

Diuretics and antidiuretics

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Background & definitions

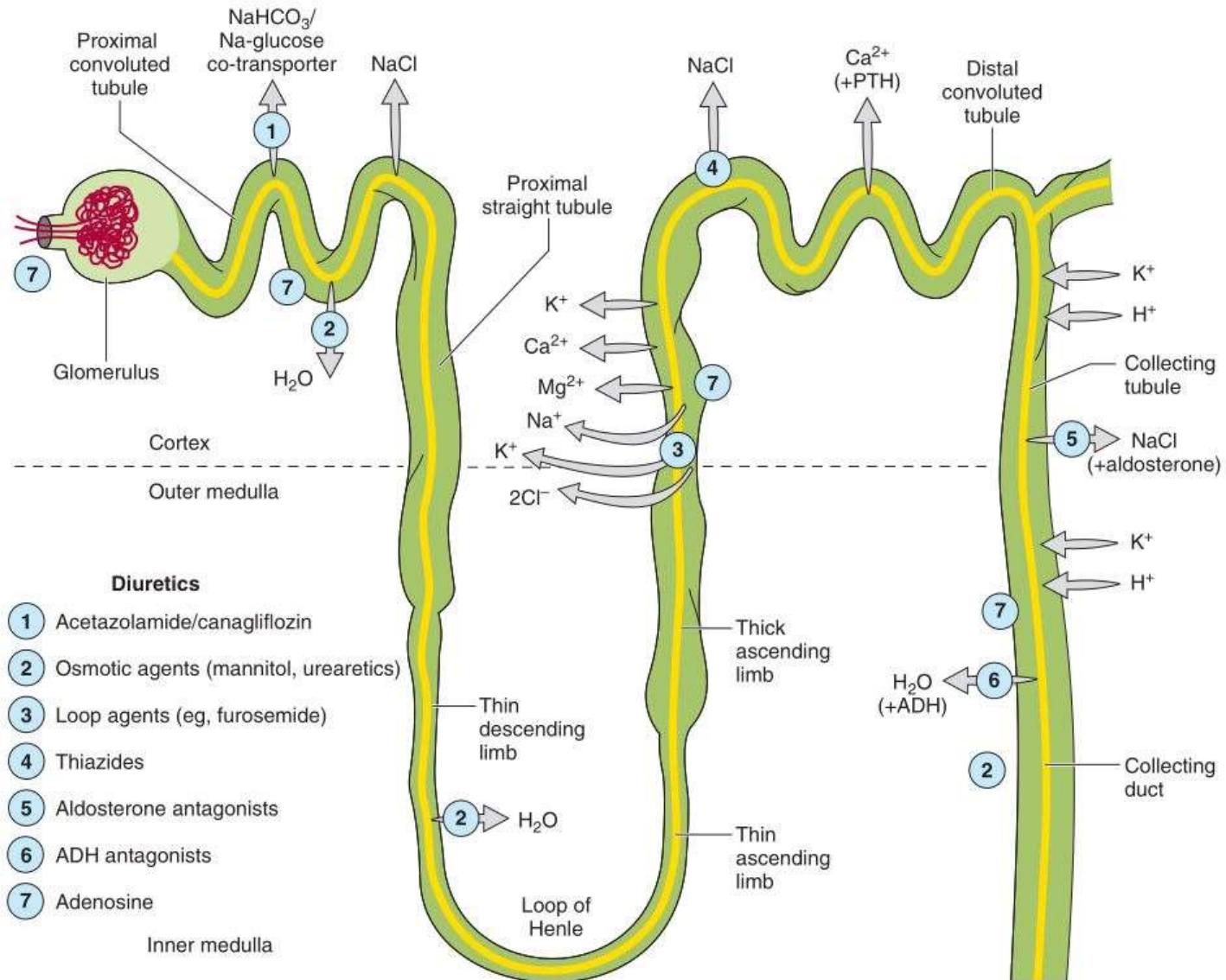
- kidneys regulate fluid volume + electrolyte content
- diseases (e.g hypertension, heart failure, renal failure, nephrotic syndrome, cirrhosis) → fluid and electrolyte changes
- diuresis = ↑ excretion of urine / ↑ urine volume
 - extrarenal mechanisms
 - ↑ cardiac output – pl. digoxin
 - ↑ renal blood flow – pl. dopamine / bed rest
 - **diuretics**
 - drugs that influence renal tubular transport functions

Classification of diuretics

according to targets

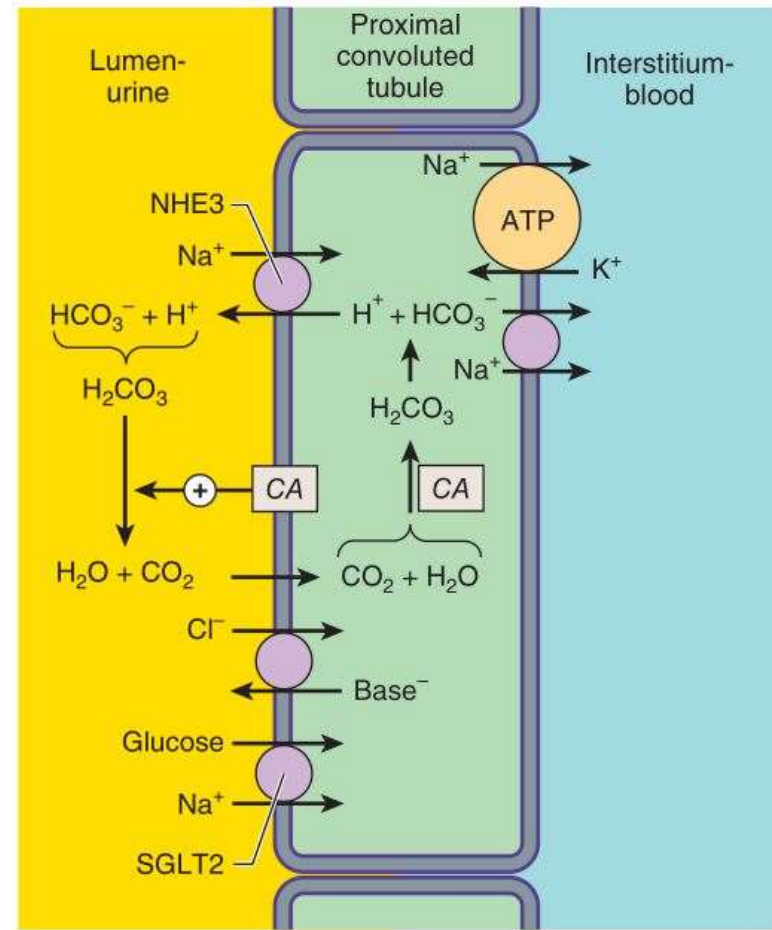
- membrane transport proteins in renal tubular epithelial cells
 - $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ symport inhibitors – **loop diuretics** (high ceiling)
 - Na^+/Cl^- symport inhibitors – **thiazides** / thiazide-likes
 - renal epithelial Na^+ channel inhibitors – K^+ sparing
 - (SGLT-2 inhibitors) – diabetes
- enzymes
 - **carbonic anhydrase inhibitors**
- hormone receptors in renal epithelial cells
 - **aldosterone antagonists** – K^+ sparing
 - vasopressin receptor agonists and antagonists
- no target – osmotic effect
 - mannitol

Nephron structure and site of action of diuretics



Carbonic anhydrase inhibitors

- **acetazolamide** - oral
- almost all CA must be blocked to see the effect
- ↓ NaHCO_3 / water reabsorption
- metabolic acidosis
 - alkaline urine
- efficacy ↓ with use



Clinical use of CAIs

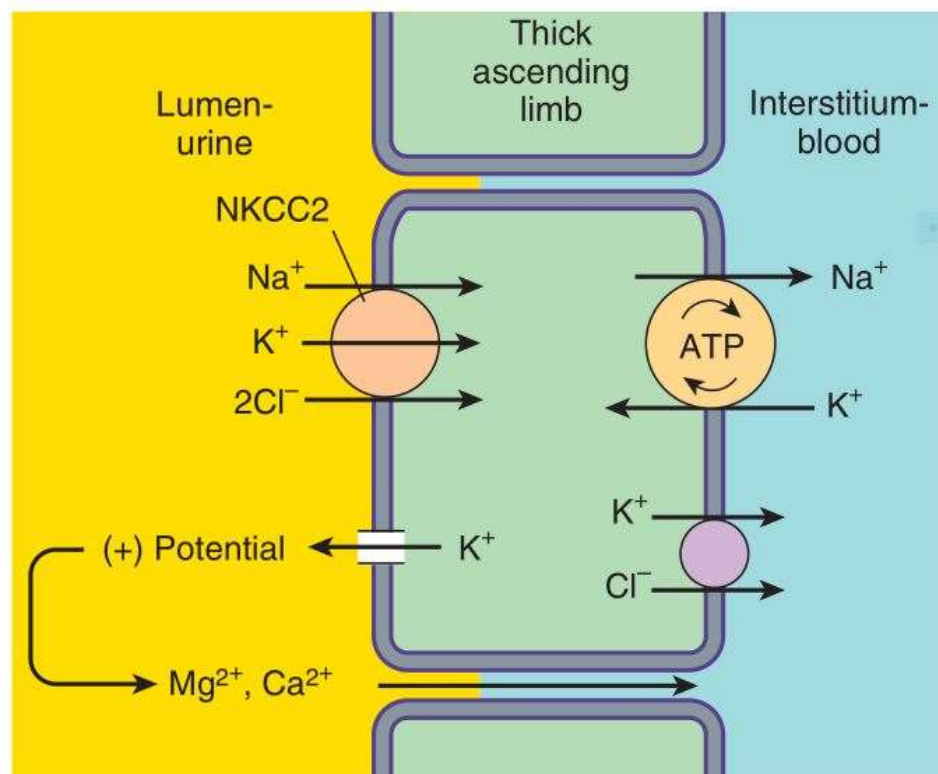
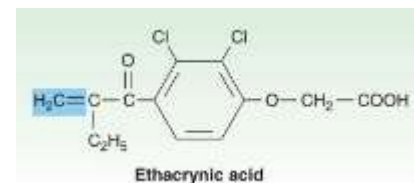
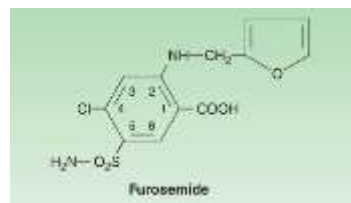
- now rarely used as diuretic
- specific applications
 - **glaucoma**
 - topical dorzolamide, brinzolamide
 - acute mountain sickness
 - mild metabolic acidosis → ↑ ventilation
 - urinary alkalinization
 - rare, in cystin or urate stones
 - metabolic alkalosis
 - epilepsy

Adverse effects / contraindications of CAI

- hyperchloremic **metabolic acidosis**
- renal stones
 - calcium phosphate
- renal **K⁺ wasting**
 - partly reabsorbed Na⁺ in collecting tubule → lumen negative potential → K⁺ secretion
- **contraindicated in cirrhosis**
 - alkalization of the urine ↓ urinary excretion of NH₄⁺ → as NH₃ is reabsorbed

Loop agents (high ceiling)

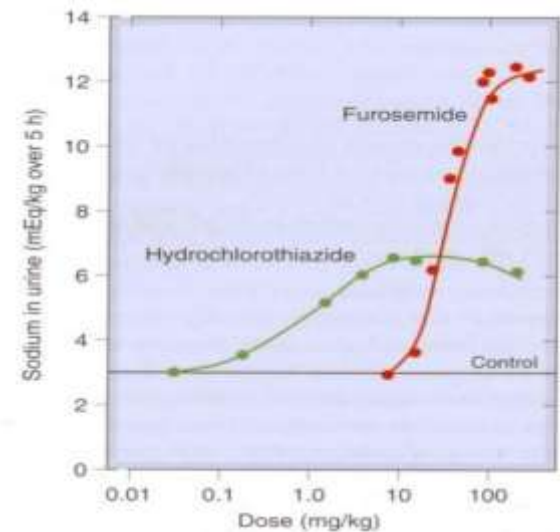
- **furosemide, ethacrynic acid**
- highest efficacy
- hypokalemic metabolic alkalosis
- \downarrow lumen-positive potential $\rightarrow \uparrow$ **$\text{Ca}^{2+}/\text{Mg}^{2+}$ excretion**
- $\text{COX-2} \uparrow \rightarrow \text{PGE2} \uparrow \rightarrow \uparrow$ salt transport in TAL / vasodilation



PK: rapid absorption / short duration of action

Clinical use of loop diuretics

- common
 - **acute pulmonary edema** / other edemas (heart failure)
 - hypertension (renal insufficiency)
- less frequent
 - hypercalcemia
 - hyperkalemia
 - acute renal failure
 - anion (Br^- , F^- , I^-) overdose



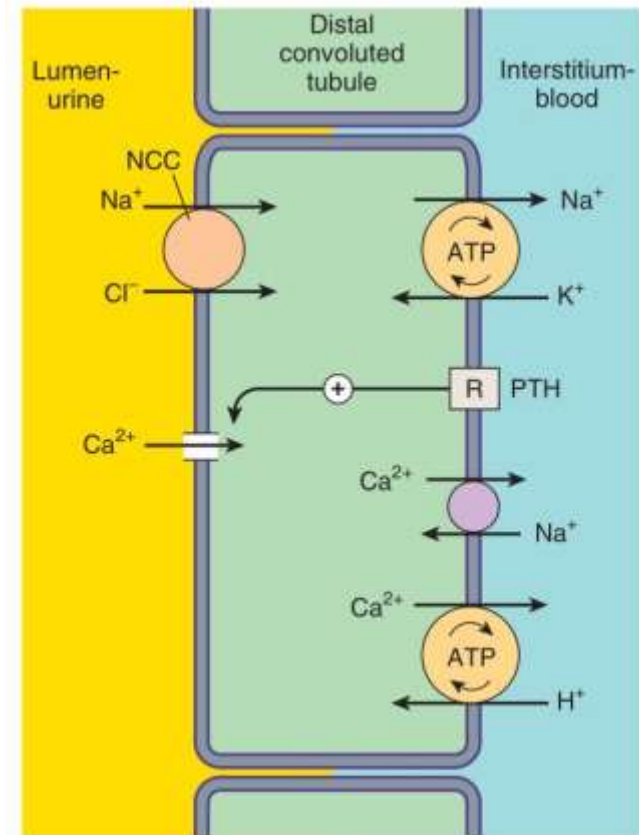
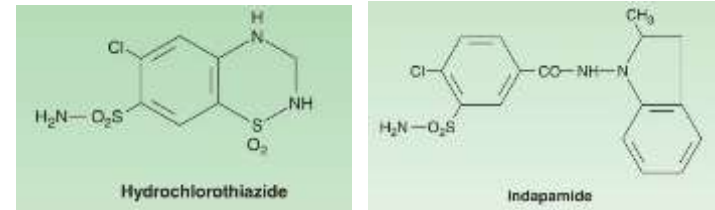
“high ceiling”

Adverse effects / contraindications of loop diuretics

- **hypokalemic metabolic alkalosis**
- ototoxicity
 - dose related / reversible
- hyperuricemia
 - avoid hypovolemia (lower doses)
- hypomagnesemia
- allergic reactions
 - potential cross allergenicity

Thiazides / thiazide-like

- **hydrochlorothiazide**
- indapamide / clopamide
- lower efficacy
- hypokalemic metabolic alkalosis
- ↓ Ca^{2+} excretion
- compete with uric acid secretion in PCT

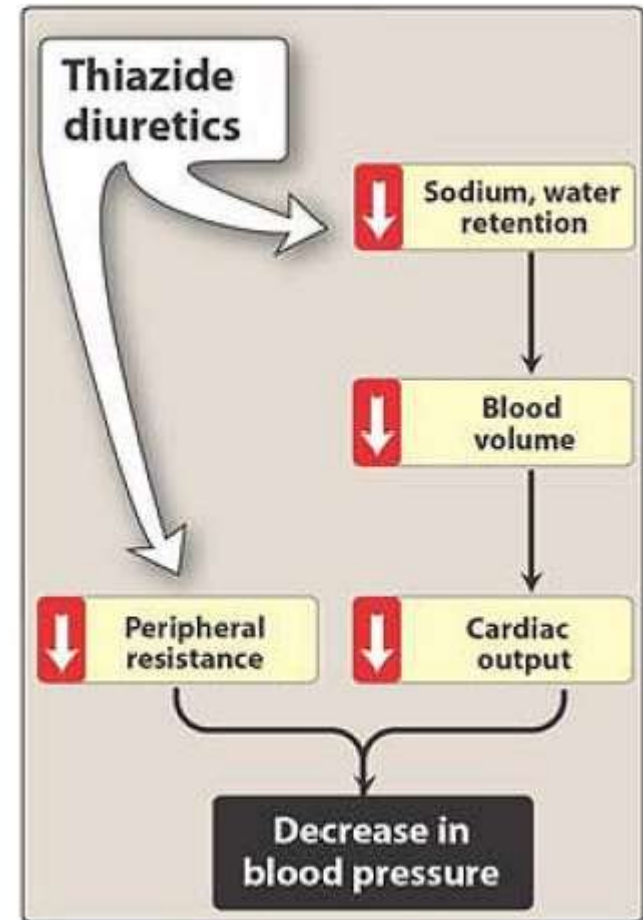


Clinical use of thiazide diuretics

- **hypertension**
 - details on next slide
- heart failure
 - mild, loop agents preferred
- idiopathic hypercalciuria
 - nephrolithiasis
- nephrogenic diabetes insipidus
 - no response to ADH
 - cause: Li therapy of bipolar disease
 - mechanism?
 - ↑ osmolality in the inner medulla
 - ↑ aquaporin-2 expression

Thiazide diuretics in hypertension

- widely used
- exact antihyp. eff. ?
 - low dose
- initially - ↓ ECV / CO
- later - ↓ TPR
- no effect in renal insuff. (GFR < 30 ml/min)

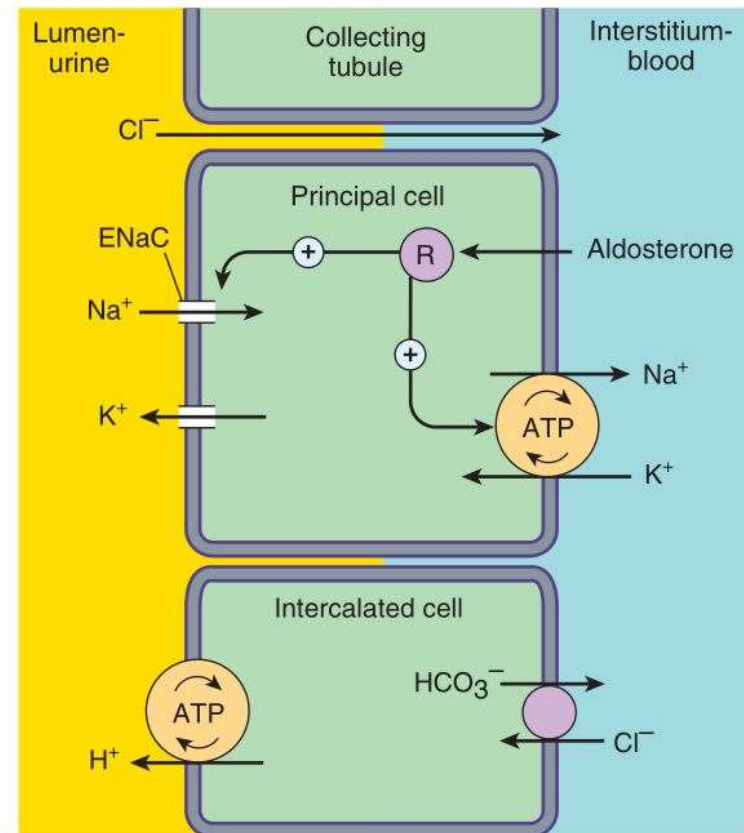
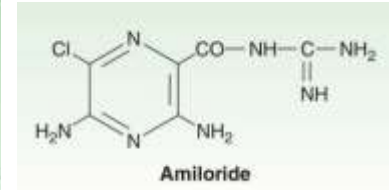
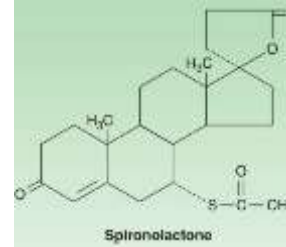


Adverse effects / contraindications of thiazide diuretics

- **hypokalemic metabolic alkalosis**
- hyperglycemia
 - dose related
- hyperlipidemia
- **hyponatremia**
- hyperuricemia
- allergic reactions
 - potential cross allergenicity

K⁺ sparing diuretics

- **spironolactone / eplerenone**
- **amiloride / triamterene**
- ↓ Na absorption
- ↓ K⁺ and H⁺ excret.
 - hyperkalemia
 - acidosis
- comb. with thiazides
- most eff. in case of ↑ aldosterone



Clinical use of K⁺ sparing diuretics

- hyperaldosteronism
 - primary – Conn's syndrome, ectopic ACTH prod.
 - secondary – e.g. **heart failure**, cirrhosis
- in comb. with K⁺ wasting diuretics



Adverse effects / contraindications of K⁺ sparing diuretics

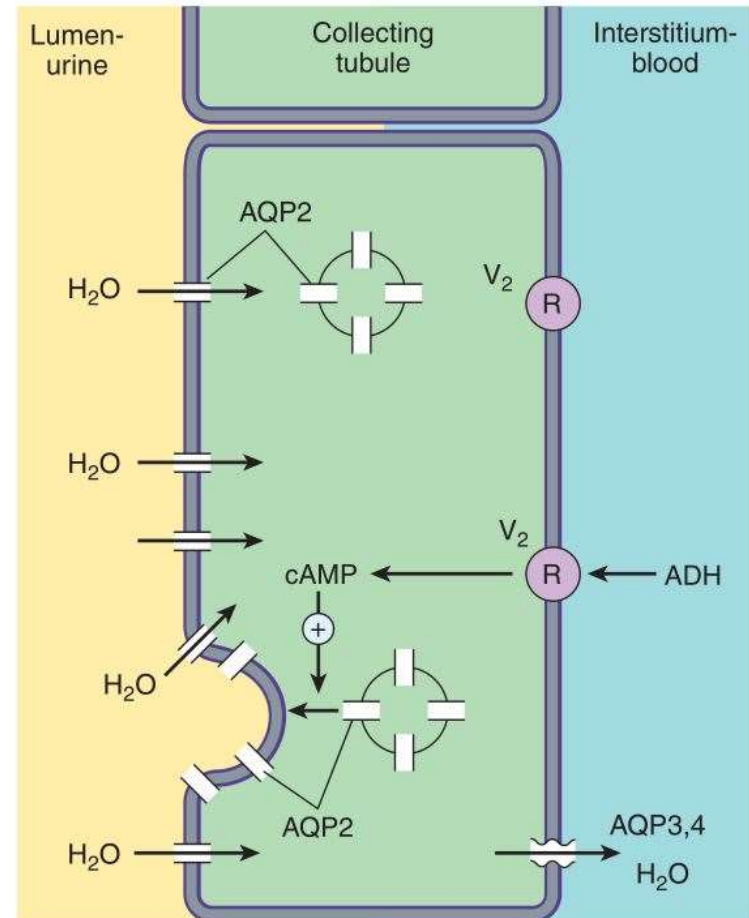
- hyperkalemia
 - renal disease
 - RAAS inhibition
 - β blockers, ACE inhibitors, angiotensin receptor blockers
- **metabolic acidosis**
- antiandrogenic effects
 - gynecomastia, impotence
 - difference between spironolactone and eplerenone

Osmotic diuretics

- filtered and not reabsorbed osmotically active
 - retain water
- mannitol iv.
 - also see hyperglycemia / glucose
- used to
 - ↓ intracranial / intraocular pressure
 - maintain high urine flow
 - ↓ renal blood flow / hemolysis, rhabdomyolysis, tumor lysis
- initial expansion of ECV and hyponatremia
 - danger in pulmonary edema / renal insuff.
- may result in acute renal failure (6-7%)

Antidiuretic hormone agonists and antagonists

- agonists
 - vasopressin / desmopressin
- antagonists
 - conivaptan / tolvaptan (V_2)
 - (demeclocycline / lithium)
- used in hyponatremia / adj. to diuretics in CHF



SGLT-2 inhibitors

- dapagliflozin, canagliflozin, empagliflozin
- oral, metabolized, rifampin interaction
- indication: **diabetes** (3rd line)
- weight loss, drop in blood pressure, diuresis, acute kidney injury (?)
- rare hypoglycemia / infections (genital, UT)

