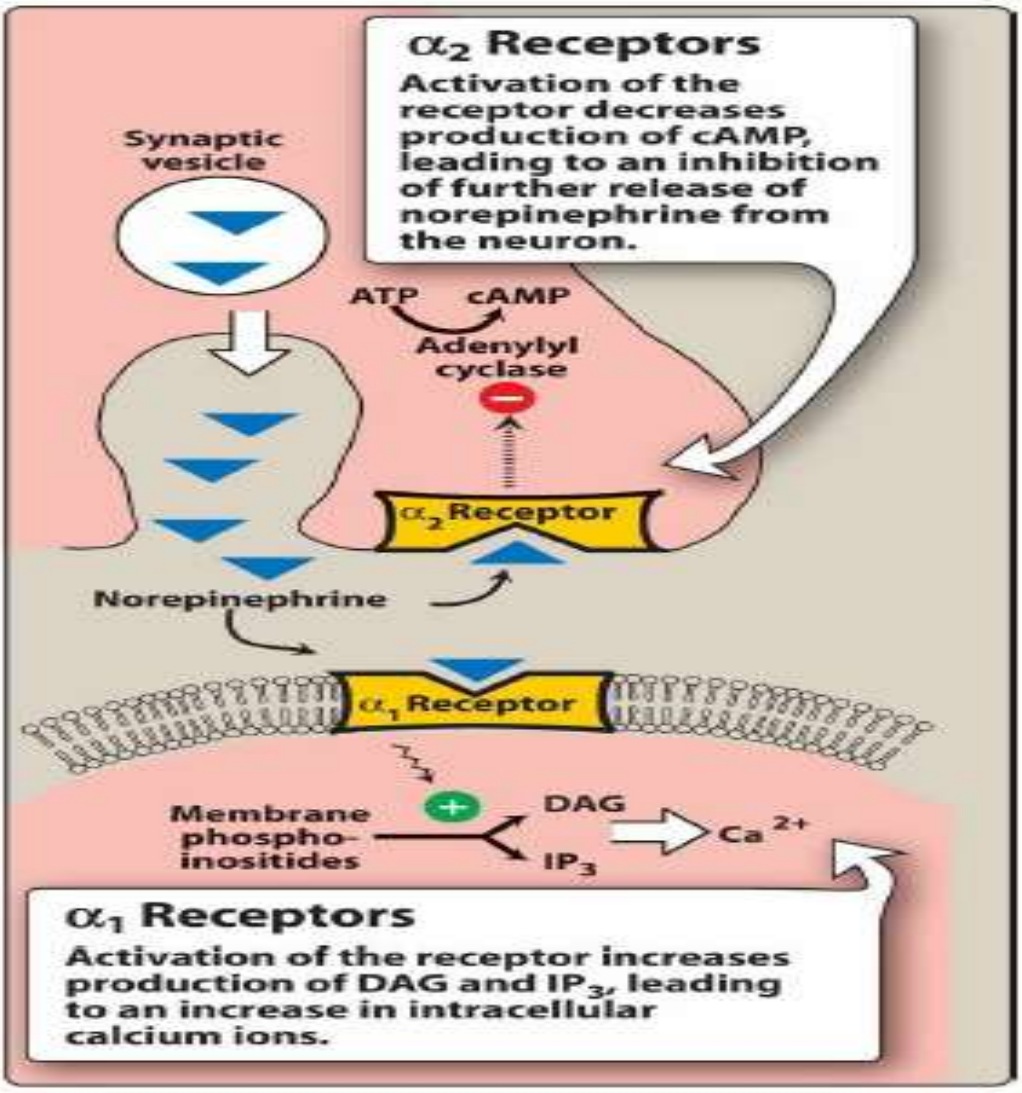
Bethanechol • Used in treatment of urinary retention • Binds preferentially at muscarinic receptors	***Physostigmine*** • Increases intestinal and bladder motility • Reverses CNS and cardiac effects of tricyclic antidepressants • Reverses CNS effects of *atropine* • Uncharged, tertiary amine that can penetrate the CNS	***Rivastigmine, galantamine, donepezil*** • Used as first-line treatments for Alzheimer disease, though confers modest benefit • Have not been shown to reduce healthcare costs or delay institutionalization • Can be used with *memantine* (*N*-methyl-D-aspartate antagonist) in moderate to severe disease
Carbachol • Binds to both muscarinic and nicotinic receptors • Produces miosis during ocular surgery • Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to *pilocarpine*	***Neostigmine*** • Prevents postoperative abdominal distention and urinary retention • Used in treatment of myasthenia gravis • Used as an antidote for competitive neuromuscular blockers • Has intermediate duration of action (0.5 to 2 h)	***Echothiophate*** • Used in treatment of open-angle glaucoma • Has long duration of action (100 h)
Pilocarpine • Reduces intraocular pressure in open-angle and narrow-angle glaucoma • Binds preferentially at muscarinic receptors • Uncharged, tertiary amine that can penetrate the CNS	***Edrophonium*** • Used for diagnosis of myasthenia gravis • Used as an antidote for competitive neuromuscular blockers • Has short duration of action (10 to 20 min)	***Acetylcholine*** • Used to produce miosis in ophthalmic surgery

Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl *Benztropine*	● Treatment of Parkinson disease ● Management of antipsychotic-induced extrapyramidal effects
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	● Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	● To treat spastic disorders of the GI tract ● To treat organophosphate poisoning ● To suppress respiratory secretions prior to surgery ● To treat bradycardia
Scopolamine	● To prevent motion sickness
Aclidinium *Glycopyrrolate* *Ipratropium* *Tiotropium*	● Treatment of COPD
Ganglionic blockers	
Nicotine	● Smoking cessation

Sympathetic Nervous System (Adrenergic Nervous System)






α2 Receptors
Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron.
Synaptic vesicle
ATP
cAMP
Adenylyl cyclase
α2 Receptor
Norepinephrine
α1 Receptor
Membrane phospho-inositides
DAG
IP3
Ca 2+
α1 Receptors
Activation of the receptor increases production of DAG and IP3, leading to an increase in intracellular calcium ions.

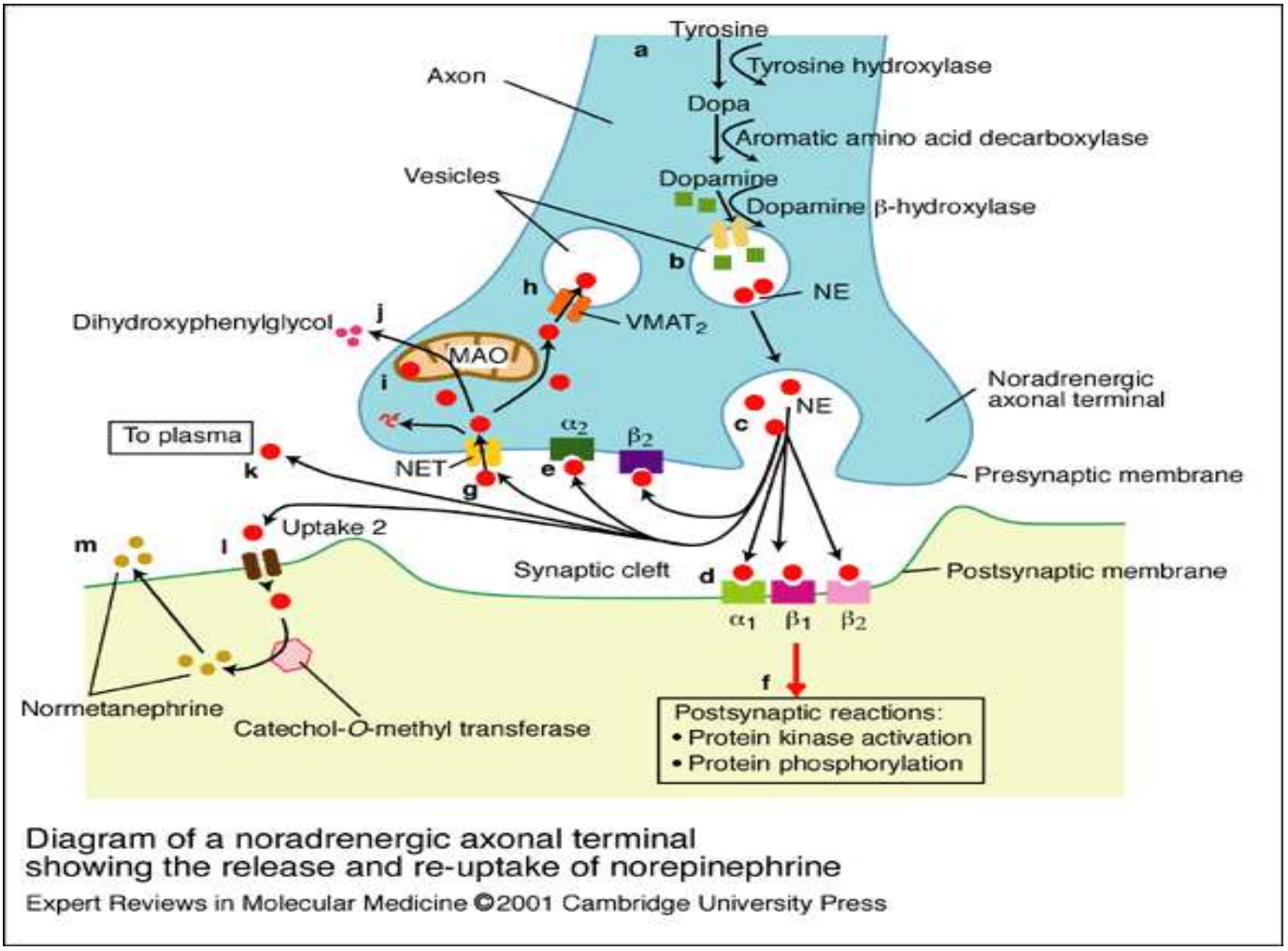
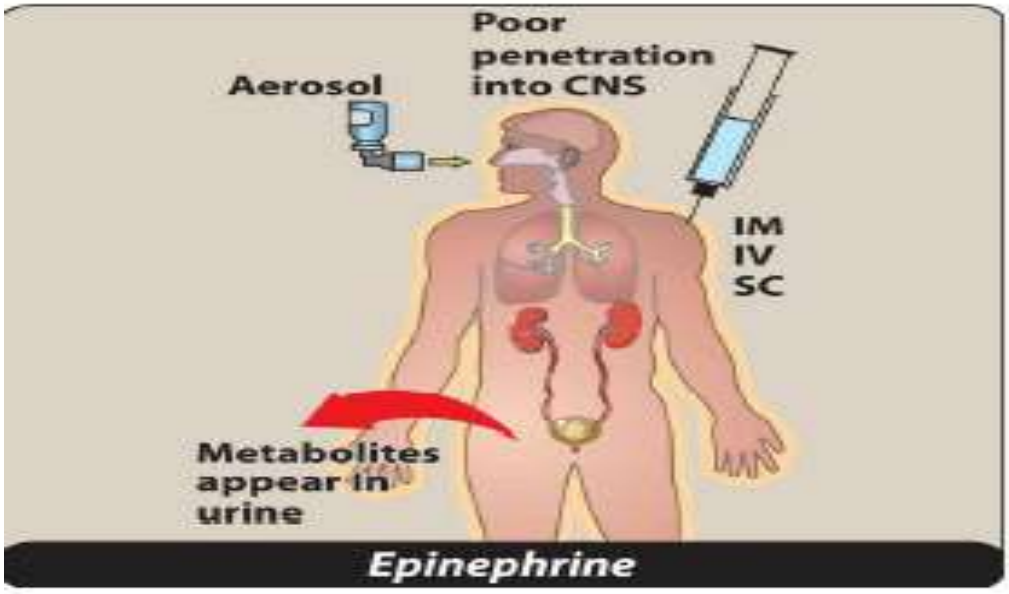


Diagram of a noradrenergic axonal terminal showing the release and re-uptake of norepinephrine

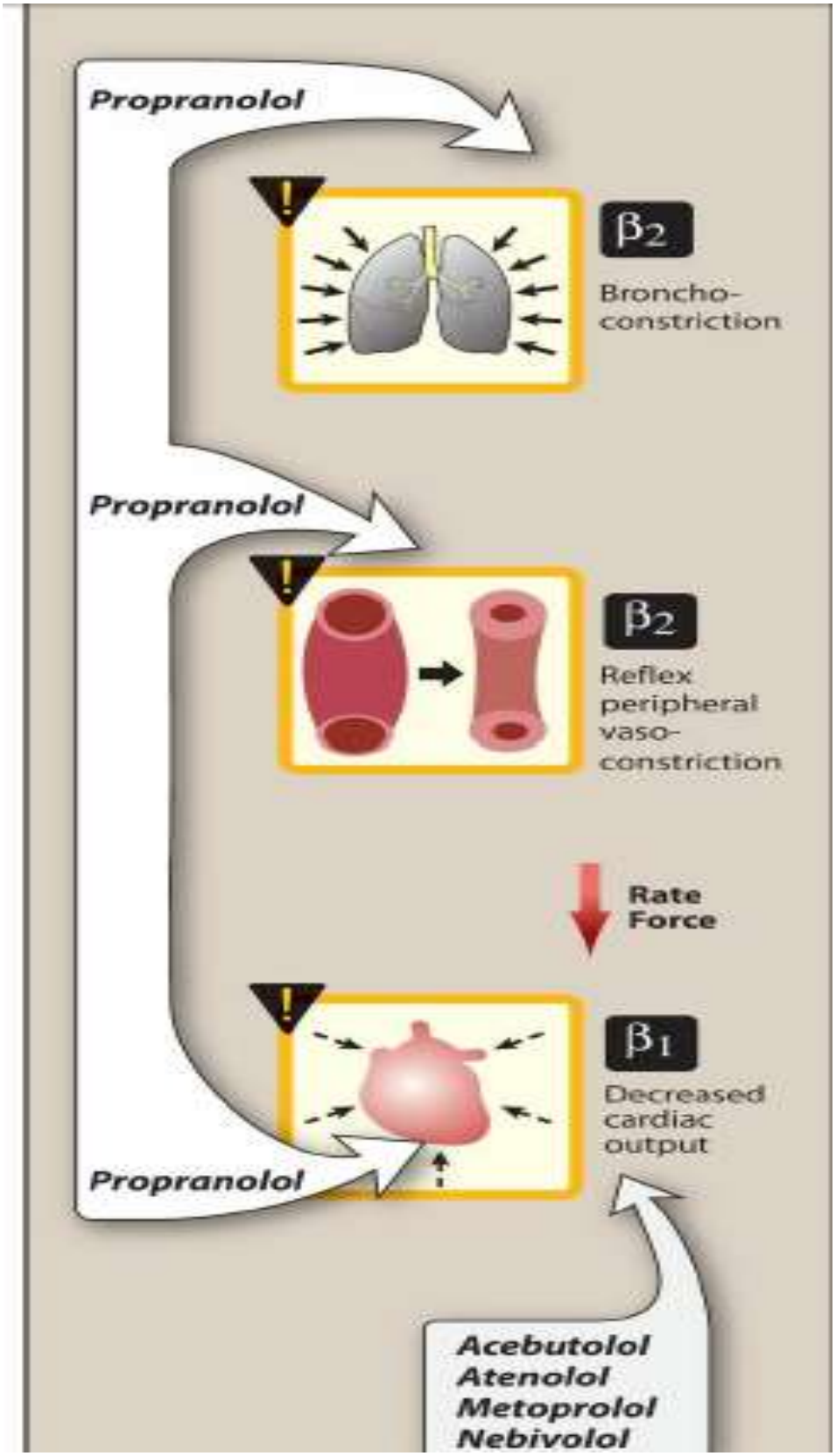
Expert Reviews in Molecular Medicine ©2001 Cambridge University Press

Epinephrine



TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogenesis	—
Adipose tissue	β_1, β_3	↑ Lipolysis	α_2-Adrenergic receptors
Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2, β_3	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

	DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
CATECHOLAMINES • Rapid onset of action • Brief duration of action • Not administered orally • Do not penetrate the blood-brain barrier	*Epinephrine*	α_1, α_2 β_1, β_2	Anaphylactic shock Cardiac arrest In local anesthetics to increase duration of action
	Norepinephrine	α_1, α_2 β_1	Treatment of shock
	Isoproterenol	β_1, β_2	As a cardiac stimulant
	Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
	Dobutamine	β_1	Treatment of acute heart failure
NONCATECHOL-AMINES Compared to catecholamines: • Longer duration of action • All can be administered orally or via inhalation	*Oxymetazoline*	α_1	As a nasal decongestant For relief of eye redness
	Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
	Clonidine	α_2	Treatment of hypertension
	Albuterol *Metaproterenol* *Terbutaline*	β_2	Treatment of bronchospasm (short-acting)
	Arformoterol *Formoterol* *Indacaterol* *Salmeterol*	β_2	Treatment of bronchospasm (long-acting)
	Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with ADHD, narcolepsy, and for appetite control
	Ephedrine *Pseudoephedrine*	α, β, CNS	Raise blood pressure As a nasal decongestant


Propranolol
β2
Broncho-constriction
Propranolol
β2
Reflex peripheral vaso-constriction
Rate
Force
β1
Decreased cardiac output
Propranolol
Acebutolol
Atenolol
Metoprolol
Nebivolol

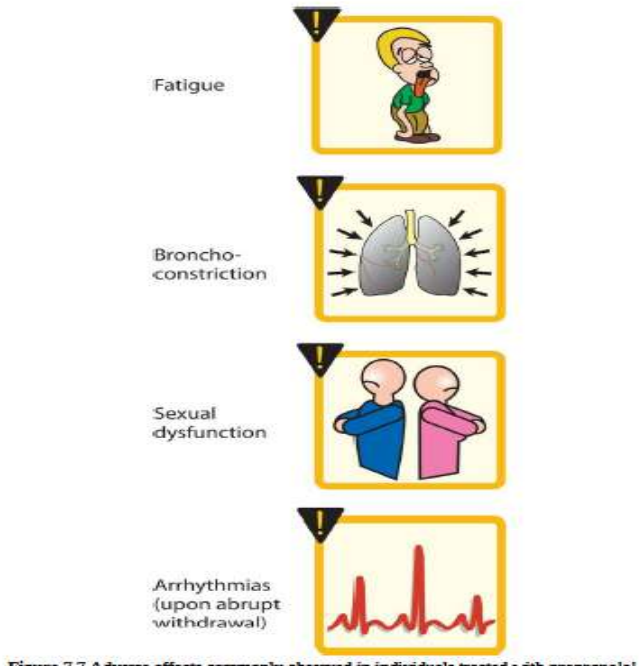


Figure 1Propranolol Adverse Effects

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction Atrial fibrillation
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension

Angina Pectoris

Definition:- Angina pectoris is the classical symptom of ischemic heart. It is usually due to imbalance between:- Myocardial oxygen *supply and demand*.

Classification:-

A) **Exertional angina:** It is characterized by:

1) Cardiac pain which develops on exertion e.g. exercise, eating, cold weather or emotional stress.

2) Significant fixed coronary stenosis (atherosclerotic) and/or excess myocardial demand are create.

ECG shows depressed ST segment.

3) If the cardiac pain happens at minor exertion or at rest, it is called ***unstable angina.***

B) variant or prinzmetal's angina:

It is characterized by:

1) Patient develops cardiac pain at rest and ECG shows elevated ST segment.

2) It is due to vasospasm of coronary artery with resulting decrease of coronary blood flow.

3) It may occur spontaneously or may be induced by exposure to cold , emotional stress or vasoconstricting agents e.g. ergot derivative drugs.

1-Organic nitrates :

***Examples*:**

Nitroglycerine,

Isosorbide mononitrate & Isosorbide dinitrate.

***Mechanism*:**

Nitrates changed in vascular smooth muscle cell into ***nitric oxide (NO)***. NO then activates ***guanylyl cyclase*** enzyme which increases the cellular level of ***cGMP & cGMP-dependent protein kinase***.

This in turn leads to reduction in both ***myosin light chain phosphorylation & cytosolic calcium*** concentration.

The net result is ***vascular relaxation.***

At low concentrations:-

Nitroglycerine preferentially *dilates the veins more than the arterioles*, with consequent reduction of preload, decrease of left and right ventricular chamber size, and end diastolic pressure.

Consequently, the cardiac work and oxygen demand of the heart decrease and anginal chest pain relieves.

Nitrates may also improve myocardial blood flow by dilating collateral coronary blood vessels so that blood redistributes from normal to ischemic regions.

Arteriolar dilatation at these concentrations may affect arterioles of the face ***(causing flushing)*** and meningeal arterioles ***(causing pulsating headache)***.

At higher concentrations:-

Nitrate induced venodilatation is associated with arteriolar dilatation & reduced peripheral resistance leading to reduced blood pressure, cardiac output and compensatory ***sympathetic reflex tachycardia.***

***Tolerance*:**

Frequently repeated or continuous exposure to high dose of organic nitrates leads to marked decrease in the magnitude of their pharmacological effect. Many theories have been suggested to explain the tolerance to nitrates but no settled one has been yet confirmed.

To *restore responsiveness and avoid tolerance*, interrupted therapy for 8-12 hours each day of organic nitrates allows the return of efficacy of the drug.

Side effects:

1) Pulsating headache and dizziness ***(It is beneficial side effect HOW?)***

2) Postural hypotension (nitrate syncope). It is treated by change the position of the patient (let head down and leg elevated). Don't use vasoconstricting agent (like epinephrine).

3) Marked fall in blood pressure and even death if given concomitantly with sildenafil (Viagra). Both drugs are vasodilators.

Therapeutic uses:

1- Angina pectoris:

- ***In acute attack,***
- sublingual nitroglycerine is the drug of choice.
- It acts in about 1-2 minutes. Sublingual route allows absorption of drug rapidly from buccal mucosa, with avoidance of extensive first pass effect if swallowed orally.
- The dose (0.3, 0.4, 0.6 mg) may be repeated at 3-5 minutes intervals.
- Nitroglycerine buccal spray is also available as metered delivery system (0.4 mg).
- Pain not responding to three tablets or lasting more than 20 minutes, may ***represent infarction*** that needs medical attention.

In between attacks:

To prevent a new attack, any of the following nitrates preparations are indicated:

1) Short-acting nitrates as nitroglycerine sublingual (0.3-0.6 mg) or isosorbide dinitrate sublingual (2.5-10 mg) to be taken 5 minutes before any activity that may precipitate angina.

2) Long acting nitrates to be taken as a maintenance therapy such as nitroglycerine in the form of:

oral sustained release capsules, ointment, or transdermal patches, oral isosorbide dinitrate.

NB

Oral isosorbide mononitrate (better bioavailability, less first pass metabolism and longer half-life in comparison with isosorbide dinitrate).

2- Heart failure (as a vasodilator) especially if heart failure is associated with cardiac ischemia.

3- Hypertensive emergency, it is given by i.v. route.

2- Beta adrenergic blockers

Mechanism:-

They prevent angina through reduction of heart rate, myocardial contractility and to lesser extent blood pressure leading to reduction of myocardial oxygen requirement during exertion and stress. They prolong the life in patients with coronary disease.

Beta blockers with ISA like pindolol are less desirable because they may exacerbate angina.

In prinzmetal's (vasospastic) angina, use of beta blockers opens the way for catecholamines to act on unopposed coronary alpha receptors which may increases coronary spasm. Therefore, β-blockers are not preferred in prinzmetal's vasospastic angina.

3- Calcium channel blocker

Mechanism:

Calcium channel blockers inhibit the L-type calcium channels in the vascular smooth muscle of coronary arteries → coronary vasodilatation, improve coronary blood flow and increased oxygen supply to the heart.

Therefore, in patients with coronary vasospasm (e.g. prinzmetal's or vasospastic angina), they are the drugs of choice.

Pharmacological actions:

Verapamil and diltiazem:

In addition to their vasodilator effect, *they decrease the heart rate through a depressant effect on SA node and slowing the A-V nodal conduction.*

Also, they have a *negative inotropic effect*.

Therefore, it is not advisable to combine any of them with β-blockers for fear of heart block or heart failure.

Nifedipine on the other hand has no A-V blocking activity and is more potent as arterial vasodilator.

So, its reducing effect on blood pressure may be associated with reflex sympathetic stimulation and tachycardia. ***Accordingly, it is advisable to combine it with a β-blocker in patients with angina.***

- ***Therapeutic uses:***

1) Angina pectoris.

2) Hypertension.

3) Supraventricular tachycardia (verapamil or diltiazem, but not nifedipine).

4) Migraine headache (verapamil as a prophylaxis).