Drug Excretion

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- **Excretion** *is defined as the process whereby drugs and/or their metabolites are irreversibly transferred from internal to external environment.*

- Excretion of unchanged or intact drug is important in the termination of its pharmacological action.

- The principal organs of excretion are kidneys.

- Excretion of drug by kidneys is called as **renal excretion**.

- *Excretion by organs other than kidneys such as lungs, biliary system, intestine, salivary glands and sweat glands is known as* **nonrenal excretion**.

RENAL EXCRETION OF DRUGS

- Almost all drugs and their metabolites are excreted by the kidneys to some extent or the other. Some drugs such as gentamicin are exclusively eliminated by renal route only.

- Agents that are excreted in urine are –
  - Water-soluble.
  - Non-volatile.
  - Small in molecular size (less than 500 Daltons).
  - The ones that are metabolised slowly.

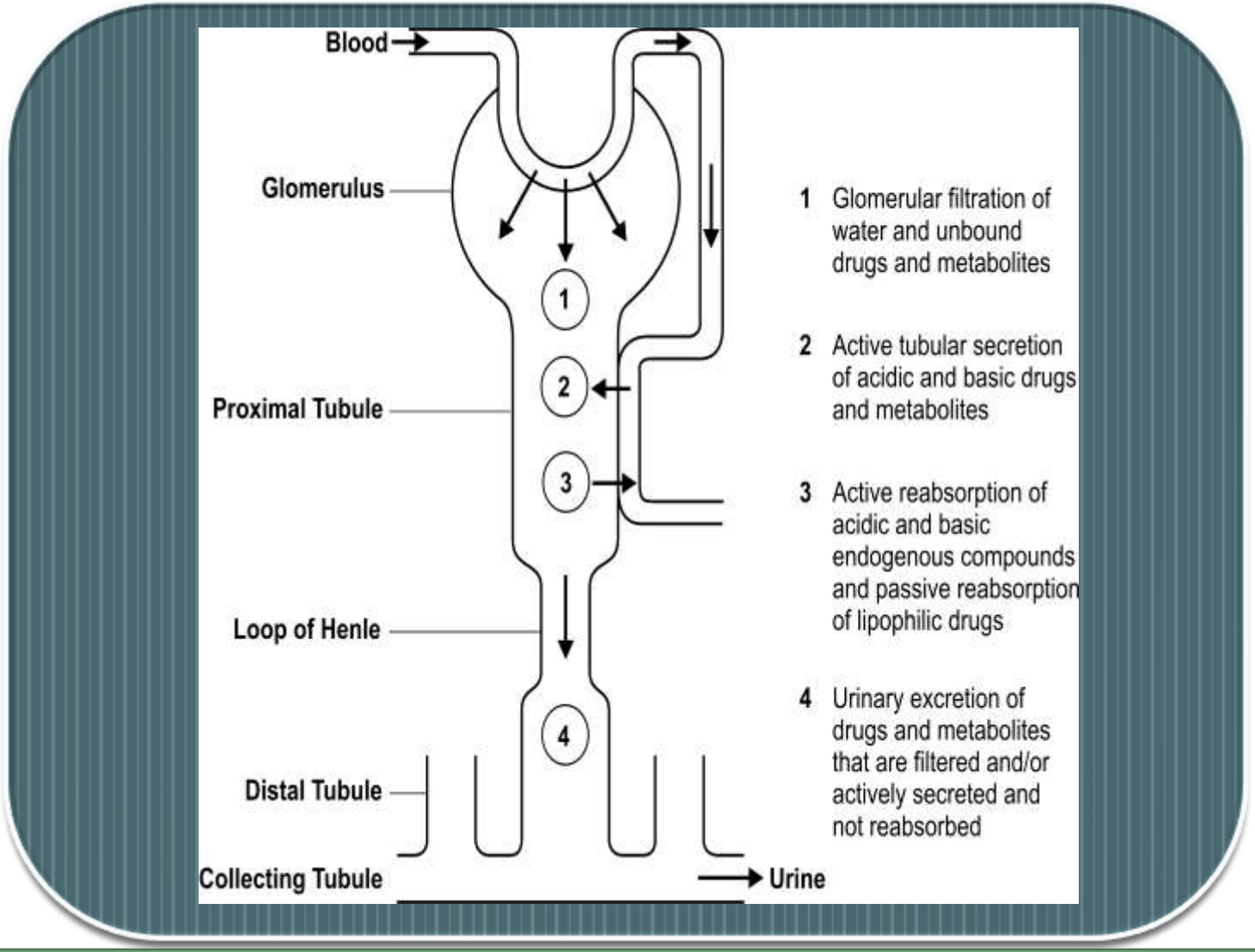
- The basic functional unit of kidney involved in excretion is the **Nephron**.

- Each kidney comprises of one million nephrons.

- Each nephron is made up of the glomerulus, the proximal tubule, the loop of Henle, the distal tubule and the collecting tubule.

- The **principal processes** that determine the urinary excretion of a drug are –
    - Glomerular filtration.
    - Active tubular secretion.
    - Active or passive tubular reabsorption.

PROCESSES INVOLVED IN THE URINARY EXCRETION OF DRUGS



- Glomerular filtration and active tubular secretion tend to increase the concentration of drugs in lumen and hence facilitate excretion whereas tubular reabsorption decreases it and prevents the movement of drug out of the body.

- Thus, the rate of excretion can be given by equation:

Rate of Excretion = Rate of Filtration + Rate of Secretion – Rate of Reabsoprtion

GLOMERULAR FILTRATION

- Glomerular filtration is a non-selective, unidirectional process whereby most compounds, ionised or unionised, are filtered except those that are bound to plasma proteins or blood cells and thus behave as macromolecules.

- The glomerulus also acts as a negatively charged selective barrier promoting retention of anionic compounds.

- The driving force for filtration through the glomerulus is the hydrostatic pressure of the blood flowing in the capillaries.

- Out of the 25% of cardiac output or 1.2 litres of blood/min that goes to the kidneys via renal artery, only 10% or 120 to 130 ml/min is filtered through the glomeruli, the rate being called as the **Glomerular Filtration Rate** (GFR).

- 180 litres of protein and cell free ultrafiltrate pass through the glomeruli each day, only about 1.5 litres is excreted as urine, the remainder being reabsorbed from the tubules.

- The GFR can be determined by an agent that is excreted exclusively by filtration and is neither secreted nor reabsorbed in the tubules.

- The excretion rate value of such an agent is 120 to 130 ml/min.

- Creatinine, inulin, mannitol and sodium thiosulphate are used to estimate GFR of which the former two are widely used to estimate renal function.

ACTIVE TUBULAR SECRETION

- It is a carrier-mediated process which requires energy for transportation of compounds against
- The concentration gradient.
- The system is capacity-limited and saturable.
- Two active tubular secretion mechanisms have been identified:

1. **System for secretion of organic acids/anions** like penicillins, salicylates, glucuronides, sulphates, etc. It is the same system by which endogenous acids such as uric acid are secreted.

2. **System for secretion of organic bases/cations** like morphine, mecamylamine, hexamethonium and endogenous amines such as catecholamines, choline, histamine,

- Both the systems are relatively non-selective and independent of each other but both can be bidirectional i.e. agents may both be secreted as well as reabsorbed actively, for example, uric acid.

- Active secretion is unaffected by changes in pH and protein binding since the bound drug rapidly dissociates the moment the unbound drug gets excreted.

- But in contrast to glomerular filtration, it is dependent upon renal blood flow.

- Drugs undergoing active secretion have excretion rate values greater than the normal GFR value of 130 ml/min;
    - For example, penicillin has renal clearance value of 500 ml/min. Such a high value is indicative of both glomerular filtration as well as tubular secretion.

- Agents that are used to measure active tubular secretion are the ones that are filtered as well as secreted to such an extent that they are removed from the blood in a single pass through the kidneys i.e. their clearance reflects the renal plasma flow rate which is 600 to 700 ml/min.

- **Para Amino Hippuric acid (PAH)**, a highly polar agent and **Iodopyracet** are used to determine active secretion.

- Active secretion occurs predominantly in the proximal tubule region of the nephron.

- Two structurally similar drugs having similar ionic charge and employing the same carrier-mediated process for excretion enter into *competition*.

- A drug with greater rate of clearance will retard the excretion of the other drug with which it competes.
- The half-life of both the drugs is increased since the total sites for active secretion are limited.
- This may result in accumulation of drugs and thus, precipitation of toxicity.
- Example :- Anionic agent **Probenecid.**
  - *Probenecid inhibits the active tubular secretion of organic acids* such as penicillins, PAS, PAH, 17-keto steroids, etc. thus increasing their concentration in plasma by at least two fold.

TUBULAR REABSORPTION

- Tubular reabsorption occurs after the glomerular filtration of drug
- It takes place all along the renal tubule.
- Reabsoprtion of a drug is indicated when the excretion rate values are less than the GFR of 130 ml/min.
- An agent such as glucose that is completely reabsorbed after filtration has a clearance value of zero.
- *Contrary to tubular secretion, reabsorption results in an increase in the half-life of a drug.*
- Tubular reabsorption can either be an:
    - Active process, or
    - Passive process.

ACTIVE TUBULAR REABSORPTION

- **Active tubular reabsorption** is commonly seen with high threshold endogenous substances or nutrients that the body needs to conserve such as electrolytes, glucose, vitamins, amino acids, etc.

- Uric acid is also actively reabsorbed (inhibited by the uricosuric agents). Very few drugs are known to undergo reabsorption actively e.g. oxopurinol.

PASSIVE TUBULAR REABSORPTION

- **Passive tubular reabsorption** is common for a large number of exogenous substances including drugs.
- The driving force for such a process i.e. the concentration gradient is established by the back diffusion or reabsorption of water along with sodium and other inorganic ions.
- If a drug is neither secreted nor reabsorbed, its concentration in the urine will be 100 times that of free drug in plasma due to water reabsorption since less than 1% of glomerular filtrate is excreted as urine.
- The primary determinant in the passive reabsorption of drugs is their lipophilicity.

- Lipophilic substances are extensively reabsorbed while polar molecules are not. Since a majority of drugs are weak electrolytes (weak acids or weak bases), diffusion of such agents through the lipoidal tubular membrane depend upon the degree of ionisation which in turn depends on three factors:

  - ✓ pH of the urine.
  - ✓ pKa of the drug.
  - ✓ Urine flow rate.

URINE pH

- It is an important factor in the sense that it is not constant like the plasma pH but varies between 4.5 to 7.5, the two extremes.Thus, a large pH gradient may exist between urine and plasma.

- The pH of the urine is dependent upon diet, drug intake and pathophysiology of the patient. Food rich in carbohydrates result in higher urinary pH whereas proteins lower it.

- Drugs such as acetazolamide and antacids such as sodium bicarbonate produce alkaline urine while ascorbic acid makes it acidic.

- More significant alteration in urine pH is brought about by i.v. infusion of solutions of sodium bicarbonate and ammonium chloride which are used in the treatment of acid-base imbalance.

- Respiratory and metabolic acidosis and alkalosis result in acidification and alkalinisation of the urine respectively.
- The significance of pH dependent excretion for any particular compound is greatly dependent upon its pKa and lipid solubility.
- A characteristic of drugs, pKa values govern the degree of ionisation at a particular pH.
- Reabsorption is also affected by the lipid solubility of drug; an ionised but lipophilic drug will be reabsorbed while an unionised but polar one will be excreted.

The combined effect of urine pH and drug pKa and lipid solubility on reabsorption of drugs is *summarized* as follows:

- An acidic drug such as **Penicillin** or a basic drug such as **Gentamicin** which is polar in its unionised form, is not reabsorbed passively, irrespective of the extent of ionisation in urine. Excretion of such drugs is independent of pH of urine and its flow rate. Their rate of excretion is the sum of rate of filtration and rate of active secretion.

- Very weakly acidic, nonpolar drugs (pKa > 8.0) such as **Phenytoin** or very weakly basic, nonpolar drugs (pKa < 6.0) such as **Propoxyphene** are mostly unionised throughout the entire range of urine pH and are therefore extensively reabsorbed passively at all values of urine pH. The rate of excretion of such drugs is always low and insensitive to urine pH.

- A strongly acidic drug (pKa $\leq$ 2.0) such as **Cromoglycic acid** or a strongly basic drug (pKa $\geq$ 12.0) such **as Guanethidine,** is completely ionised at all values of urine pH and are, therefore, not reabsorbed. Their rate of excretion is always high and insensitive to pH of urine.

- Only for an acidic drug in the pKa range 3.0 to 8.0 (e.g. several NSAIDs) and for a basic drug in the pKa range 6.0 to 12.0 (e.g. morphine analogs, tricyclic antidepressants, etc.) the extent of reabsorption is greatly dependent upon urine pH and varies from negligible to almost complete; for example, the amount of dexamphetamine excreted in the urine varies from 3 to 55% of the administered dose as the urine pH varies from 8.0 to 5.0.

- The toxicity due to overdosage of drugs whose excretion is sensitive to pH change can be treated by acidification or alkalinisation of the urine with ammonium chloride or sodium bicarbonate respectively.

- Thus, crystalluria caused by precipitation of sulphonamides in the renal tubules and subsequent kidney damage can be overcome by alkalinising the urine.

- Excretion of basic drugs can be promoted by acidification of urine.

- The therapeutic activity of the urinary antiseptic hexamine also depends on the urine pH. It is not converted to active form i.e. formaldehyde unless the urine is acidic.

URINE FLOW RATE

- In addition to urine pH and drug pKa, the rate of urine flow also influences the extent of reabsorption.

- Polar drugs whose excretion is independent of urine pH and are not reabsorbed, are unaffected by urine flow rate.

- An increase in urine flow in case of such drugs will only produce more dilute urine. Only those drugs whose reabsorption is pH-sensitive, for example, weak acids and weak bases, show dependence on urine flow rate. For such agents, reabsorption is inversely proportional to the urinary flow.

- Urine flow rate can be increased by forced diuresis. **Forced diuresis** *is the increase in urine flow induced by large fluid intake or administration of mannitol or other diuretics.*

- The principle can be used in an intoxicated person to remove excessive drug by promoting its excretion and decreasing the time for reabsorption.

- Both urine pH control and forced diuresis can be used to treat toxicity with drug overdose when –
    - Urinary excretion is the major route for elimination of drug.
    - The drug is extensively reabsorbed passively from the renal tubules.
    - The reabsorption is sensitive to urine pH (and urine flow rate).

FACTORS AFFECTING RENAL EXCRETION OR RENAL CLEARANCE

1. Physicochemical properties of the drug
2. Plasma concentration of the drug
3. Distribution and binding characteristics of the drug
4. Urine pH
5. Blood flow to the kidneys
6. Biological factors
7. Drug interactions
8. Disease states