Pharmacology of the Urinary System

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Main functions of The kidney

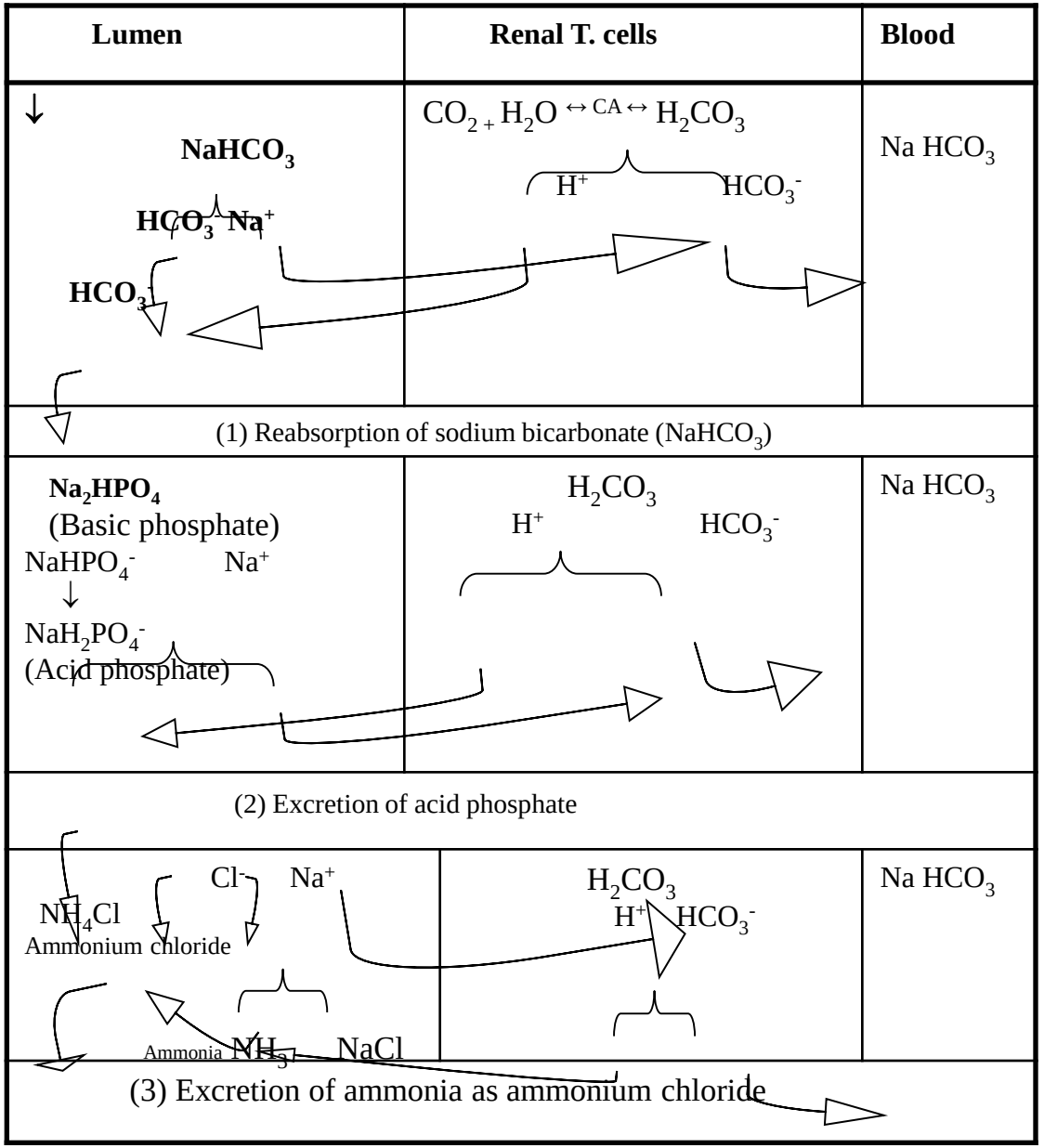
- **Excretion of waste products such as urea, uric acid and creatinine.**
- **Regulation of the salt, electrolyte contents and volume of extracellular fluids.**
- **Maintance of acid-base balance in the body fluids.**
- **Regulation of body temperature.**

The urine is formed by filtration of blood plasma through the glomeruli.

The filtrate is called **glomerular filtrate (GF)** or diluted urine.

Water and salts are reabsorbed to the blood via H+ ion and Na+ ion exchange.

The source of H+ ions is carbonic acid which is formed from $CO_2 + H_2O$ by the aid of carbonic anhydrase (CA) enzyme in tubular cells.


Lumen
Renal T. cells
Blood
NaHCO3
HCO3- Na+
HCO3-
CO2 + H2O ↔ CA ↔ H2CO3
H+
HCO3-
Na HCO3
(1) Reabsorption of sodium bicarbonate (NaHCO3)
Na2HPO4
(Basic phosphate)
NaHPO4- Na+
NaH2PO4-
(Acid phosphate)
H2CO3
H+
HCO3-
Na HCO3
(2) Excretion of acid phosphate
Cl- Na+
NH4Cl
Ammonium chloride
H2CO3
H+ HCO3-
Na HCO3
Ammonia NH3
NaCl
(3) Excretion of ammonia as ammonium chloride

The results of H+ and Na- ions exchanges are:

Reabsorption of sodium bicarbonate (NaHCO3) to the blood.

Excretion of acid phosphate (NaH2PO4) in the urine.

Excretion of ammonia as ammonium chloride in the urine.

Diuretics

These are drugs which increase the volume of urine voided in a certain period (usually 24 hours).

Therapeutic uses of diuretics

1. For acute pulmonary oedema and ascitis
2. For oedema due to heart failure and liver diseases.
3. For moderate hypertension
4. hypercalcaemia and hyperkalaemia.
5. Poisoning to aid excretion of the poison in the urine.
6. Fever to lower the abnormal rise of body temperature.

Classification of Diuretics

1-Enzyme inhibitor diuretics.

A. Carbonic anhydrase inhibitors

B. Inhibitors of enzymes containing SH group

2- Osmotic diuretics

3- Acid diuretics

4-Potassium loosing diuretics

A- Thiazides

B- Loop diuretics

5- Potassium sparing (retaining) diuretics

A- Aldosterone antagonists

B- Non Aldosterone antagonists

6- Cardiovascular (Secondary) diuretics

1-Enzyme inhibitor diuretics.

A.Carbonic anhydrase inhibitors such as **Acetazolamide and Methazolamide.**

They inhibit CA enzyme in the proximal and distal convoluted tubules so inhibit Na +and H +exchange.

Therefore, they prevent reabsorption of ($NaHCO_3$) and alkaline diuresis result.

They are used for of glaucoma in man as they decrease formation of aqueous humor and intraocular pressure.

B- Inhibitors of enzymes containing SH group

(mercurial diuretics)

mersalyl and salyrgan.

action on the ascending loop of Henle where they inhibit the enzymes containing “SH” group that are responsible for reabsorption of Na+ and Cl- ions,

so they prevent reabsorption of Na+ and Cl- ions which are excreted with an equivalent amount of water and diuresis occur.

irritant effect on the endothelial lining of the renal glomeruli so increase their permeability and cause diuresis due to an increase of the glomerular filtrate.

2-Osmotic diuretics

They increase osmotic pressure in the **glomerular filtrate** and they are excreted with an equivalent amount of water and cause diuresis.

They are classified into:

a- Saline such as sodium and potassium citrate, acetate and lactate.

b- Non saline such as glucose and manitol.

3-Acid diuretics: calcium chloride and ammonium chloride.

These salts give chloride ions in plasma (hyperchloremia) and excreted by the kidney, when they exceed the renal threshold, with equivalent amounts of water and acid diuresis occurs.

4- Potassium loosing diuretics:

A-Thiazides such as **hydochlorothiazide, chlorothiazide** and **chlorthalidone**.

They act as moderate diuretics by inhibiting the reabsorption of Na+ and Cl- ions in proximal part of the distal convoluted tubules resulting in an increase excretion of sodium content (5-10 %) in the glomerular filtrate. They also cause a significant potassium excretion (so called Potassium loosing diuretics).

***B- Loop diuretics* (High efficacy diuretics)** such as **furosemide (lasix), bumetanide and ethacrynic acid**.

They act on the ascending limb of loop of Henle;

They inhibit the transport of Na+ and Cl- ions out of the renal tubules.

They are effective for the treatment of all types of oedema (pulmonary, cerebral, dietary, traumatic and inflammatory).

In man, ethacrynic acid is less potent than furosemide, but bumetanide is about 40 times more potent.

5- Potassium sparing (retaining) diuretics

A-Aldosterone antagonists such as:

Spironolactone and **amphenone B**.

B-Non Aldosterone antagonists such as:

amiloride and **triameterene**

Spironolactone

is aldosterone antagonist so it causes an increase in Na+ ions secretion, but causes K+ ions retention by its action on the distal tubules.

Amiloride and **triameterene**

are mild naturetic causing excretion of 5% of sodium in the glomerular filtrate.

They act on the distal tubules inhibiting Na+ ions reabsorption and K+ ions excretion hence they called potassium sparing diuretics.

On the other hand, they promote uric acid excretion.

Comparison between thiazides and loop Diuretics

Differences	Thiazides	Loop diuretic
Examples	Chlorothiazide Hydrochrothiazide Bendrofluazide	Furosemide Bumetanide Ethacrynic acid
Sit & of action	Distal convoluted tubules	Ascending Loop of Henle
Onset of action	Slow (1 -2 hours)	Rapid (min.) 1/2 h.
Potency	Less potent than loop (moderate diuretics)	More potent than thiazides (powerful diuretic) (High efficacy diuretics)
Mechanism of action	They inhibit the active reabsorption of Na+ and Cl- in distal tubules causing their excretion	They inhibit transport of Na & Cl out of the tubules to interstitial tissues.
Duration of action	Long (2-3 days)	Short (2-4 hours)
Uses	Mainly for of mild hypertension in man and oedema in dog	For oedema and electrolyte disturbance.

6- Cardiovascular (Secondary) diuretics

1. **cardiac glycosides (digitalis, strophanthus and squill)**
2. **methylxanthine (caffeine, theophylline and theobromine).**

They act extra-renal on the myocardium acting as a cardiac stimulant. They cause relaxation of smooth muscle of renal blood vessels leading to vasodilatation of renal blood vessels.

The increased cardiac output accompanied with renal vasodilatation cause an increase in the glomerular filtrate with subsequent mild diuresis.

They are used for oedema due to congestive heart failure in dogs (digoxin and aminophylline)

II- Uricosurics

These are drugs which increase excretion of uric acid in the urine by preventing uric acid reabsorption in the proximal convoluted tubules.

They are useful for treatment of gout.

Examples of uricosurics are:

1- *Sulphinpyrazone*: It is a congener of phenylbutazone which causes a powerful inhibitory effect of uric acid reabsorption in the proximal convoluted tubules with subsequent increase of uric acid secretion in the urine.

II- Uricosurics

2- *Indacrinone*: It is a derivative of Ethacrynic acid which causes diuretic effect accompanied with increase uric acid excretion and so called uricosuric diuretic.

Drugs used for treatment of gout (Acute Arthritis) include:

- **Drugs which prevent uric acid synthesis such as allopurinol which inhibit xanthine oxidase enzyme so inhibit uric acid synthesis from xanthine.**
- **Drugs which increase uric acid secretion in the urine such as sulphinpyrazone and indacrinone.**
- **Drug which prevent leukocytic migration into the joint such as colchicine.**
- **Non steroidal anti-inflammatory drugs such as diclofenac, proxicam and tenoxicam which reduce the inflammation.**

III- Urinary Alkalinizers

They are salts which make the urine alkaline such as

sodium and potassium citrate or acetate or lactate they act also as saline diuretics.

Alkalinization of urine is very useful in the following conditions:

It increases the antibacterial activity of aminoglucoside antibiotics during treatment of urinary tract infection.

It increases solubility of sulphonamides and prevents crystalurea with renal damage, because sulphonamides are more soluble in alkaline medium.

It increases excretion of acidic drugs such as acetylsalicylic acid (aspirin), salicylates and some barbiturates.

IV- Urinary Acidifiers

They are salts which render the urine acidic such as **ammonium chloride, calcium chloride, sodium acid phosphate (NaH_2PO_4) and vitamin c.**

Urinary acidification is useful in the following cases:

1-It helps the excretion of basic drugs such as amphetamine.

2-It improves the antibacterial activity of hexamine, penicillins and tetracyclines during treatment of the urinary tract infection and acidification of urine may itself inhibit the bacterial growth of some microorganisms.

3-It is commonly used for dissolving urethral obstruction in the cat.

V- Urinary Antiseptics

They are drugs which kill or inhibit the growth of microorganisms in the urinary tract and used for treatment of the urinary tract infection such as in **pyelonephritis, cystitis and urethritis.**

Urinary antiseptics are classified into:

I- Drugs which change the pH of the urine

II- Drugs which release an antiseptic substance in acidic urine

III- Specific urinary antiseptic

I- Drugs which change the pH of the urine:

A. Urinary alkalinizers such as Na, K citrate, acetate.

B. Urinary acidifiers such as calcium chloride and ammonium chloride.

II- Drugs which release an antiseptic substance in acidic urine such as:

A. *Hexamine* (Urotropine®).

In acid urine, **hexamine** is hydrolyzed into **formaldehyde** and **ammonia**. The formaldehyde act as a reducing antiseptic which kill the microorganisms. Ammonia is excreted as ammonium chloride.

B. Sodium mandillate

It is converted in the urine into mandilic acid which render the urine acid so kill microorganisms causing infection.

III- Specific urinary antiseptic

They include some **sulphonamides** such a**s sulphafurazol, sulphamethoxasole** and **sulphamethoxypyridazine** and some **antibiotics** such as **penicillins** and **gentamicin** as well as some **quinolones** such as **nalidixic acid, oxonilic acid, ciprofloxacin** and **norfloxacin.**