Pharmacokinetics (I)

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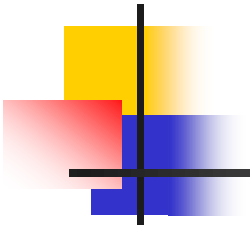
- The goal of drug therapy is to **prevent, cure, or control diseases**
- To achieve this goal, adequate drug doses must be delivered to the target tissues so that therapeutic yet nontoxic levels are obtained

Pharmacokinetics (PK)

- Greek: **Phrmaco**= **drug**
  Kinein = **to move**

- **Definition PK:** examines movement of a drug over time through body

- **Pathways of drug movement: (ADME)**
- **A**bsorption
- **D**istribution
- **M**etabolism,
- **E**limination



Clinicians must recognize that:

- Speed of onset of drug action
- Intensity of drug's effect
- Duration of drug action are controlled by four fundamental pathways **(ADME)**

- Knowledge of these four processes **(ADME)** influences clinician's decision of:
  - Route of administration for drug
  - Amount and frequency of each dose, and the dosing intervals

Pathways of PK

- **Absorption:**

- Is transfer of a drug from its site of administration to bloodstream

- **Distribution:**

- Drug leaves bloodstream and distributes into interstitial & intracellular fluids

- **Metabolism:**

  - By liver, kidney, or other tissue

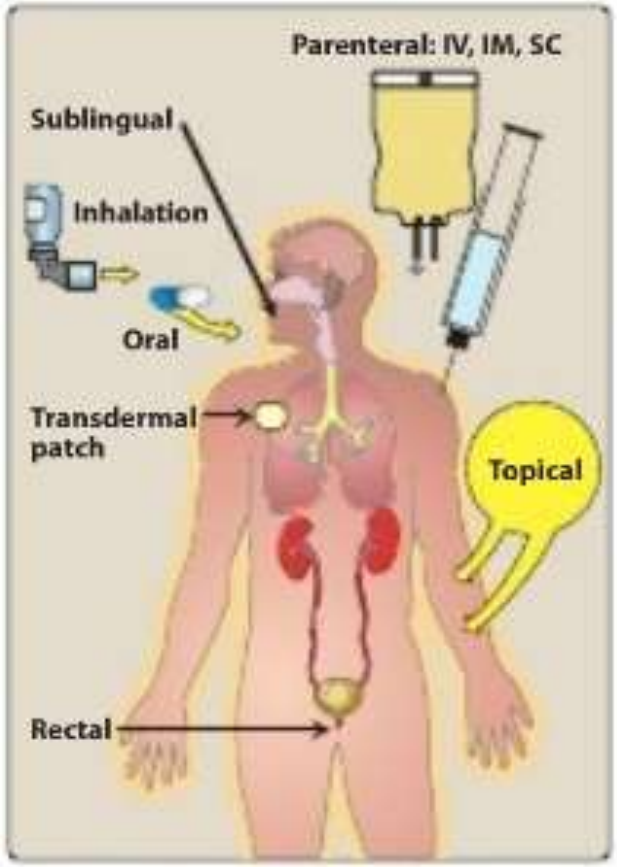
- **Elimination:**

- Removal of drug & its metabolites from body in urine, bile, or feces

Absorption

- Rate & efficiency of absorption depend on route of administration
- **Routes of drug administration:**
  - **Enteral:** (by mouth) oral, subligual
  - **Parenteral:** intravenous (IV), intramuscular (IM), subcutaneous (Sc)
  - **Others:** inhalation, intranasal, intrathecal, topical, rectal

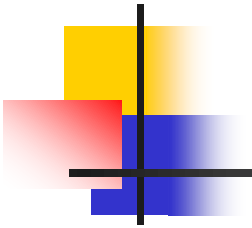
Routes of drug administration:



- **IV absorption** is **complete**

  (total dose of drug reaches systemic circulation)

- Drug delivery by other routes may result in **partial absorption** and, thus, lower bioavailability



- For example, **oral route** requires that a drug dissolve in GI fluid and then pen-etrate epithelial cells of intestinal mucosa, disease states or presence of food may affect this process

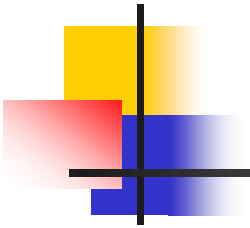
Absorption

A. **Transport of drug from GI tract:**

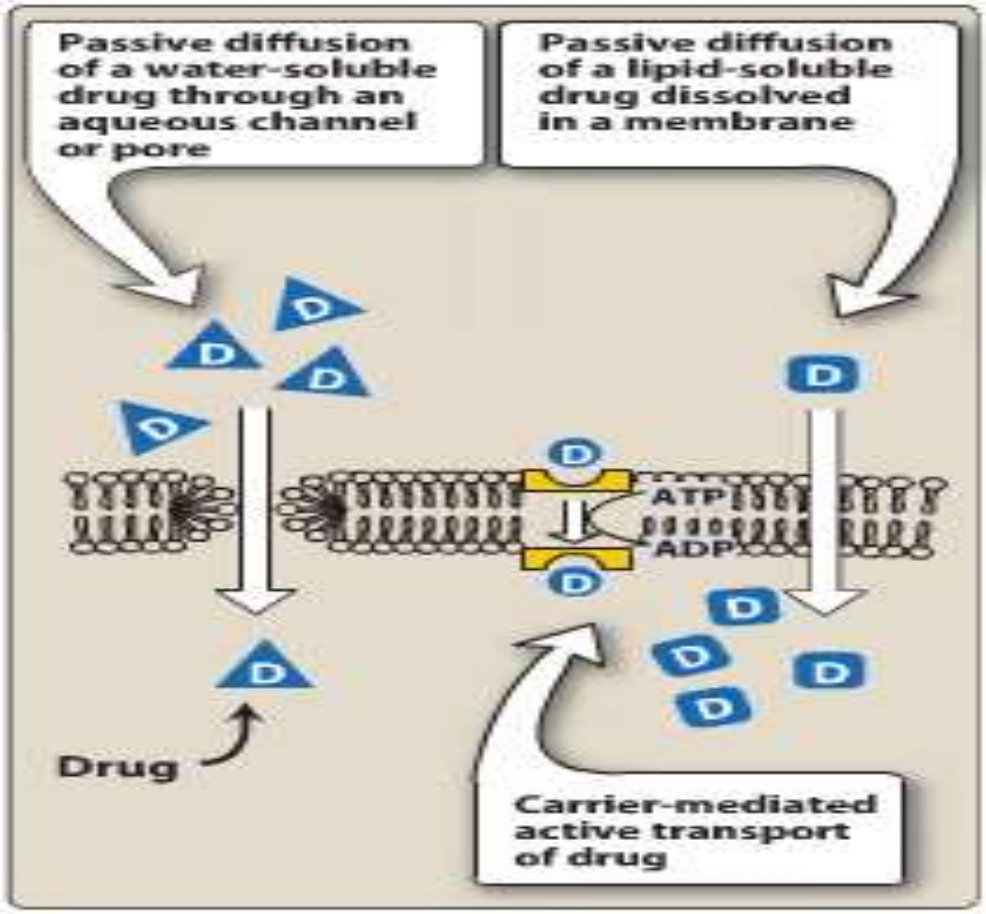
- Depending on chemical properties
- Drugs may be absorbed from GI tract by either passive diffusion or active transport

1. Passive diffusion:

- Drug move from **high concentration to one of lower concentration**
- The vast majority of drugs gain access to body by this mechanism
- **Lipid-soluble drugs:** readily move across biological membranes due to their solubility in membrane bilayers



- **Water-soluble drugs:** penetrate cell membrane through aqueous channels or pores
- Other drugs enter cell through specialised transmembrane carrier proteins (large molecules)


Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
D
ATP
ADP
Drug
Carrier-mediated active transport of drug

2. Active transport:

- Involves **specific carrier proteins**
- Is **energy-dependent** & is driven by hydrolysis of ATP
- Moving drugs against concentration gradient

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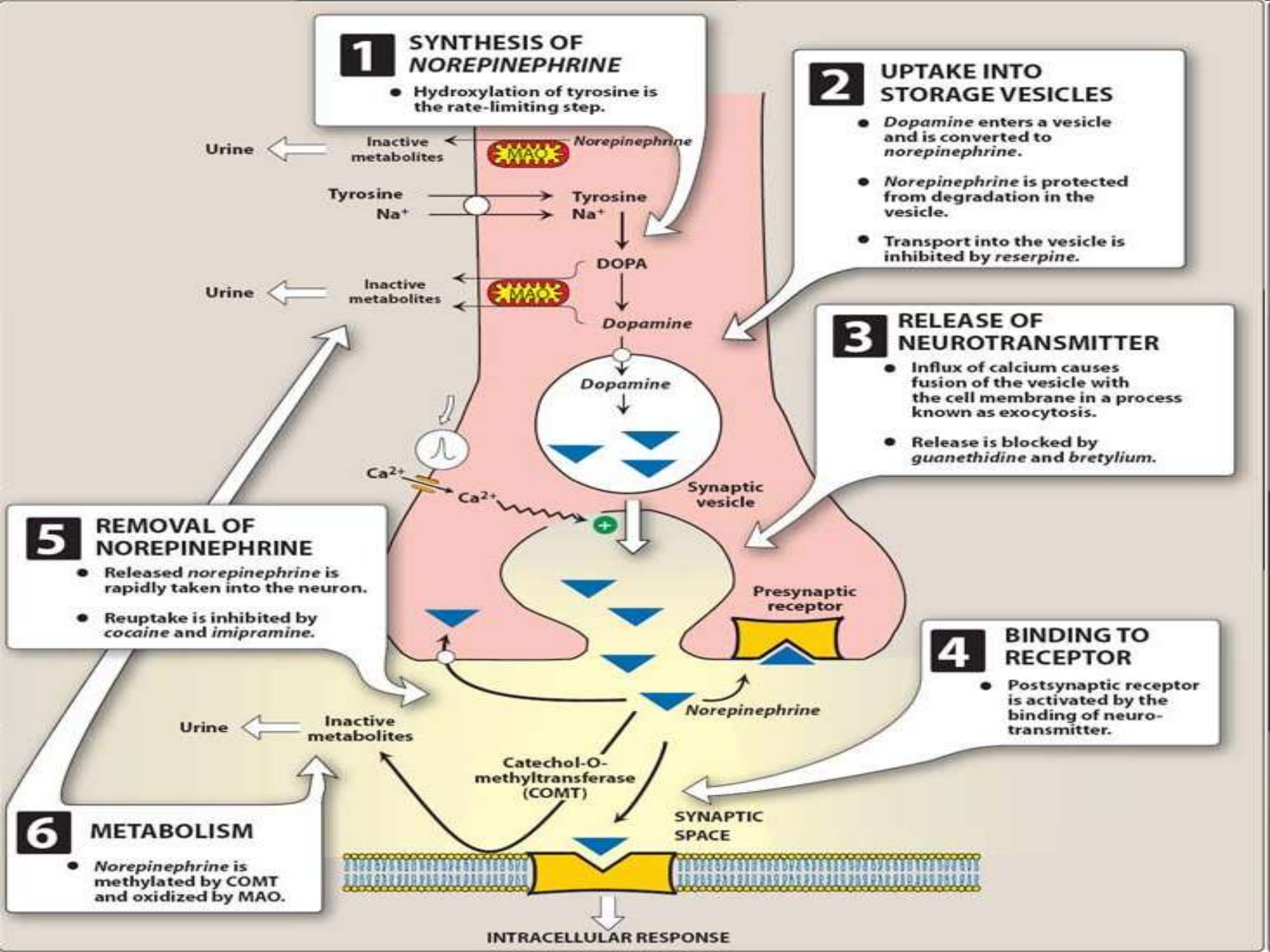
3. Endocytosis & exocytosis

- **Endocytosis** involves engulfment of a drug molecule by cell membrane
- For example, vitamin B12 is transported across gut wall by endocytosis

- **Exocytosis** is reverse of endocytosis and is used by cells to secrete many substances
- Certain neurotransmitters (Norepinephrine) are stored in membrane-vesicles in nerve terminal & are released by exocytosis


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
Release is blocked by guanethidine and bretylium.
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by cocaine and imipramine.
6 METABOLISM
Norepinephrine is methylated by COMT and oxidized by MAO.
Urine
Inactive metabolites
MAO
Norepinephrine
Tyrosine
Na+
DOPA
Dopamine
Ca2+
Synaptic vesicle
Presynaptic receptor
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE
INTRACELLULAR RESPONSE

B. Effect of pH on drug absorption:

- Most drugs are either weak acids or weak bases
- **Uncharged drugs** passes through membranes readily

Physical factors influencing absorption:

- Blood flow to absorption site
- Total surface area available for abs
- Contact time at abs surface

(in severe diarrhea, drug is not well absorbed)

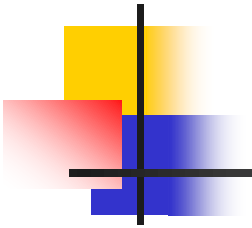
- Presence of food in stomach: dilutes drug & slow gastric emptying & delay abs in small intestine

Bioavailability

- Is fraction of administered drug that reaches systemic circulation in a chemically unchanged form
- Bioavailability is determined by comparing plasma levels of drug after particular route of administration with plasma drug levels after IV injection

- **Bioavailability** for drugs delivered **IV is 100%**
- **When drug is given orally, only part of the administered dose appears in plasma, bioavailability is less 100%**

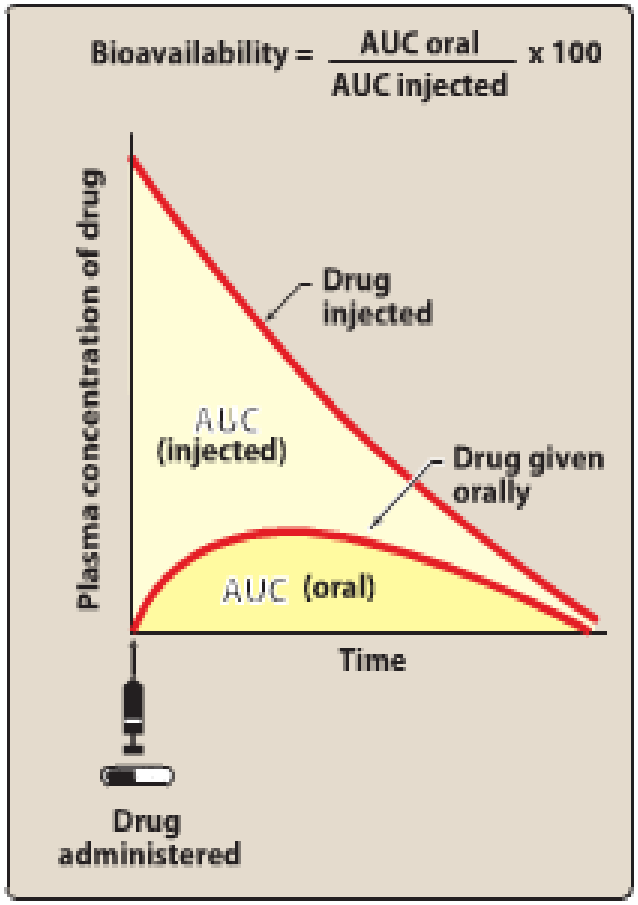
- Bioavailability= $\frac{\text{AUC orally}}{\text{AUC IV}}$ *100



- If 100 mg of drug are administered orally, 70 mg are absorbed unchanged, bioavailability 70%

- **Area under the curve (AUC):** by plotting plasma concentration of drug versus time
- Bioavailability of orally administered drug is ratio of AUC for oral admin compared with AUC for IV injection

Determination of bioavailability

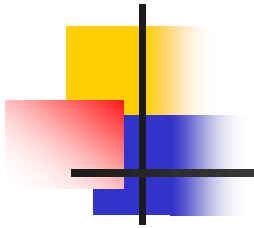


Factors influencing bioavailability

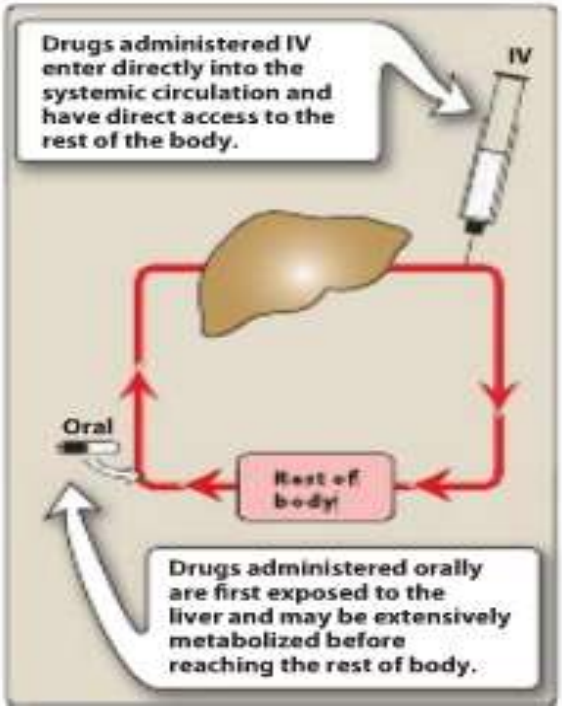
A- First-pass hepatic metabolism:

- When drug is absorbed across GI tract, it enters portal circulation before entering systemic circulation

- If drug is rapidly metabolised by liver, amount of unchanged drug that enters systemic circulation is decreased



- **Propranolol, lidocaine** undergo significant metabolism during passage through liver



First-pass metabolism occurs with orally administered drugs

B- Solubility of drug:

- **Hydrophilic drugs** are poorly absorbed because of their inability to cross lipid-rich cell membrane

C- Chemical instability:

- **Benzylpenicillin (Penicillin G)** unstable in pH of stomach, is given IV
- **Phenoxymethylpenicillin (Penicillin V)** is used **orally,** it is **acid-stable** & is not destroyed by gastric acid
- **Insulin** destroyed by enzymes in GI tract, is given IV

Bioequivalence:

- Two related drugs **are bioequivalent** if they show comparable bioavailability & similar times to achieve peak blood concentrations