Diuretics

Chapter 18

Drugs that increased urine flow are called diuretics. These agents are inhibitors of renal ion transporters that decrease the reabsorption of Na^+ at different sites in the nephron.

As a result Na^+ & other ions such as Cl^- enter the urine greater than normal along with water to maintain osmotic equilibrium.

The nephron comprising Bowman's capsule, proximal, distal tubule & the collecting duct.

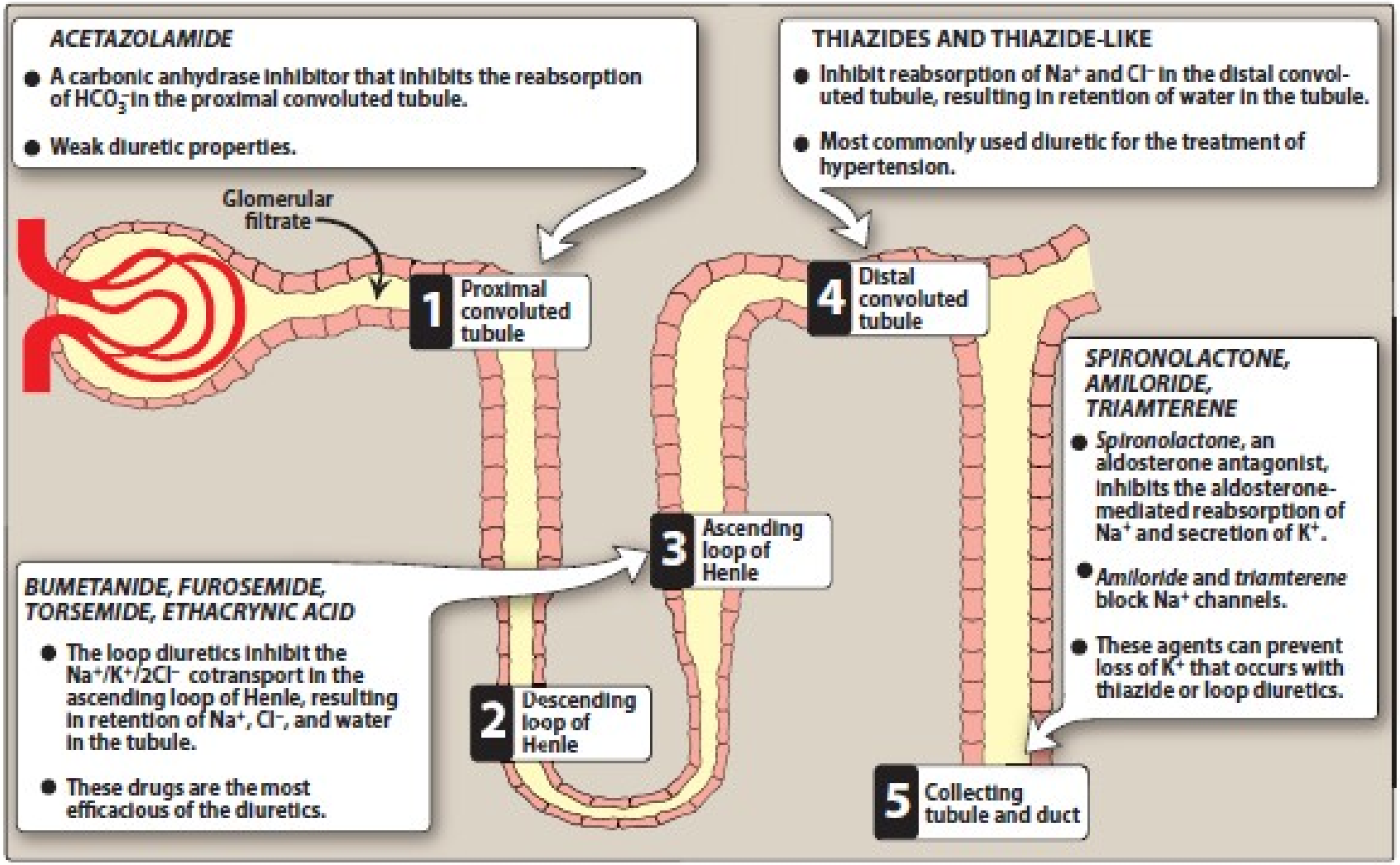

Figure 18.2

Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

Normal Regulation of Fluid & Electrolytes by the Kidneys

Approximately 16% to 20% of the blood plasma entering the kidneys is filtered from the glomerular capillaries into Bowman's capsule.

The filtrate, although normally free of proteins and blood cells, contains most of the low molecular weight plasma components in concentrations similar to that in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as Na+, K+, and Cl−.

A. Proximal convoluted tubule

In the proximal convoluted tubule located in the cortex of the kidney, almost all the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed. Approximately two-thirds of the Na^+ is also reabsorbed. Chloride enters the lumen of the tubule in exchange for an anion, such as oxalate, as well as paracellularly through the lumen.

Water follows passively from the lumen to the blood to maintain osmolar equality. Carbonic anhydrase in the luminal membrane and cytoplasm of the proximal tubular cells modulates the reabsorption of bicarbonate.

The proximal tubule is the site of organic acid & base secretary systems that secrete a variety of organic acids, such as uric acid, some antibiotics & diuretics from blood stream into proximal tubules lumens.

The bases that secreted by this system are creatinine (a normal constituent of urine & it is a product of protein metabolism]) & choline. The organic acid-base secretary system is saturable system.

2. Dessending Loop of Henle

The remaining filtrate is isotonic which next enter the descending loop of henle in which the osmolarity increase because of the counter current mechanism that responsible for reabsorption of water; result in the increasing salt concentrations. Osmotic diuretic exert it is part of action in this region.

3. Ascending Loop of Henle

This region of the nephron is a diluting region in which active reabsorption of Na^+, K^+, & Cl^- mediated by a $Na^+/K^+/2Cl^-$ cotransporter. Both Mg^{2+} & Ca^{2+} enter the interstitial fluid via the paracellular pathway. The epithelial cells of ascending loop are impermeable to water thus this portion is considered as diluting portion.

Approximately 25% to 30% of the tubular sodium chloride returns to the interstitial fluid, thereby helping to maintain high osmolarity. The drugs that act at this portion are the most efficacious diuretic which termed loop diuretics; because the ascending loop of henle is the major site for salt reabsorption.

4. Distal Convoluted Tubule

The cells of the distal convoluted tubule are also impermeable to water. About 10% of the filtered sodium chloride is reabsorbed via a Na^+/Cl^- transporter that is sensitive to thiazide diuretics.

Calcium reabsorption is mediated by passage through a channel and then transported by a Na^+/Ca^{2+}-exchanger into the interstitial fluid. The mechanism, thus, differs from that in the loop of Henle. Additionally, Ca^{2+} excretion is regulated by parathyroid hormone in this portion of the tubule.

Humans usually have four parathyroid glands, which are usually located in variable manner on the posterior surface of the thyroid gland, or, in rare cases, within the thyroid gland itself or in the chest (mediastinum) or even the thymus.

Parathyroid glands control the amount of calcium in the blood and within the bones. Parathyroid hormone increase reabsorption of Ca^{2+} from the tubules).

5. Collected tubule & Duct

At this site Na^+ is reabsorbed into the blood under the effect of Na^+ /K^+ ATPase. Aldosterone receptors in the cells of the collected tubule & duct are influence Na^+ reabsorption & K^+ secretion. Aldosterone increases the synthesis of Na^+ channels and of the Na^+ /K^+ -ATPase pump, which when combined increase Na^+ reabsorption.

Antidiuretic hormone (ADH; vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts.

Diuretic Drugs

I. Thiazide & related agents

The thiazides are the most widely used diuretics. They are sulfonamide derivatives. All thiazides affect the distal tubule, & all have equal maximum diuretic effects, differing only in potency.

Thiazide diuretics are named ceiling diuretics because increase the dose above normal does not promote a further diuretic response.

1. Thiazides (Chlorothiazide, Hydrochlorothiazide)

Mechanism of action

The thiazide and thiazide-like diuretics act mainly in the cortical region of the ascending loop of Henle and the distal convoluted tubule to decrease the reabsorption of Na^+, apparently by inhibition of a Na^+/Cl^- cotransporter on the luminal membrane of the tubules.

They have a lesser effect in the proximal tubule. As a result, these drugs increase the concentration of Na^+ and Cl^- in the tubular fluid.

Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.

The efficacy of these agents may be diminished with concomitant use of NSAIDs, such as indomethacin, which inhibit production of renal prostaglandins, thereby reducing renal blood flow.

Therapeutically thiazides are indicated in:

a. **<u>Hypertension</u>**: Thiazides are a mainstay of antihypertensive medication, because they are inexpensive, convenient to administer, and well tolerated. They are effective in reducing blood pressure in the majority of patients with mild to moderate essential hypertension.

Blood pressure can be maintained with a daily dose of thiazide, which causes lower peripheral resistance without having a major diuretic effect.

b. <u>Heart failure</u>: Loop diuretics (not thiazides) are the diuretics of choice in reducing extracellular volume in heart failure. However, thiazide diuretics may be added if additional diuresis is needed.

When given in combination, thiazides should be administered 30 minutes prior to loop diuretics in order to allow the thiazide time to reach the site of action and produce effect.

c. **<u>Hypercalciuria</u>:** The thiazides can be useful in treating idiopathic hypercalciuria, because they inhibit urinary Ca^{2+} excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.

d. <u>Diabetes Insipidus</u>: Thiazides can substitute ADH in treating patients having nephrogenic diabetes insipidus. The urine vol. may drop from 11 L/day to about 3 L/day.

Adverse effects of thiazide diuretics

a. Potassium depletion (hypokalemia):

Hypokalemia is the most frequent problem with the thiazide diuretics, and it can predispose patients who are taking *digoxin to ventricular arrhythmias.*

Often, K^+ can be supplemented by dietary measures such as increasing the consumption of citrus fruits, bananas, and prunes. In some cases, K^+ supplementation may be necessary.

Thiazides decrease the intravascular volume, resulting in activation of the renin–angiotensin–aldosterone system. Increased aldosterone contributes significantly to urinary K^+ losses. Under these circumstances,

the K^+ deficiency can be overcome by spironolactone, which interferes with aldosterone action, or by administering triamterene or amiloride, which act to retain K^+. Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.

b. Hyponatremia:

Hyponatremia may develop due to elevation of ADH as a result of hypovolemia, as well as diminished diluting capacity of the kidney and increased thirst. Limiting water intake and lowering the diuretic dose can prevent hyponatremia.

c. Hyperuricemia:

Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system. Being insoluble, uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.

d. Volume depletion: This can cause orthostatic hypotension or light-headedness.

e. Hypercalcemia: The thiazides inhibit the secretion of Ca^{2+}, sometimes leading to hypercalcemia (elevated levels of Ca^{2+} in the blood).

f. **Hyperglycemia:** Therapy with thiazides can lead to glucose intolerance, possibly due to impaired release of insulin and tissue uptake of glucose.

2. Thiazide-like diuretics

- These compounds lack the thiazide structure but have the same mechanism.
- Chlorthalidone: it is given once/day because it has long duration of action.
- Metolazone: it is more potent than thiazide & cause Na^+ excretion in advanced renal failure.
- Indapamide: It is metabolized & excreted by the GIT so it is useful to treat patient with renal failure.

II. Loop or High Ceiling Diuretics

Bumetanide, Furosemide, Torsemide & Ethacrynic acid have action at the ascending limb of the loop of henle. Furosemide is the most commonly used of these drugs. Bumetanide and torsemide are much more potent than furosemide, and the use of these agents is increasing. Ethacrynic acid is used infrequently due to its adverse effect profile.

Mechanism of action:

Loop diuretics inhibit the cotransport of $Na^+/K^+/2Cl^-$ in the luminal membrane in the ascending limb of henle loop. Therefore the absorption of these ions is decreased. They are the most efficacious of diuretic drugs because the ascending limb account for reabsorption of 25-30% of filtered Nacl.

Therapeutic Uses:

The loop diuretics are the drugs of choice for reducing acute pulmonary edema and acute/chronic peripheral edema caused from heart failure or renal impairment. Because of their rapid onset of action, particularly when given intravenously,

the drugs are useful in emergency situations such as acute pulmonary edema. Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular Ca^{2+} excretion. They also are useful in the treatment of hyperkalemia.

Adverse effects

a. Ototoxicity: hearing can be affected particularly when use with aminoglycosides. Ethacrynic acid can produce deafness.

b. Hyperuricemia: Furosemide & Ethacynic acid compete with uric acid for the renal & biliary secretary systems, thus blockining it is secretion, thereby causing or exacerbating gouty attacks.

c. Acute hypovolemia: Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.

d. Potassium depletion: The heavy load of Na^+ presented to the collecting tubule results in increased exchange of tubular Na^+ for K^+, leading to the possibility of hypokalemia.

The loss of K+ from cells in exchange for H+ leads to hypokalemic alkalosis. Use of potassium-sparing diuretics or supplementation with K^+ can prevent the development of hypokalemia.

e. Hypomagnesemia: Chronic use of loop diuretics combined with low dietary intake of Mg^{2+}can lead to hypomagnesemia, particularly in the elderly. This can be corrected by oral supplementation.

III. Potassium Sparing Diuretics

Act in the collecting tubule to inhibit Na^+ reabsorption & K^+ excretion.

a. Aldosterone antagonists (Spironolactone & Eplerenone):

Spironolactone [spear-oh-no-LAK-tone] is a synthetic steroid that antagonizes aldosterone at intracellular cytoplasmic receptor sites rendering the spironolactone–receptor complex inactive. It prevents translocation of the receptor complex into the nucleus of the target cell, ultimately resulting in a failure to produce mediator proteins that normally stimulate the Na+/K+-exchange sites of the collecting tubule.

Thus, a lack of mediator proteins prevents Na^+ reabsorption and, therefore, K^+ and H^+ secretion. Eplerenone [eh-PLEH-reh-none] is another aldosterone receptor antagonist, which has actions comparable to those of spironolactone, although it may have less endocrine effects than spironolactone.

Therapeutically:

a. Diuretic effects: They have low efficacy in mobilizing Na^+ from the body, but have the ability for causing retention of K^+ so use in conjunction with other diuretics.

b. Secondary hyperaldosteronism

c. Heart failure: Spironolactone prevents the remodeling that occurs as compensation for progressive failure of the heart.

d. Resistant hypertension: Resistant hypertension often responds well to aldosterone antagonists.

e. Ascites: Accumulation of fluid in the abdominal cavity (ascites) is a common complication of hepatic cirrhosis. *Spironolactone* is effective in this condition.

f. Polycystic ovary syndrome: Spironolactone is often used off-label for the treatment of polycystic ovary syndrome. It blocks androgen receptors and inhibits steroid synthesis at high doses, thereby helping to offset increased androgen levels seen in this disorder.

A.E: Gynecomastia in males & menstrual irregularity in females.

Spironolactone is completely absorbed orally & is strongly bind to plasma protein & it is rapidly converted to active metabolite Canrenone. The action of Spironolactone is due to the effect of Canrenone. It induces Cyt P450.

B. Triamterene & Amiloride:

- They block Na^+ transport channels, resulting in a decrease in Na^+/K^+ exchange. They have a potassium sparing diuretic action similar to that of Spironolactone but without antagonizing the action of aldosterone. They use in combination with Thiazide or Loop diuretic.
- A.E: leg cramps, ↑ blood urea nitrogen, ↑ uric acid & K^+ retention.

IV. Carbonic Anhydrase Inhibitors

Acetazolamide [ah-set-a-ZOLE-a-mide] and other carbonic anhydrase inhibitors are more often used for their other pharmacologic actions than for their diuretic effect, because they are much less efficacious than the thiazide or loop diuretics.

Mechanism of action: It inhibits carbonic anhydrase located intracellularly (cytoplasm) & on the apical membrane of proximal tubular epithelium. Thus acetazolamide has a mild diuresis, HCO_3^- remain in the lumen → marked elevation in urinary pH.

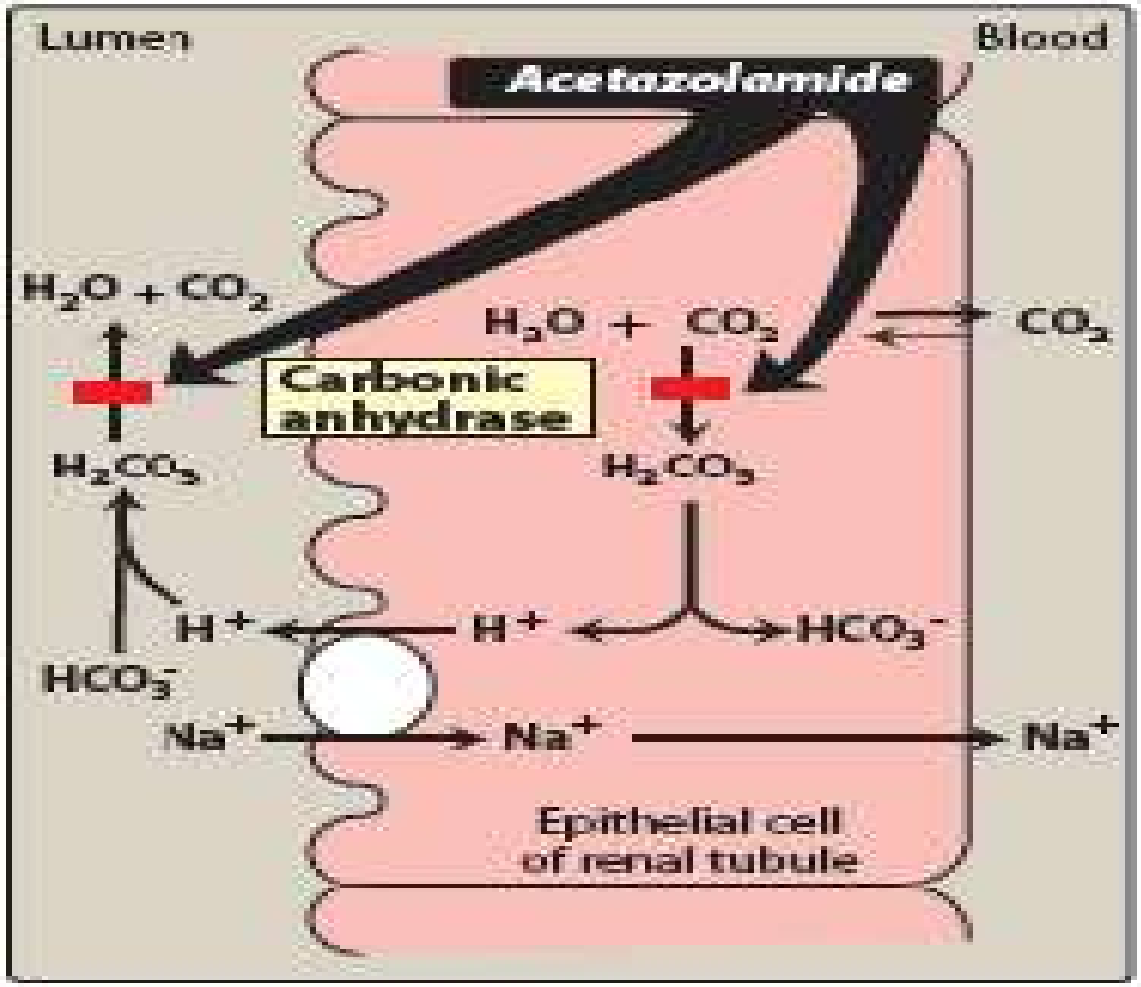

Figure 22.9
Role of carbonic anhydrase in sodium retention by epithelial cells of the renal tubule.

Therapeutic Uses:

Treatment of glaucoma is the most common use of Acetazolamide in which it reduces the intraocular pressure of open angle glaucoma. Acetazolamide reduces the production of aqueous humor by blocking carbonic anhydrase in ciliary body of the eye. It is useful in treatment of chronic glaucoma & should not use for an acute attack, since pilocarpine is preferred for an acute attack.

- Topical carbonic anhydrase inhibitors such as Dorzolamide & Brinzolamide have the advantage of not causing any systemic effects.
- Mountain Sickness it is characterized by headache, vomiting, ↑ pulse rate & dyspepsia occur on sudden change of high altitudes. A.E: it is given orally 4 times daily. The adverse effects include metabolic acidosis, potassium depletion, renal stone formation, drowsiness & paresthesia.

V. Osmotic diuretics

Manitol & urea are completely filtered through glomerulus result in some degree of diuresis. They have the ability to carry water with them into tubular fluid. These diuretics cause ↑ water excretion rather than Na^+ excrertion.

Therapeutically:

- Treating individuals ingested toxic substances.
- Treatment of patients with ↑ intracranial pressure.
- Acute renal failure.
- Drug toxicities & trauma.
- Manitol not absorb orally & should be given IV.
- A.E: Dehydration

Thank You

For

Listening