SOS in Pharmaceutical Sciences, Jiwaji University, Gwalior

Relevant Physiology of Urine Formation

SUBJECT- PHARMACEUTICAL CHEMISTRY-VII (4T2)

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ASST. PROF. (CONTRACT)

Physiology of Urine Formation

- Urine formation starts from glomerular filtration (g.f.) in a prodigal way. Normally, about 180 L of fluid is filtered everyday: all soluble constituents of blood minus the plasma proteins (along with substances bound to them) and lipids, are filtered at the glomerulus.
- More than 99% of the glomerular filtrate is reabsorbed in the tubules; about 1.5 L urine is produced in 24 hours.
- The diuretics act primarily by inhibiting tubular reabsorption: just 1% decrease in tubular reabsorption would more than double urine output.

Physiology of Urine Formation

- The mechanisms that carryout ion movement across tubular cells are complex and involve a variety of energy dependent transmembrane pumps as well as channels in between the loose fitting cells of the proximal tubule (PT).
- All Na^+ that enters tubular cells through the luminal membrane is pumped out of it into the renal interstitium at the basolateral membrane by Na^+K^+ATPase energised Na^+-K^+ antiporter. Because there is a large intracellular to extracellular gradient for K^+, it diffuses out through K^+ channels to be recirculated by the Na^+-K^+ antiporter.
- For simplification, tubular reabsorption can be divided into four sites.

Tubular Reabsorption

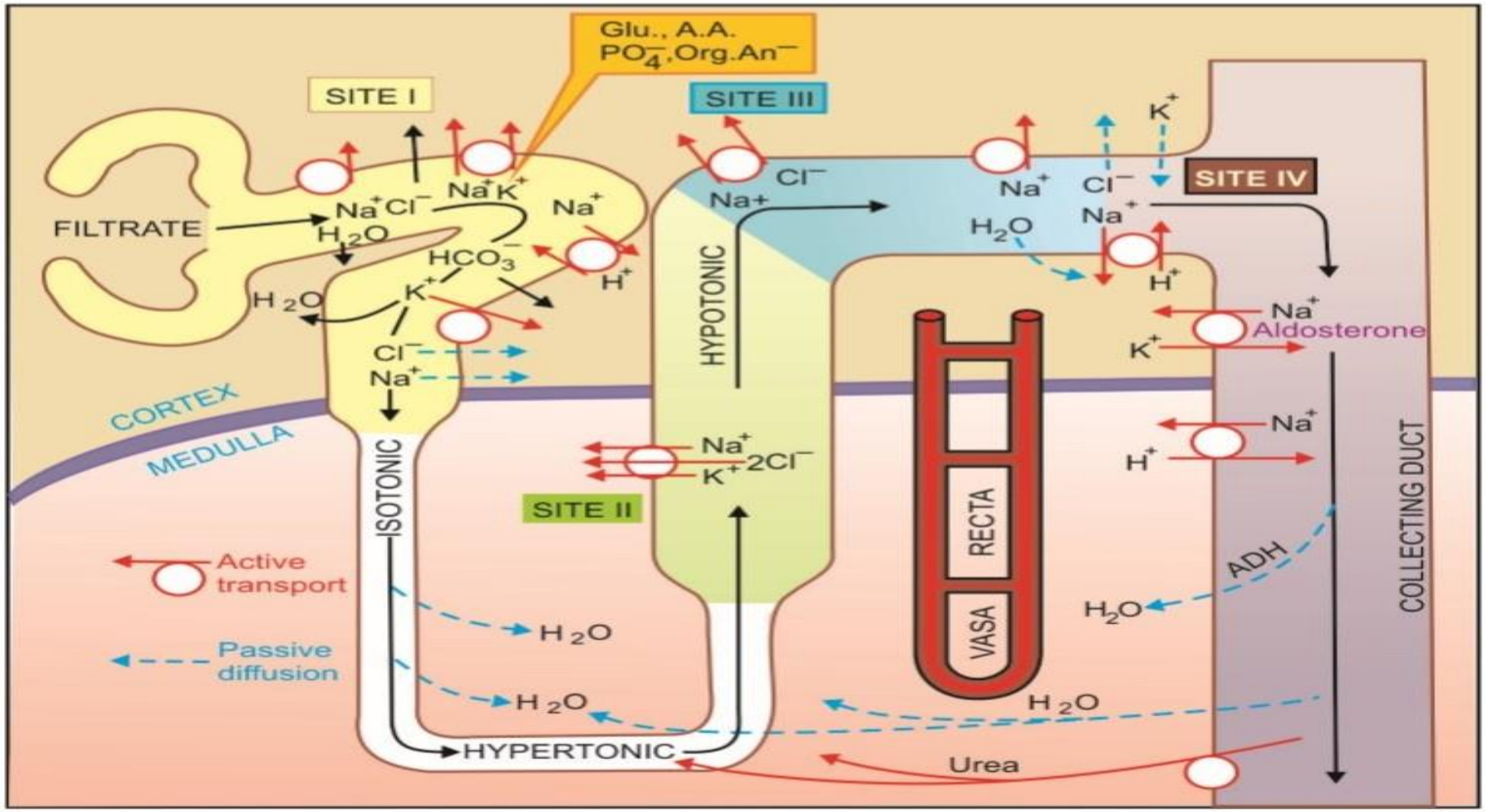

Fig. IX.1: Diagrammatic representation of nephron showing the four sites of solute reabsorption. The thick ascending limb of loop of Henle is impermeable to water; Glu.—Glucose; A.A.—Amino acid; Org. An.—Organic anions.

Site I: Proximal tubule Four mechanisms of Na^+ transport have been defined in this segment.

(a) Direct entry of Na^+ along a favourable electrochemical gradient.

(b) Transport of Na^+ and K^+ coupled to active reabsorption of glucose, amino acids, other organic anions and PO_4^{3-} through specific symporters.

(c) Exchange with H^+: The PT cells secrete H^+ with the help of a Na^+-H^+ antiporter.

(d) The disproportionately large HCO_3^-, acetate, PO_4^{3-}, amino acid and other anion reabsorption create passive driving forces for Cl^- to diffuse through the paracellular pathway, particularly in the later PT.

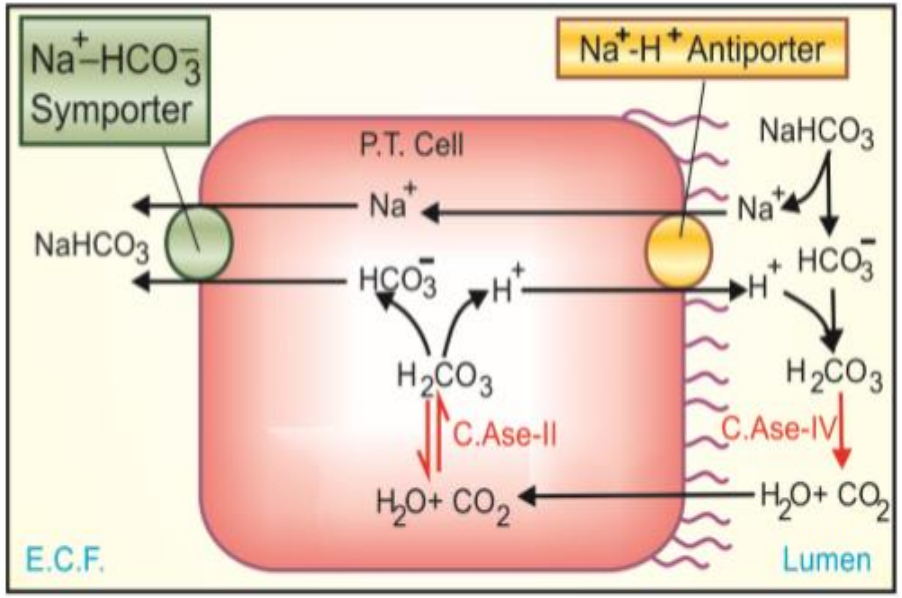

Fig. IX.2: The carbonic anhydrase (C.Ase) mediated bicarbonate absorption in proximal tubule (P.T.)

Site II: Ascending limb of loop of Henle (Asc LH)

The thick AscLH can be distinguished into two distinct portions:

(i) Medullary part lined by cuboidal cells.

(ii) Cortical part lined by flattened cells.

Both portions are relatively impermeable to water but absorb salt actively and thus dilute the tubular fluid.

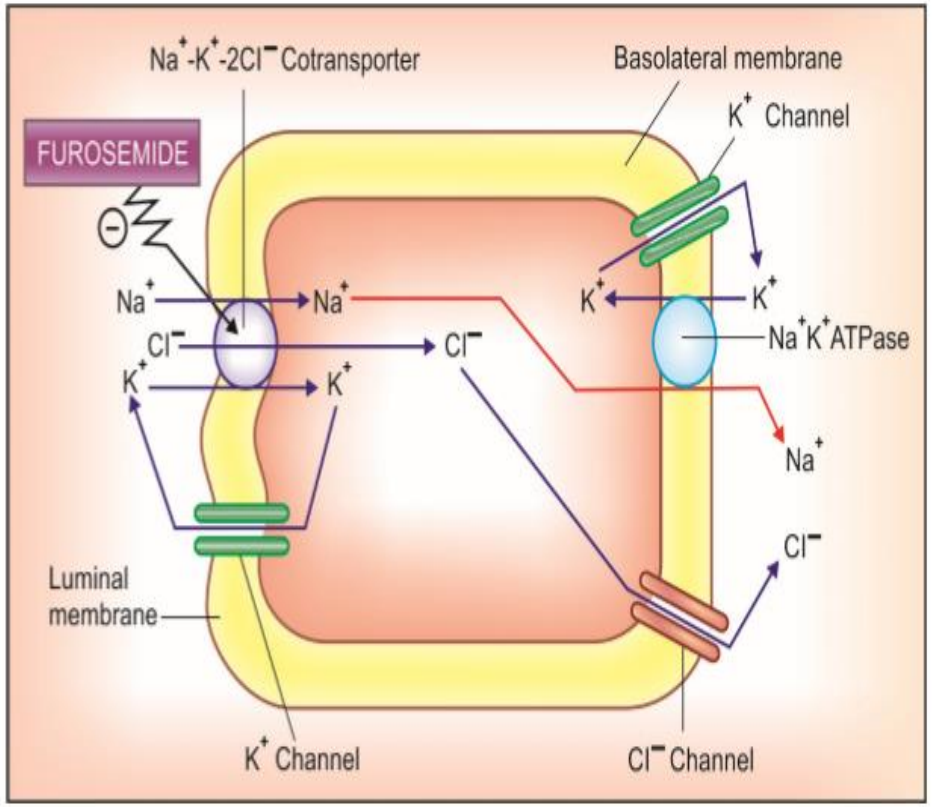

Fig. 41.1: Mechanism of salt reabsorption in the thick ascending limb of loop of Henle (AscLH) cell, and site of action of furosemide on the Na^+-K^+-$2Cl^-$ cotransporter

Site III: Cortical diluting segment of loop of Henle

This segment, also impermeable to water, continues to absorb salt, but here it is through a Na+-Cl^- symporter. Tubular fluid gets further diluted.

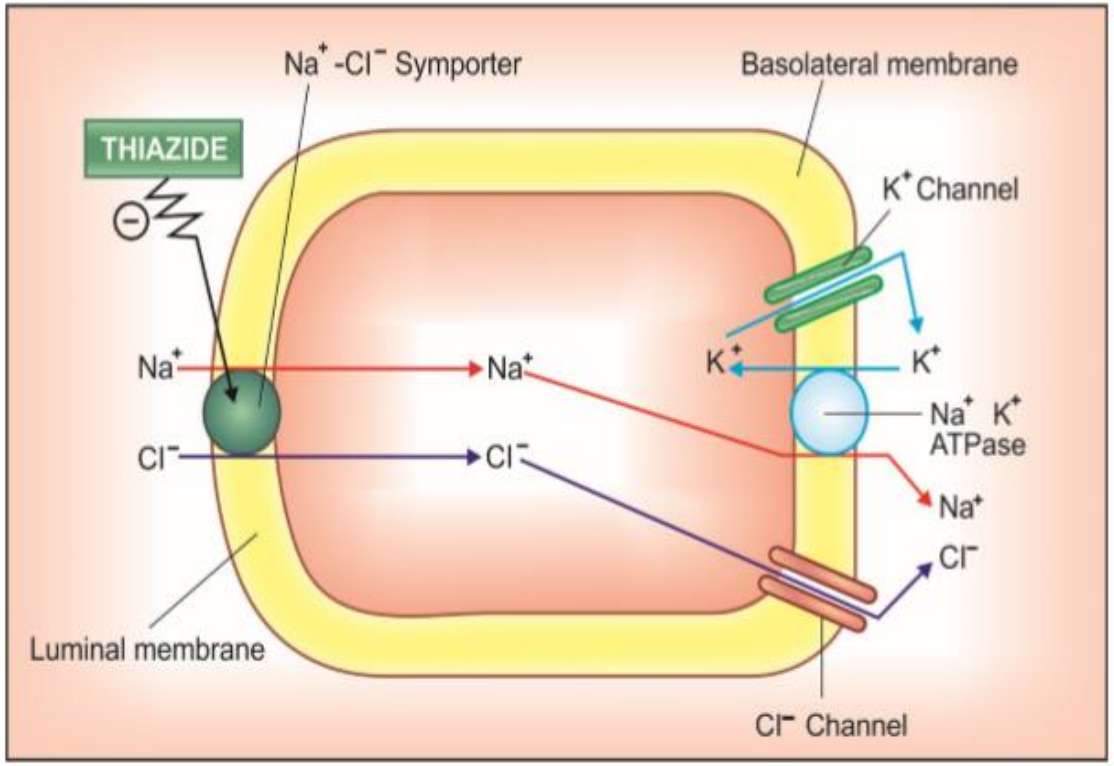

Fig. 41.2: Mechanism of salt reabsorption in early distal tubular cell and site of action of thiazide diuretics on Na^+Cl^- symporter

Site IV: Distal tubule (DT) and collecting duct (CD)

- In the late DT and CD, Na^+ is again actively reabsorbed; the cation-anion balance being maintained partly by passive Cl^- diffusion and partly by secretion of K^+ and H^+.
- Absorption of Na^+ at this site occurs

through a specific amiloride sensitive

Na^+ channel and is controlled to

a large extent by aldosterone.

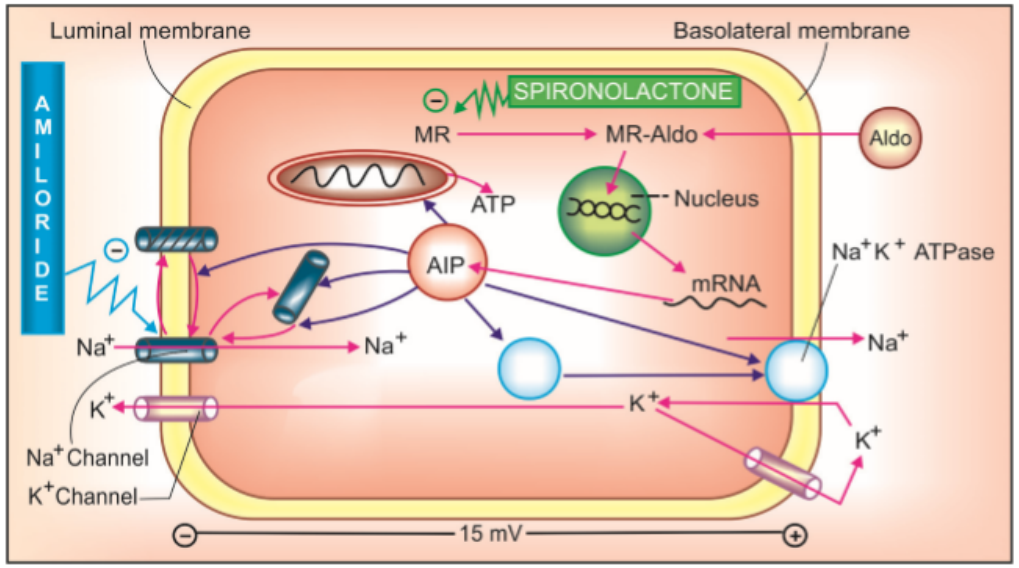

Fig. 41.3: Site and mechanism of action of potassium sparing diuretics on the late distal tubule/collecting duct cell Aldosterone (Aldo) penetrates the cell from the interstitial side and combines with the mineralocorticoid receptor (MR). The complex translocates to the nucleus—promotes gene mediated mRNA synthesis. The mRNA then directs synthesis of aldosterone induced proteins (AIPs). The AIPs include Na^+K^+ ATPase and renal epithelial (amiloride sensitive) Na^+ channels. More of these proteins are synthesized. The AIPs also activate these Na^+ channels and, translocate them from cytosolic site to luminal membrane. They also translocate Na^+K^+ATPase to the basolateral membrane. AIPs also increase ATP production by mitochondria. All these changes promote Na^+ reabsorption. More K^+ and H^+ is secreted indirectly. Spironolactone binds to MR, prevents Aldo action and produces opposite effects.

Amiloride approaches the Na^+ channel from the luminal side and blocks it—reducing the lumen negative transepithelial potential difference which governs K^+ and H^+ secretion

Regulation of renal function

- Glomerular filtration rate (g.f.r.) is dependent on the pumping action of heart, the magnitude of renal blood flow and the relative dimensions of afferent and efferent glomerular vessels. Thus, systemic and intrarenal haemodynamic changes can reflect in g.f.r.
- About 80% nephrons lie in outer cortex, have short loops of Henle and low Na^+ reabsorptive capacity; while 20% or so are juxtamedullary, possess long loops of Henle and are largely responsible for creating the corticomedullary osmotic gradient.
- Redistribution of blood flow between these two types of nephrons can alter salt and water excretion. Further, haemodynamic changes within different segments of renal vasculature can alter pressure relationships which govern flow of solute and water.

- The renin-angiotensin-aldosterone system has a profound bearing on distal tubular reabsorption of Na^+ and secretion of K^+/H^+.
- Angiotensin II produced locally in the kidney has direct effects on intrarenal vascular beds as well as on salt and water reabsorption.
- Prostaglandins (PGs) are produced locally in kidney; act as modulators of renal circulation and renin release. PGE_2 inhibits the action of ADH and has direct effects on tubular reabsorption.
- Natriuretic hormone produced by the atrium (atrial natriuretic peptide: ANP) and may be other sites also has been found to be important in inducing natriuresis in response to salt and volume overload. It mediates 'escape' from long term aldosterone action.

Relation to diuretic action

- The relative magnitudes of Na+ reabsorption at different tubular sites are:

  PT 65–70%; Asc LH 20–25%;

  DT 8–9%; CD 1–2%.

- The maximal natriuretic response to a diuretic can give a clue to its site of action. It may appear that diuretics acting on PT should be the most efficacious. However, these agents are either too weak or cause distortion of acid-base balance (CAse inhibitors). Moreover, their effect may be obscured by compensatory increase in reabsorption further down the nephron, because the reserve reabsorptive capacity of diluting segments is considerable and can overshadow more proximal actions.

Thank You…