UNIVERSITY of DEBRECEN

DIURETIC AGENTS

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Diuresis: increased excretion of urine

Extrarenal diuretic mechanisms	**i.e.**
1. To increase cardiac output	therapy for congestive failure by digitalis
2. Hydremia	forced diuresis
3. To increase renal blood flow	bed rest nycturia Dopamine 0,5-3 μg/kgBW/min.

Diuretic agents effect on renal tubular functions

Definition: They can promote the excretion of water and electrolytes by the effect on renal tubular mechanisms.

They can normalize the electrolyte disorders and the abnormal shifts in the relative or absolute amounts of fluid in the extra- and intracellular body water compartments.

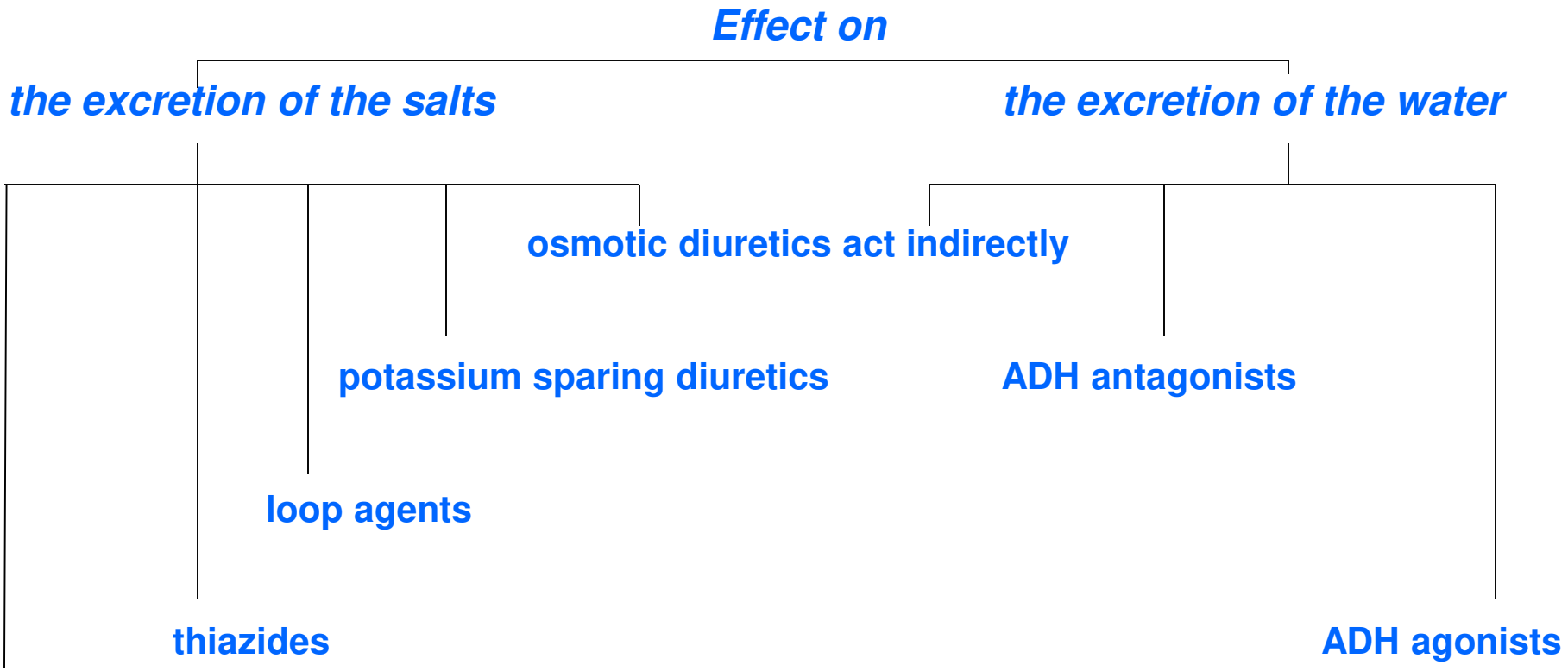
Therapeutic goals:

Mobilization and excretion of oedemas of different origins
Antihypertensive effect
To normalize acid-base disturbances and electrolyte disorders

Table 2.1 Approximate contributions to plasma osmolality

	Osmolality (mosmoles/kg)
Sodium and anions	270
Potassium and anions	7
Calcium (ionized) and anions	3+
Magnesium and anions	1+
Urea	5
Glucose	5
Protein	Approximately 1
Total	Approximately 292

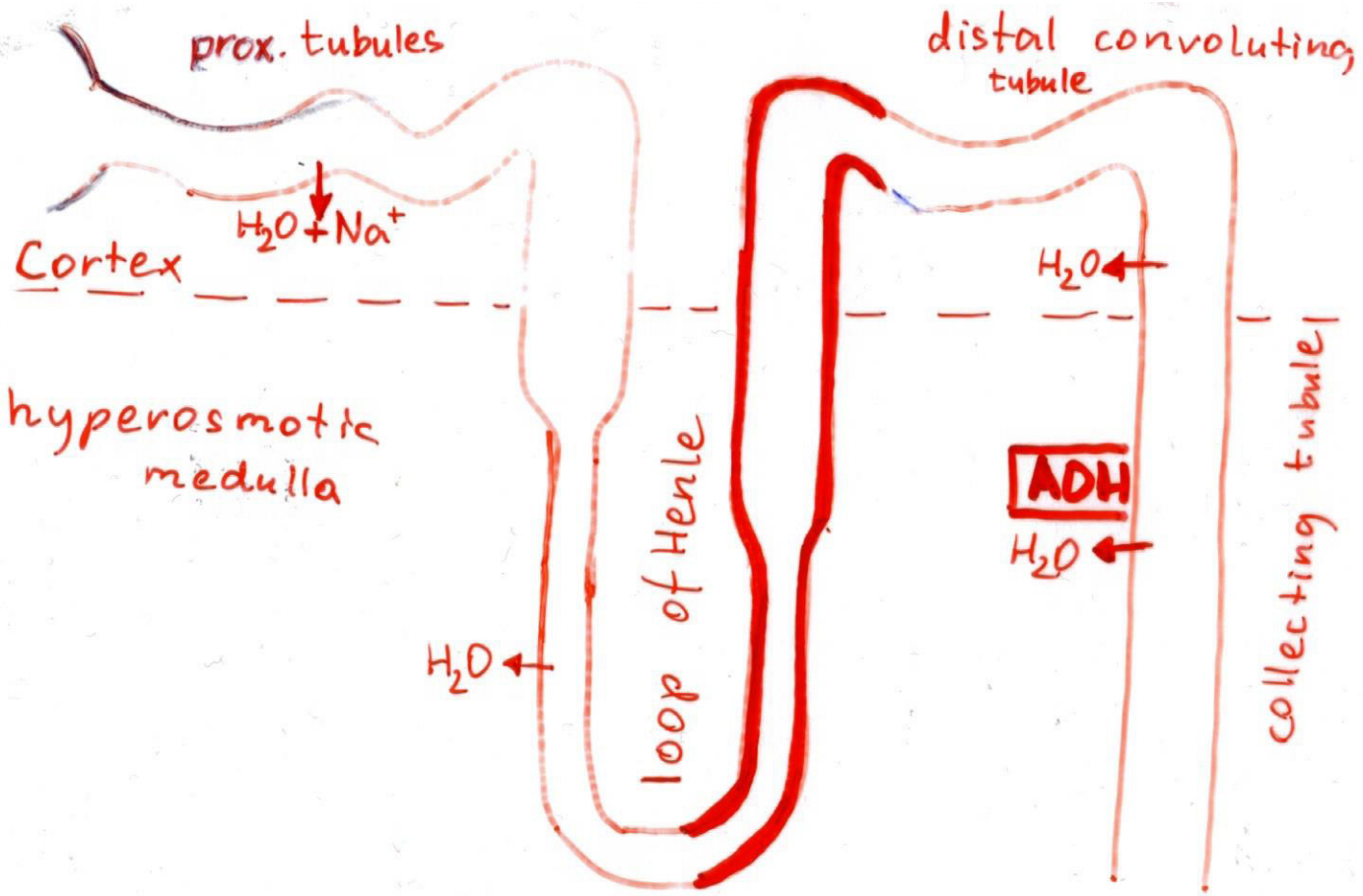
Groups of agents effecting on tubular functions



DIURETICS

Antidiuretics

The part of the nephron with water impermeability



Osmotic diuretics

Their pharmacokinetic properties are important in point of view of their effects.

Def. :
Freely filterable, poorly reabsorbable nonelectrolytes which are not metabolized by the organism.

other pharmacokinetic properties:

They are poorly absorbed so they must be given parenterally

i.e. mannitol
isosorbide

Osmotic diuretics

Pharmacodynamics	Clinical indication	Toxicity
They primarily limit water reabsorption in all segments of the nephron that are freely permeable to water. ↓ Rapidly extract water from even the intracellular compartment	ACUTE life-threatening conditions with oedemas They decrease even intracellular oedemas !! Acute renal failure to reduce intracranial or intraocular pressure before ophthalmologic procedures	Exsiccosis pulmonary oedema in congestive heart failure !!

One of the most effective diuretic group

They are useful even in combination with loop agents

e.g. mannitol+furosemide

ADH antagonists

1. Lithium salts
2. Tetracycline derivatives
   i.e. demeclocycline

} decrease cAMP

3. Vaptans – nonpeptides: conivaptan (only for iv use)

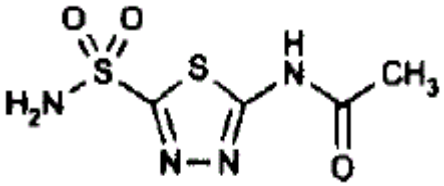
- ***Pharmacodynamics:*** They cause nephrogenic diabetes insipidus.

- ***Clinical indication:***

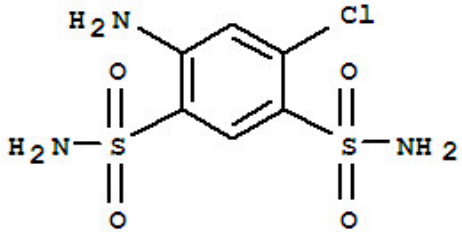
  Inappropriate ADH secretion syndrome = ADH hypersecretion

Carbonic anhydrase inhibitors

Chemistry:



acetazolamide (Fonurit)
(Huma Zolamid)



Salamide
(disulfamoylchloraniline)

Other drug: dorzolamide

Pharmacokinetics:

Effects are apparent within 30 minutes
Duration of action about 12 hours
tubular secretion

Pharmacodynamics:

site of action: prox. tubule – inhibitors of carbonic anhydrase

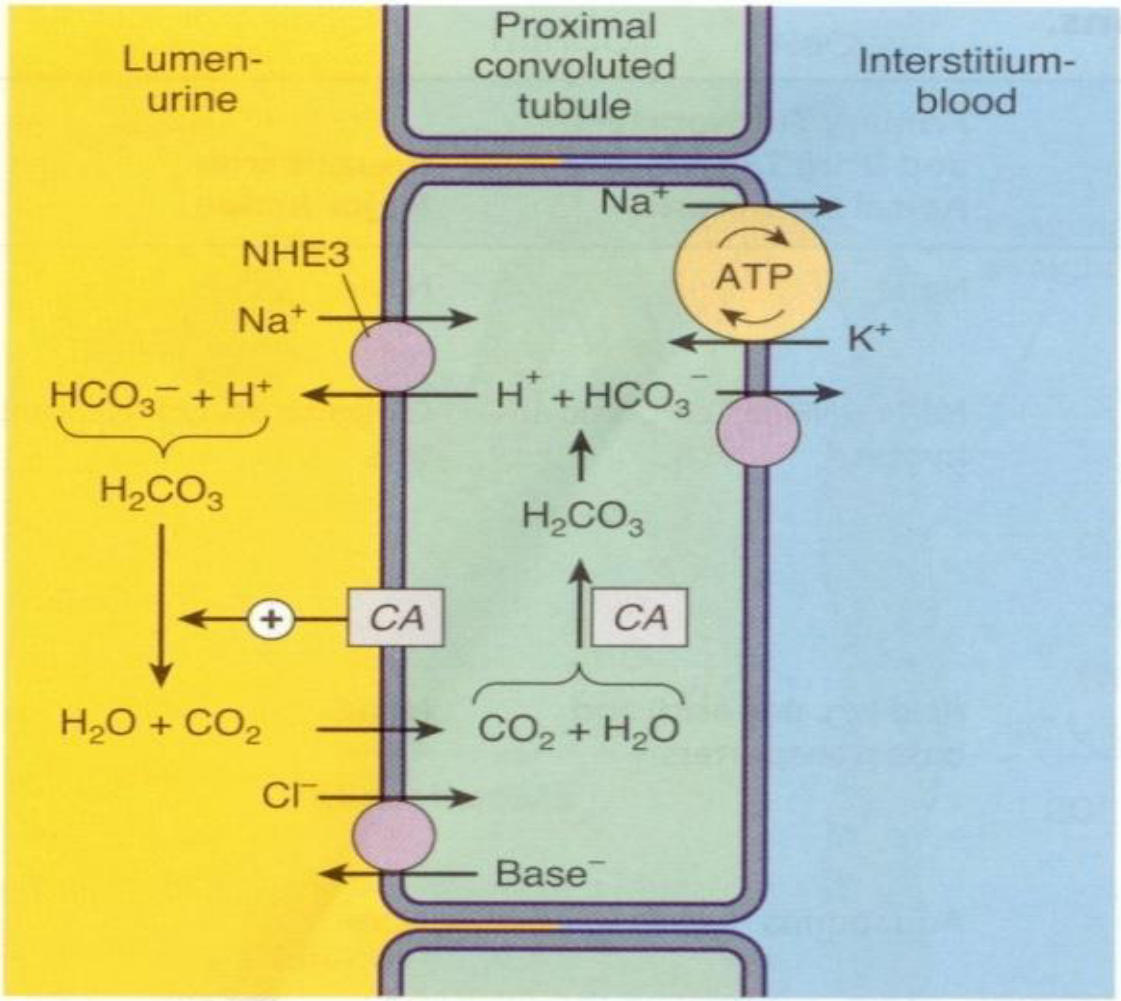


FIGURE 15–2 Apical membrane Na^+/H^+ exchange (via NHE3) and bicarbonate reabsorption in the proximal convoluted tubule cell. Na^+/K^+ ATPase is present in the basolateral membrane to maintain intracellular sodium and potassium levels within the normal range. Because of rapid equilibration, concentrations of the solutes are approximately equal in the interstitial fluid and the blood. Carbonic anhydrase (CA) is found in other locations in addition to the brush border of the luminal membrane.

Carbonic anhydrase inhibitors

Effects on urine electrolyte composition	Clinical indications	Toxicity
Prox. tub. :	cardiac oedema	
$Na^+ \uparrow$ $H^+ \downarrow$	cyclic oedema	
		hyperchloremic
alkalic urine	metabolic alkalosis	metabolic acidosis
	urinary alkalinisation	(limit of their diuretic effects)
Dist. tub. : $K^+ \uparrow$		hypokalemia
Other ions:		
$PO_4^{2-} \uparrow$	hyperphosphatemia	
citrate $\downarrow$		renal calculi
$Ca^{2+} \uparrow$		

Contraindications: hepatic cirrhosis because they decrease ammonia excretion

Carbonic anhydrase inhibitors

Extrarenal effects

Effects	Clinical indications	Toxicity
Inhibition of carbonic anhydrase		
1. the rate of aqueus humor formation decreases	glaucoma	
2. the rate of CSF formation decreases	acute mountain sickness	
3. inhibition of iodine uptake by thyroid gland		hypothyroidism **Don't use it during pregnancy!**

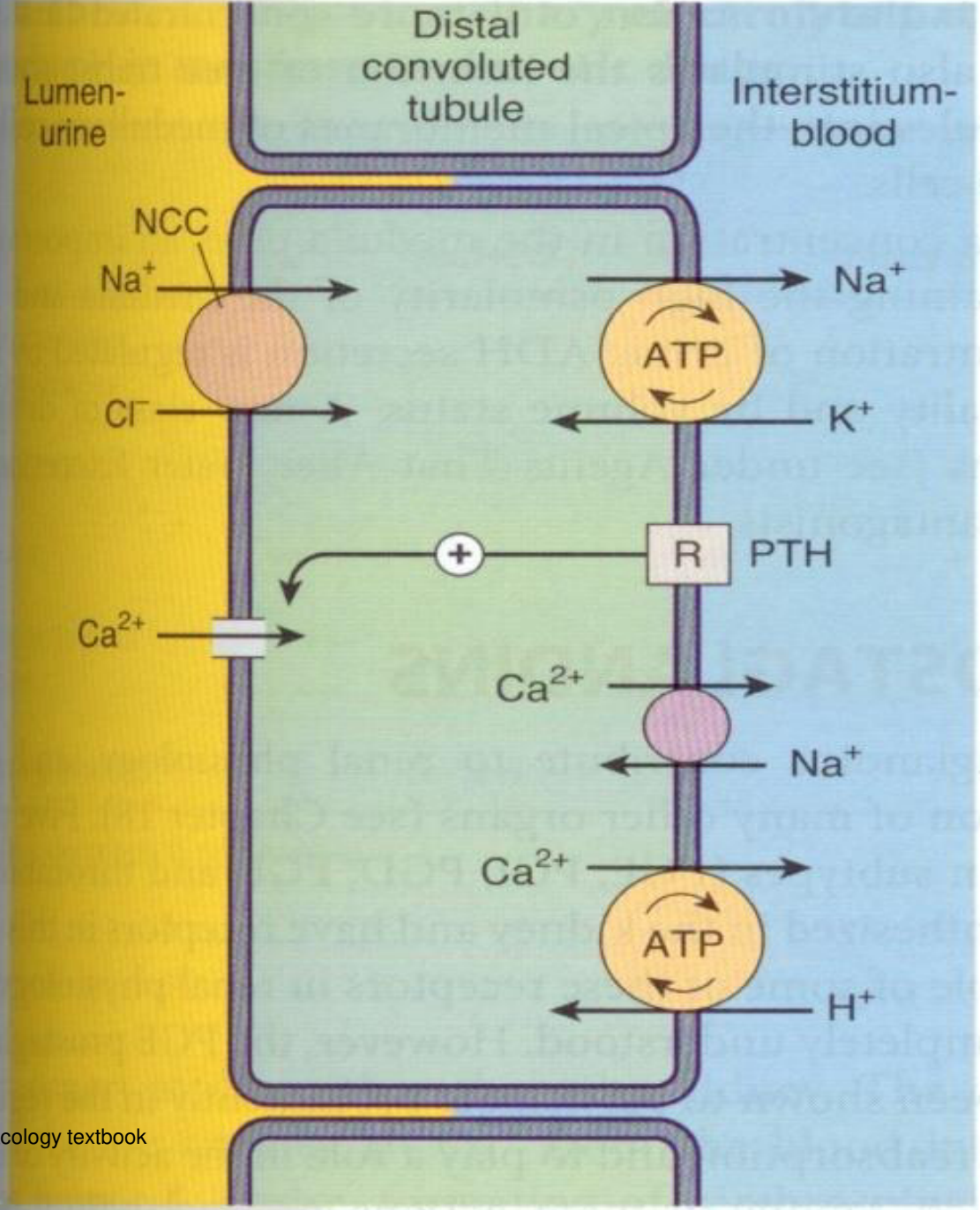
Thiazides and associated agents

Pharmacokinetics:

Effects are apparent within 1-2 hours
secretion by proximal tubule

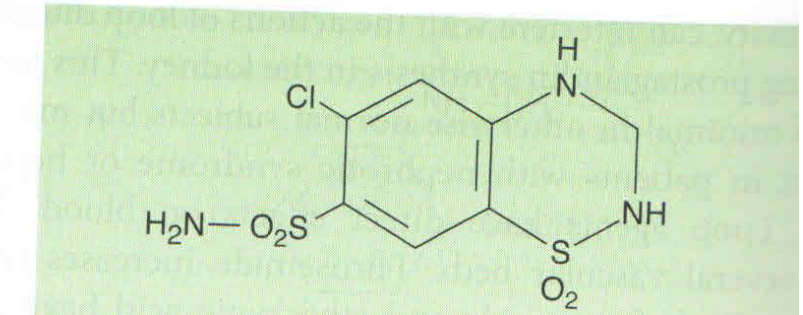
Pharmacodynamics:

Primary site of action: early segments of the distal tubule
They are ineffective if GFR < 20-30 ml/min.
Neither acidosis nor alkalosis influence their effects

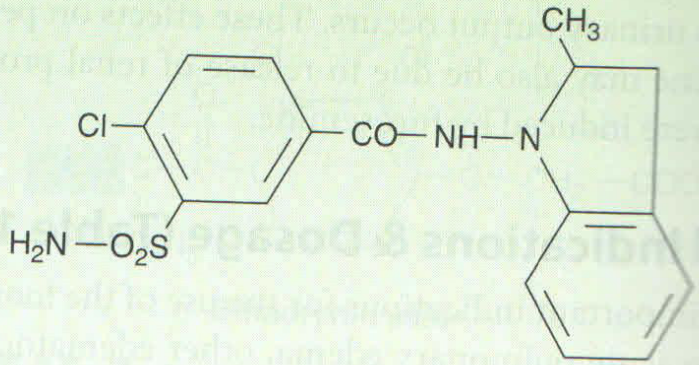


Katzung et al. Basic and Clinical Pharmacology textbook

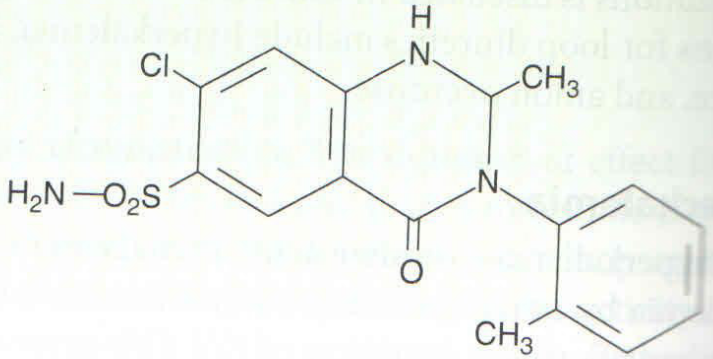
FIGURE 15–4 Ion transport pathways across the luminal and ba-



Hydrochlorothiazide



Indapamide



Metolazone

Thiazides and associated agents

Effects on urine electrolyte composition	Clinical indications	Toxicity
Na^+ ↑ Cl^- ↑	cardiac insufficiency chronic hepatic- and renal diseases	
Early segments of the distal tubule: Ca^{2+} ↓ Mg^{2+} ↑ K^+ ↑ H^+ ↑	idiopathic hypercalciurina	hypomagnesemia metabolic alkalosis with potassium depletion paresthesias Hyperuricemia,risk for gout attack
prox. tub. : secretion of uric acid ↓ and urea ↓		
Collecting tubules: inhibition of phosphodiesterase	nephrogenic diabetes insipidus	
	Extrarenal effects:	
Sensitivity of vessel wall for NA ↓ diabetogenic effects	**hypertension**	hyperlipidemia hyperglycemia

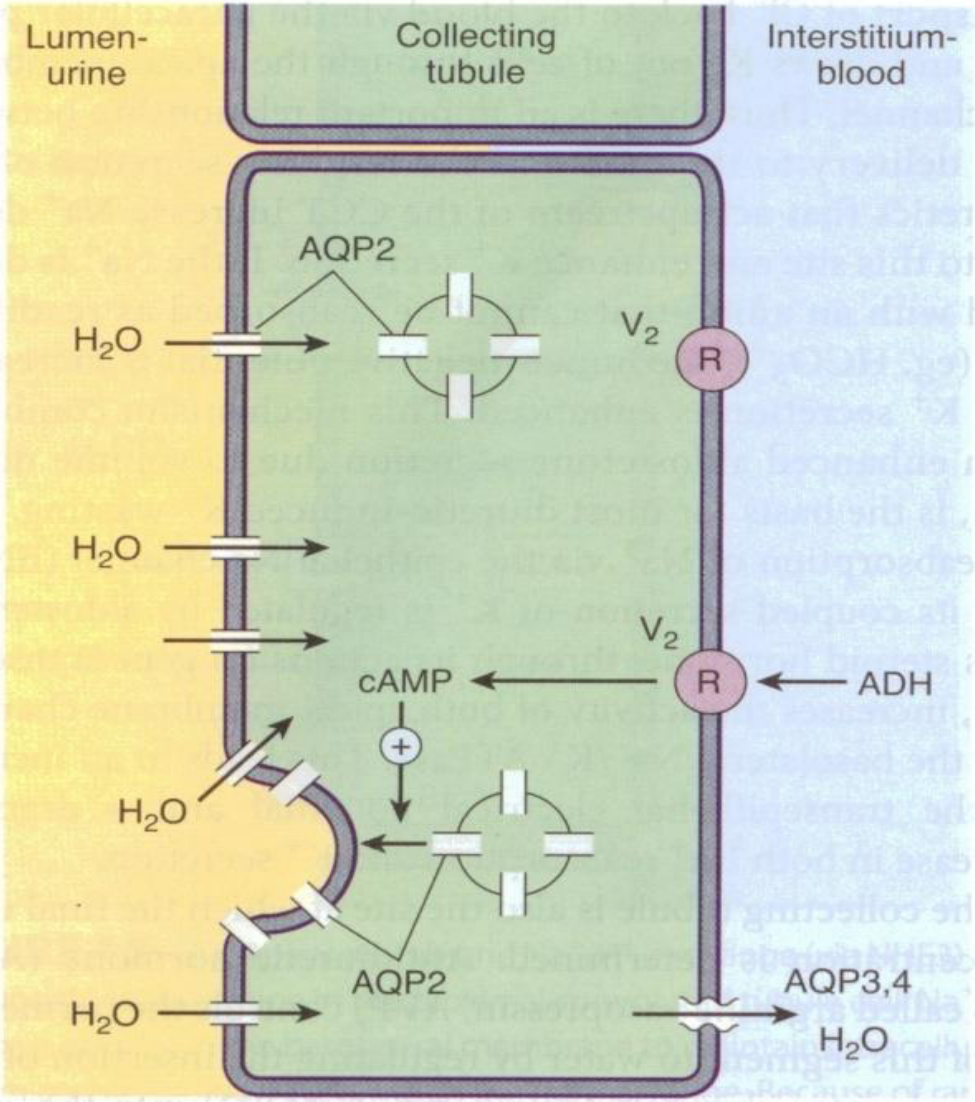
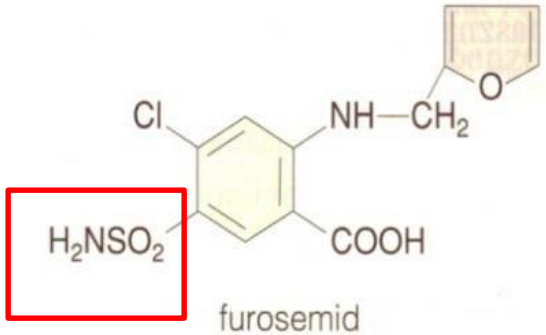
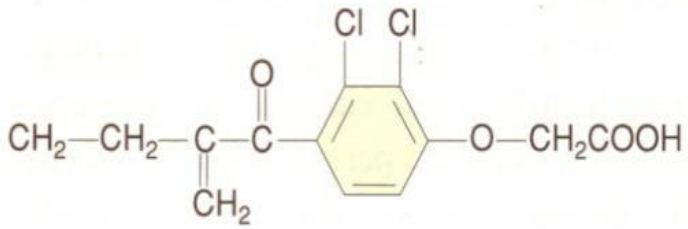


FIGURE 15–6 Water transport across the luminal and basolateral membranes of collecting duct cells. Above, low water permeability exists in the absence of antidiuretic hormone (ADH). Below, in the presence of ADH, aquaporins are inserted into the apical membrane, greatly increas-

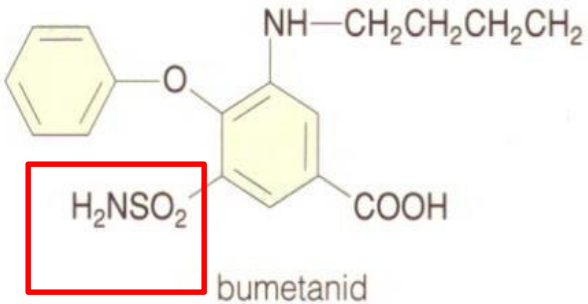
Loop agents = high-ceiling diuretics



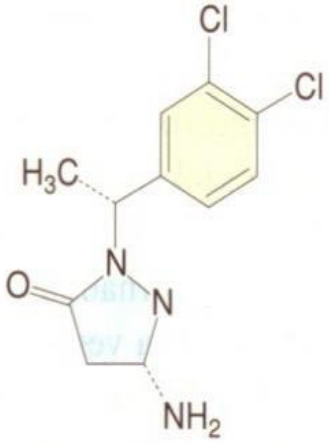
furosemid



etakrinsav



bumetanid



muzolimin

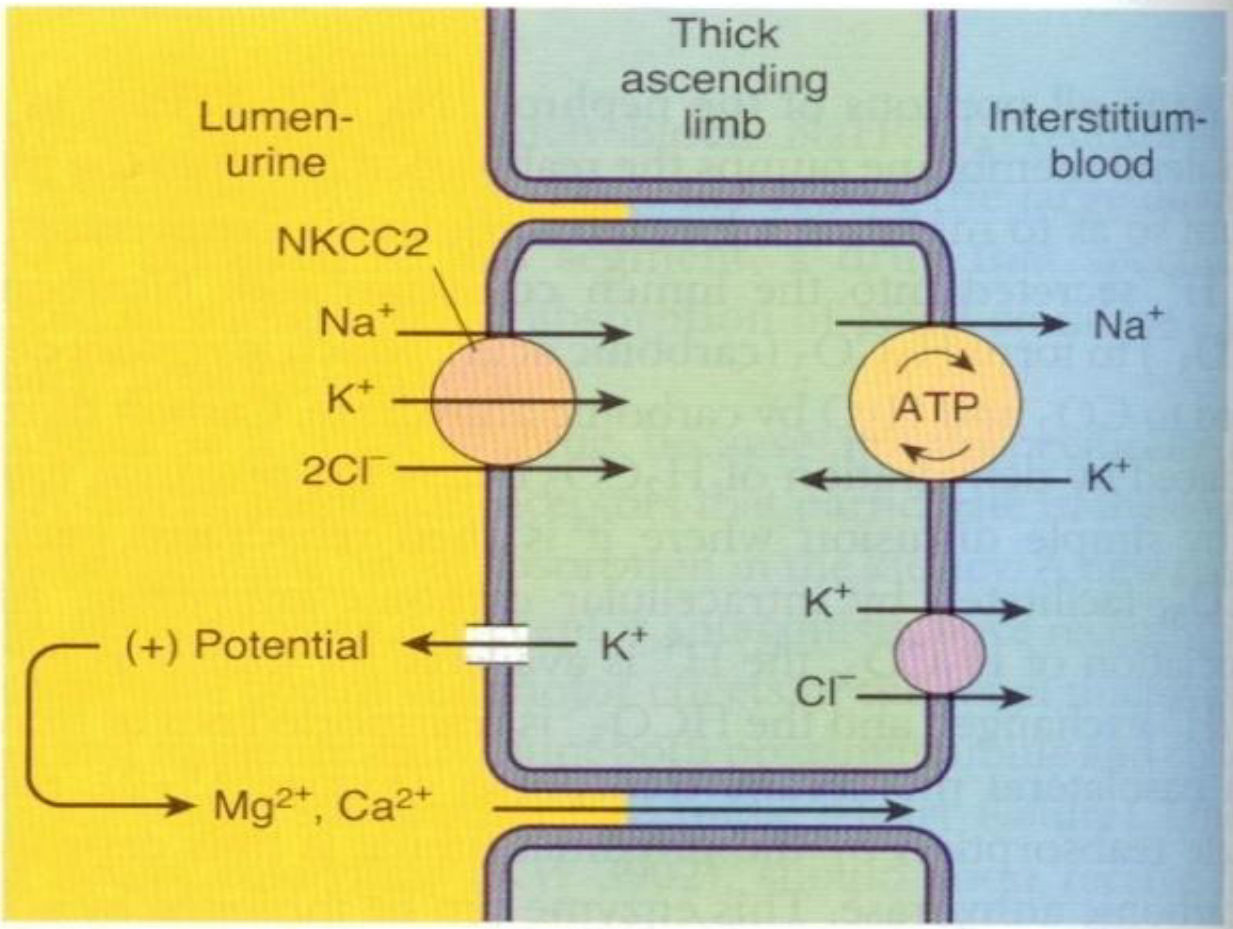


FIGURE 15–3 Ion transport pathways across the luminal and basolateral membranes of the thick ascending limb cell. The lumen positive electrical potential created by K^+ back diffusion drives divalent (and monovalent) cation reabsorption via the paracellular pathway. NKCC2 is the primary transporter in the luminal membrane.

Loop agents = high-ceiling diuretics

Pharmacokinetics:

	p. o.	i. v.
Diuretic effect appears within	60 min.	5 min.
Active secretion by prox. tub.		

Pharmacodynamics:

Primary site of action: the active chloride transport in the thick ascending limb of the loop of Henle

Furosemide and its derivatives inhibit carbonic anhydrase activity in the prox. tubules.

They are ineffective even in the case of anuria.

Loop agents

Effects on urine electrolyte composition	Clinical indications	Toxicity
GFR ↑ **thick ascending limb of the loop of Henle:** Cl^- ↑ Na^+ ↑ K ↑ concentrating power of the kidney ↓	Refractory oedema Acute renal failure Acute pulmonary oedema Cerebral oedema Congestive heart failure	Hypokalemia
Br^- ↑ F^- ↑ I^- ↑	Bromine, fluorine, iodine intoxication	
Ca^{2+} ↑	Hypercalcemia	
Dist. tub. : K^+ ↑		hypokalemia
Prox. tub. : uric acid ↓ **Furosemide:** inhibits carbonic anhydrase,		hyperuricemia metabolic alkalosis
	Extrarenal effects:	
Change of composition of endolymph Furosemide derivatives: diabetogenic potential		ototoxicity hyperglycemia

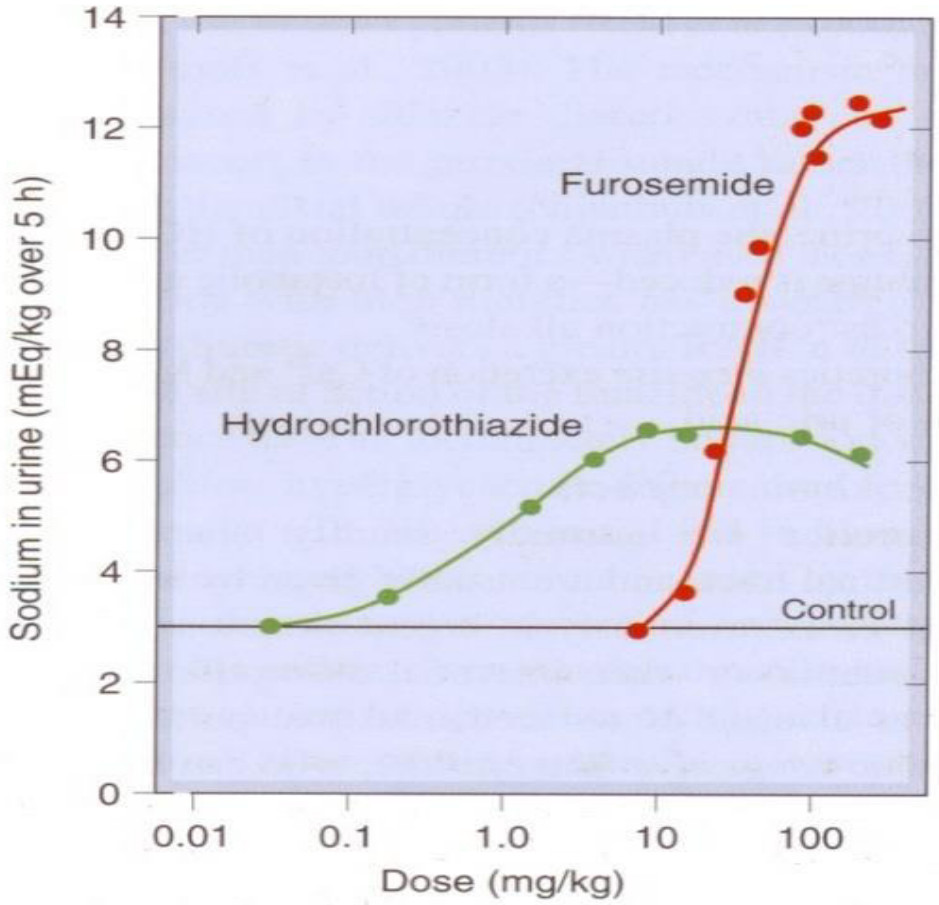


Fig. 24.6 Dose–response curves for furosemide (frusemide) and hydrochlorothiazide, showing differences in potency and maximum effect 'ceiling'. Note that these doses are not used clinically. (Adapted from Timmerman R J et al. 1964 Curr Ther Res 6: 88.)

Rang and Dale's Pharmacology textbook

Potassium-sparing diuretics
I. Spironolactone and its metabolites = aldosterone antagonists

Pharmacokinetics:

Poorly absorption orally → delayed onset of action (several days)

in liver: Spironolactone → canrenone (active)

↓ ↑

canrenoate (inactive)

eplerenone

Pharmacodynamics:

primary site of action: collecting tubules

Competitive aldosterone antagonists

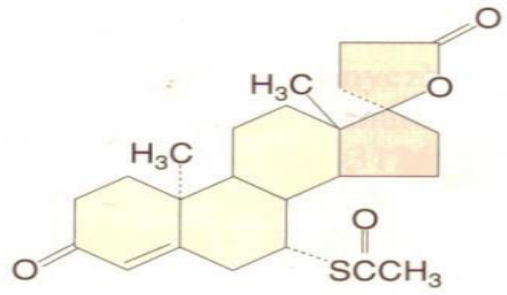
Poor effect → combined use with other diuretics

for ameliorating their hypokalemic effects of other diuretics

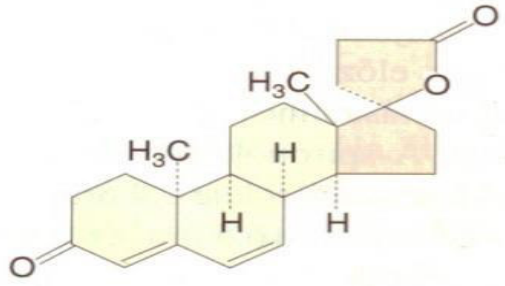
Drug Interactions: CYP3A4 enzyme !!!

e.g. ketoconazol increases plasma concentration of spironolactone

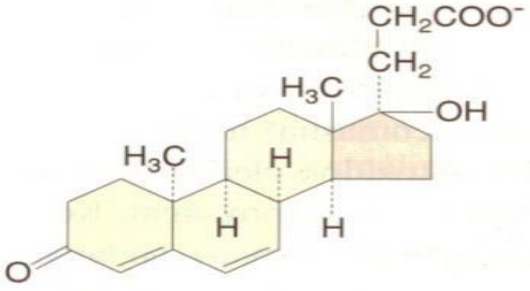
ért benne a 11-, 18-, 21- és 17-hidroxilt.



spironolacton



canrenon



canrenoat

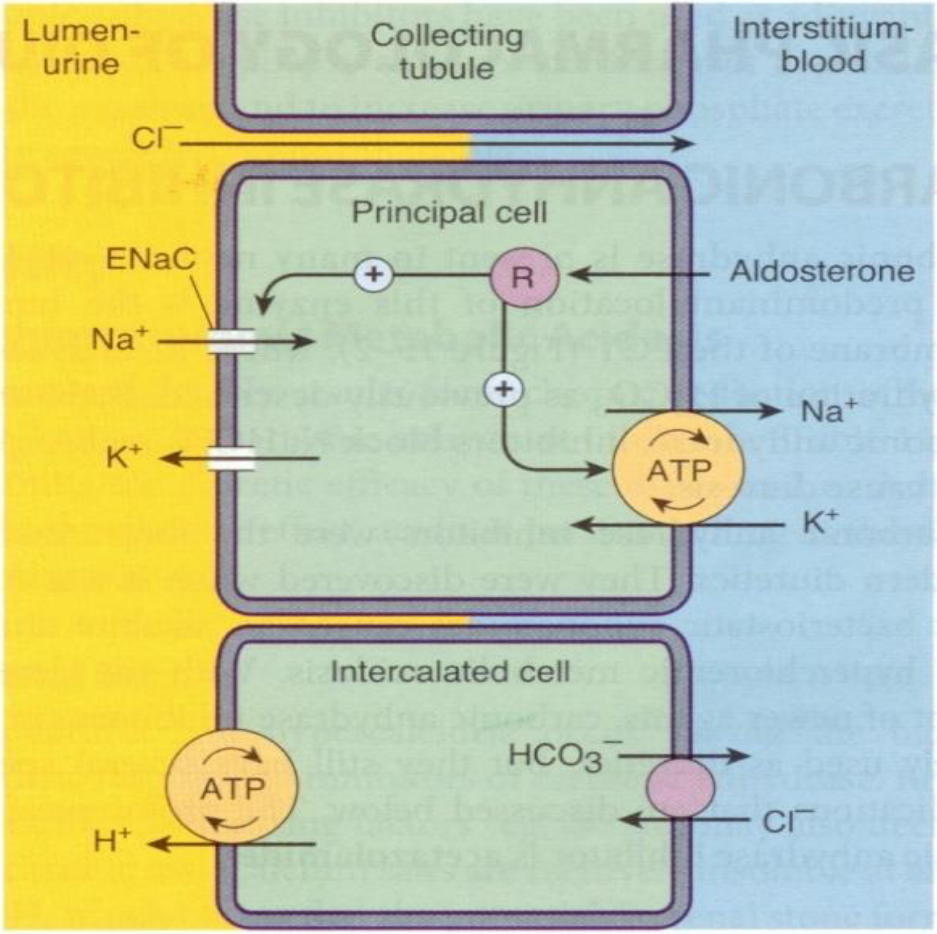


FIGURE 15–5 Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells. Inward diffusion of Na^+ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl^- and efflux of K^+. (R, aldosterone receptor.)

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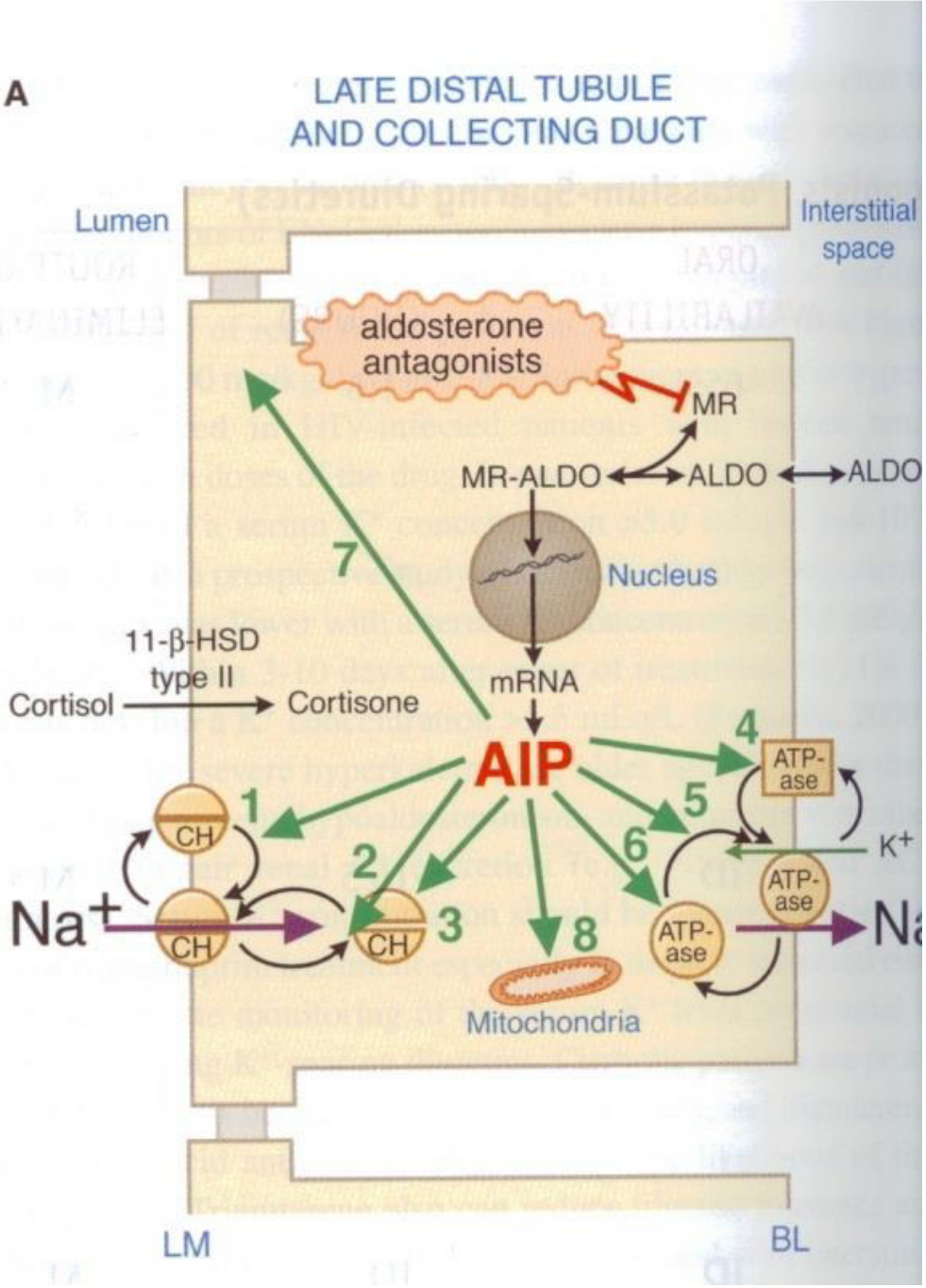
AIP =

aldosterone induced protein

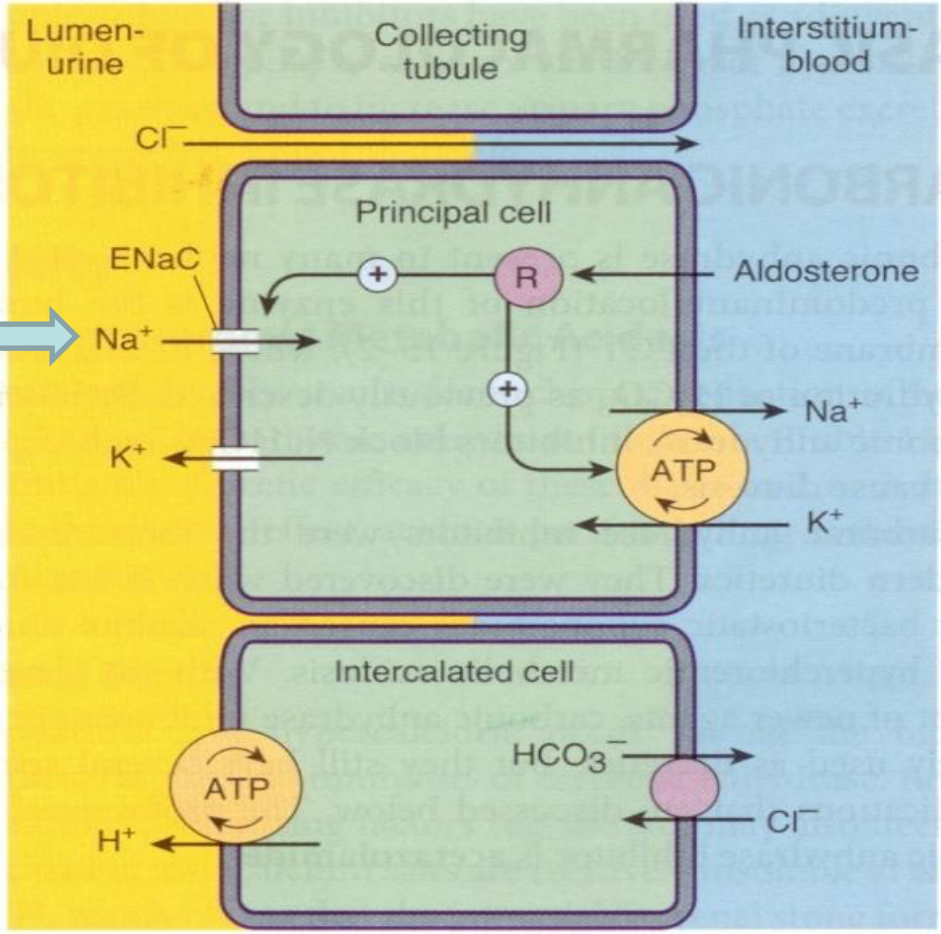


Aldosterone antagonists

Effects on urine electrolyte composition	Clinical indications	Toxicity
Dist. tubules and collecting tubules: $Na^+ \uparrow$ $Cl^- \uparrow$ Dist. tubules: $K^+ \downarrow$	Primary hyperaldosteronism: Conn's syndrome secondary hyperaldosteronism: hypertension hepatic cirrhosis nephrotic syndrome congestive heart failure	 hyperkalemia metabolic acidosis
	Extrarenal effects:	
They react on steroid receptors		gynecomastia impotence androgen effects tumotigenic in rats

Potassium-sparing diuretics
II. Non aldosterone antagonists

inhibition of sodium channels



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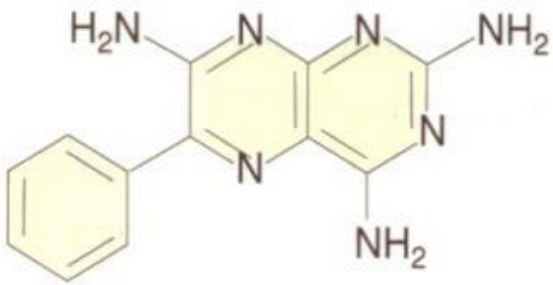
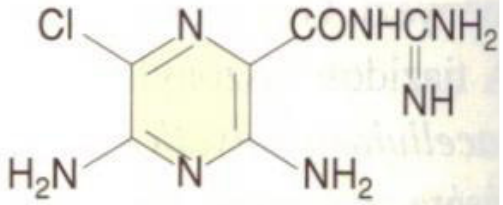
Potassium-sparing diuretics II.



triamteren



amilorid

Potassium-sparing diuretics
II. Non aldosterone antagonists

Triamterene
Amiloride

Pharmacokinetics: They are available only for oral use

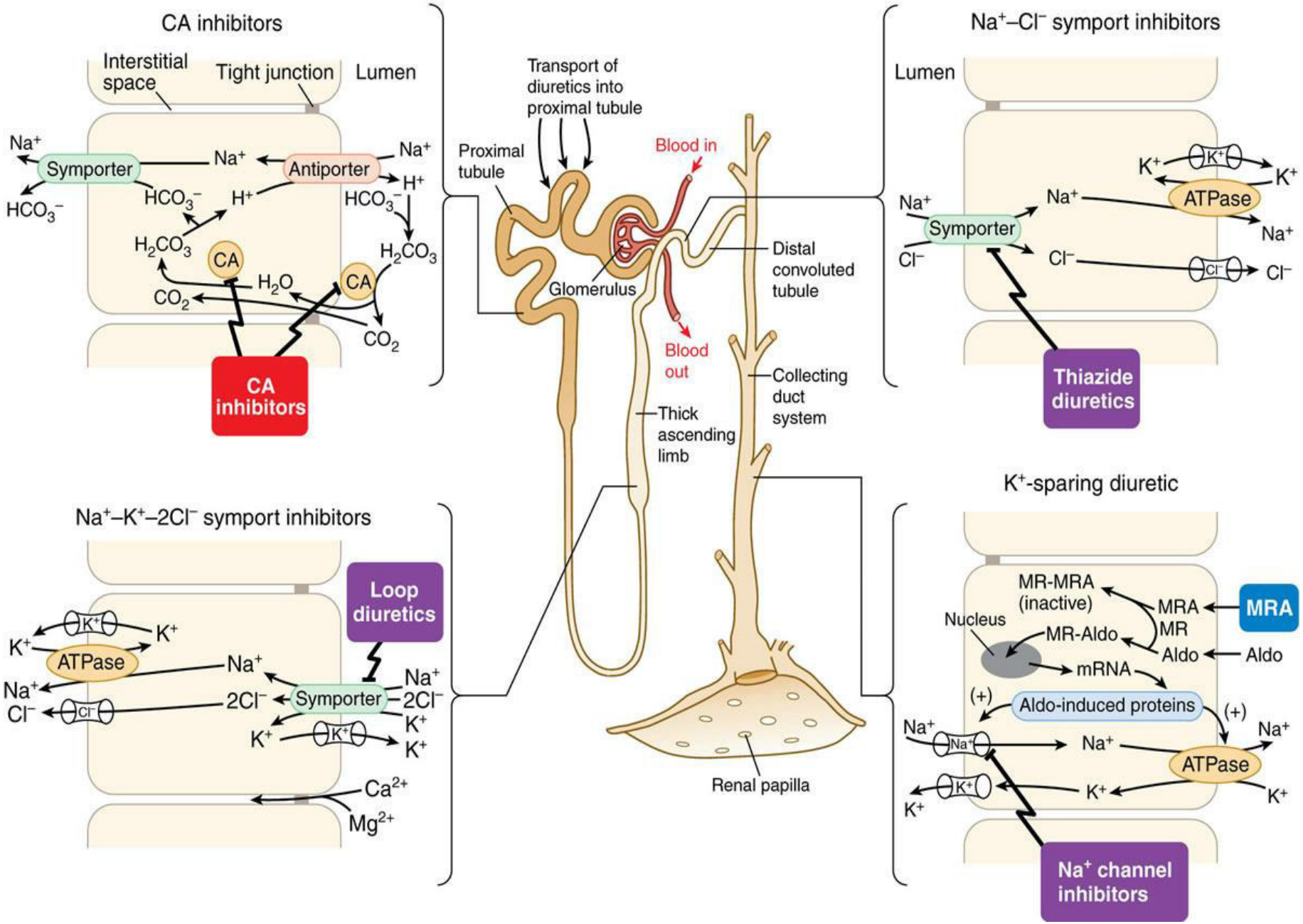
Pharmacodynamics:

primary site of action:	**Effect on urine electrolyte content:**
collecting tubules But they have no aldosterone antagonist effect	$Na^+ \uparrow K^+ \downarrow$

Toxicity: hyperkalemia – impairment of renal failure

Interaction: Triamterene + indomethacin → acute renal failure

Extrarenal effect: amilorid therapy in cystic fibrosis locally in spray to bronchi



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Causes of therapeutic failure

1. Interruption of law salt diet
   Negative sodium balance can't be achieved

2. Self-limited effects
   i. e. carbonic anhydrase inhibitors

3. The sites of action along nephron are damaged by different renal diseases

4. Function of proximal tubule is damaged
   i. e, organic acid diuretics

5. Competition for secretory system of proximal tubules:
   Interactions between medicaments
   i. e. Probenecid
   penicilline derivatives

Prevention of formation of kidney stones in nephrolithiasis

Calcium phosphate or Ca oxalate stones:

Calcium nephrolithiasis idiopathica recurrentis: thiazides

Stones containing uric acid:

pH of the urine has to be shifted to the basic direction to pH 6,2-6,7

citric acid 8% + sodium citrate 12% + potassium citrate 12% = Solutio nephrolitholytica FoNo

citric acid 10% + sodium citrate 6% = Shohl oldat

citric acid 270 mg + magnesium citrate 180 mg + sodium citrate 723 mg = Magurlit granulates

allopurinol = Milurit tabl. 100 mg

Stones containing ammoniomagnesium-phosphate:

pH of the urine has to be shifted to the acidic direction to pH <6,5

ascorbinic acid = Vitamin C drg., inj

ammonium chlorate = Ammonium chloratum tabl. 500 mg – ONLY for short-term therapy !!!!!

Desmopressine , selective V2 agonist

Antidiuretics

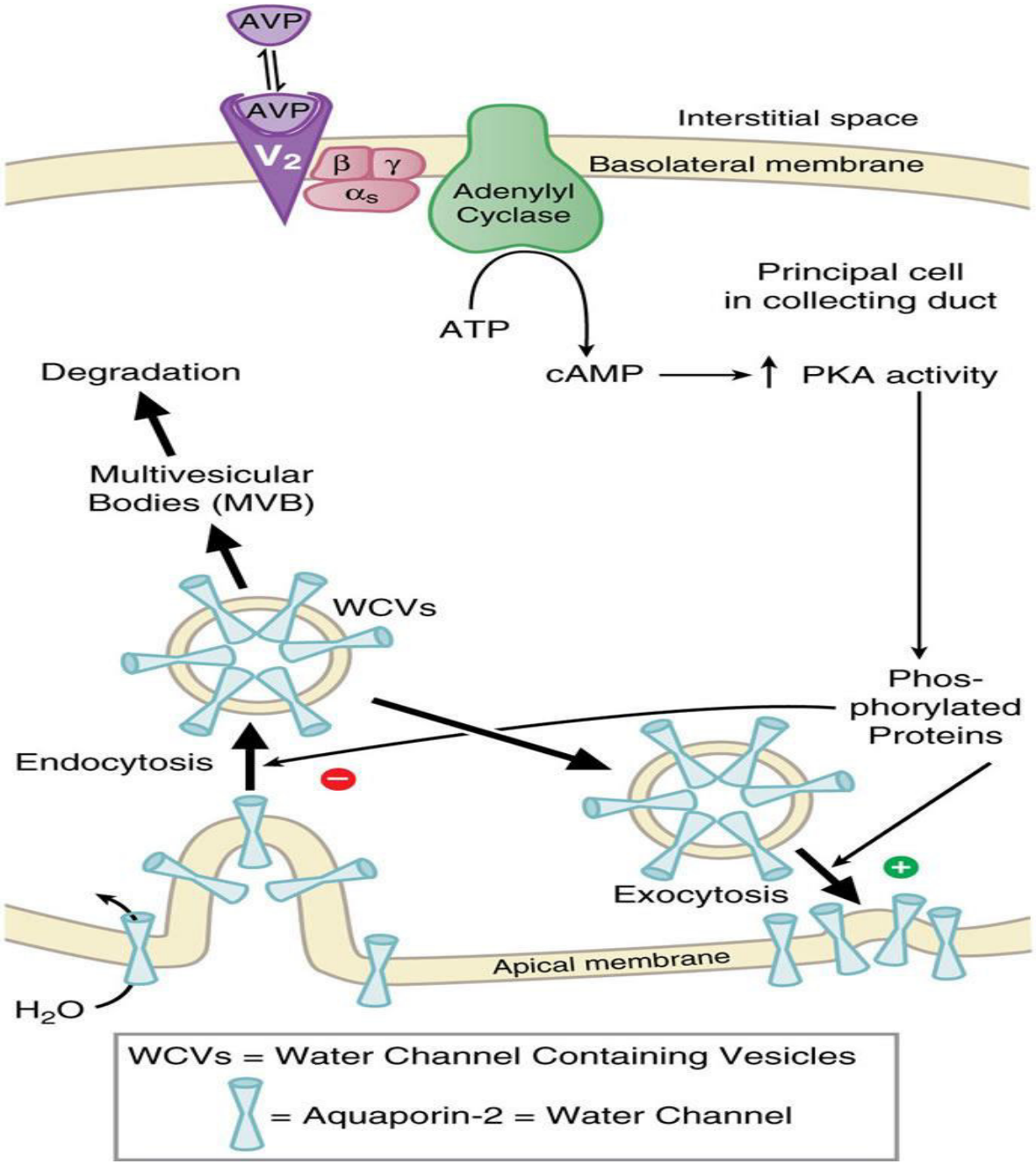
Desmopressin is a synthetic octapeptide, and an analogue of human hormone argininine vasopressin with antidiuretic and coagulant activities.

Target: V2 receptors in renal collecting ducts.

This agent also increases nitric oxide (NO) production via activation of endothelial NO synthase, thereby induces afferent arteriolar vasodilation.

Furthermore, desmopressin stimulates the release of factor VIII from endothelial cells mediated through V1a receptor, thereby promotes blood coagulation. It also stimulates the release of von Willebrand factor (vWF) from the endothelial cells, thereby increasing the levels of vWF.

Clinical indications: diabetes insipidus
Haemophilia A
von Willebrandt disease



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