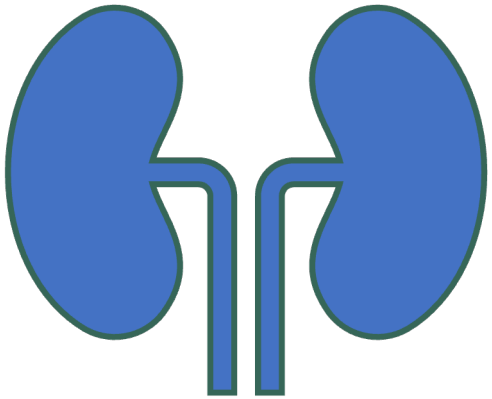

RENAL PHYSIOLOGY (VANDERS CHAPTER 5-7):

TUBULAR REABSORPTION/SECRETION, SODIUM AND WATER HANDLING, BLOOD PRESSURE REGULATION

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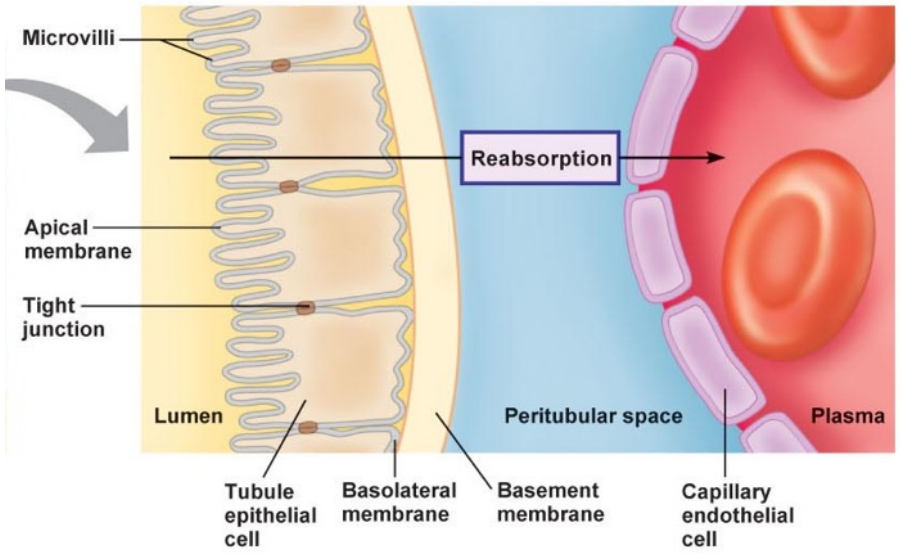
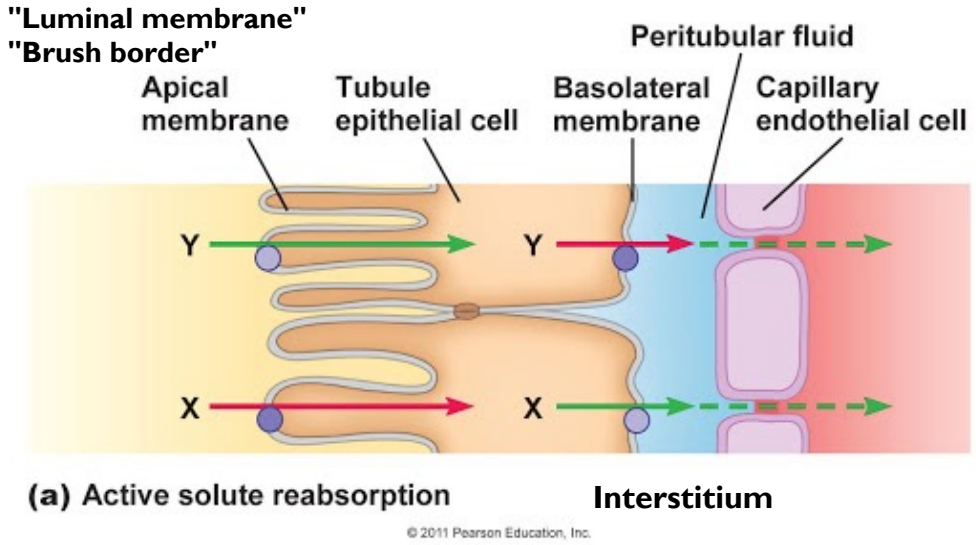
OUTLINE

1. Tubular reabsorption and secretion – focused on Na and Cl
   - K+, Ca+ and Phos to be discussed in the next BR
2. Urine concentration
3. Blood pressure regulation

RENAL TUBULAR REABSORPTION

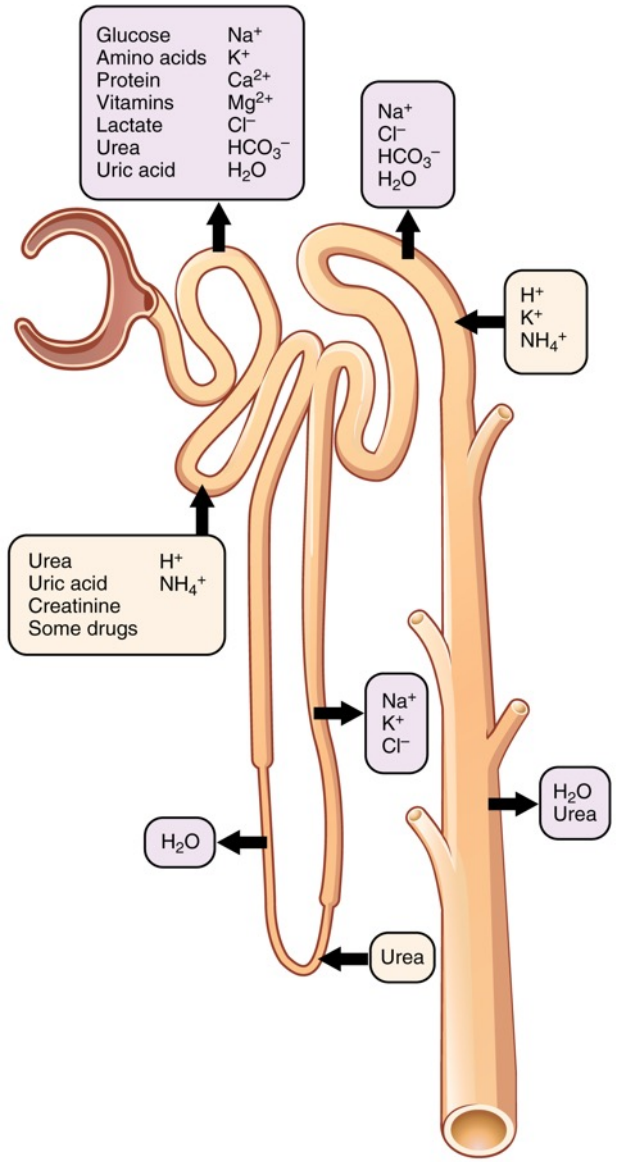
- Reabsorption = the movement of filtered solutes and water from the lumen of the tubule back into the plasma.
- Solutes must pass across 2 barriers to get from lumen into blood stream
  - Tubule epithelium and the capillary endothelium





RENAL TUBULAR SECRETION

- Secretion = movement of molecules from the plasma into the renal tubules to be included in the filtrates
- Secreted substances include K+, H+ ions, various endogenous substances (e.g. creatinine), and drugs



SUMMARY OF TUBULAR REABSORPTION/SECRETION

WATER HOMEOSTASIS

- Generally, the reabsorption of water is by osmosis and is secondary to reabsorption of solutes
- However, this is dependent on the patient's hydration status:
- The kidneys can therefore excrete water in excess of salt and vice versa - "separate salt from water"
- Renal tubular segments can reabsorb more solute than water which leaves a large volume of dilute tubular filtrate to enter the cortical collecting ducts
  - During adequate or overhydration, most of the water passes through and becomes urine
  - During dehydration, majority of the dilute urine is reabsorbed which leaves a small amount of dilute urine

WATER HOMEOSTASIS

- The two major sources of body water:
  - Metabolically produced water – from oxidation of CHO
  - "Ingested water" (from liquids or food)
- Sensible losses = loss that can be perceived by the senses and can be measure
  - GIT (defecation), kidneys (urination), lactation (if pregnant)
- Insensible losses = continuous loss of water by evaporation from the skin cells and the lining of respiratory passages for humidification
  - Approx. 20-30 mL/kg/day

WATER HANDLING IN THE KIDNEYS

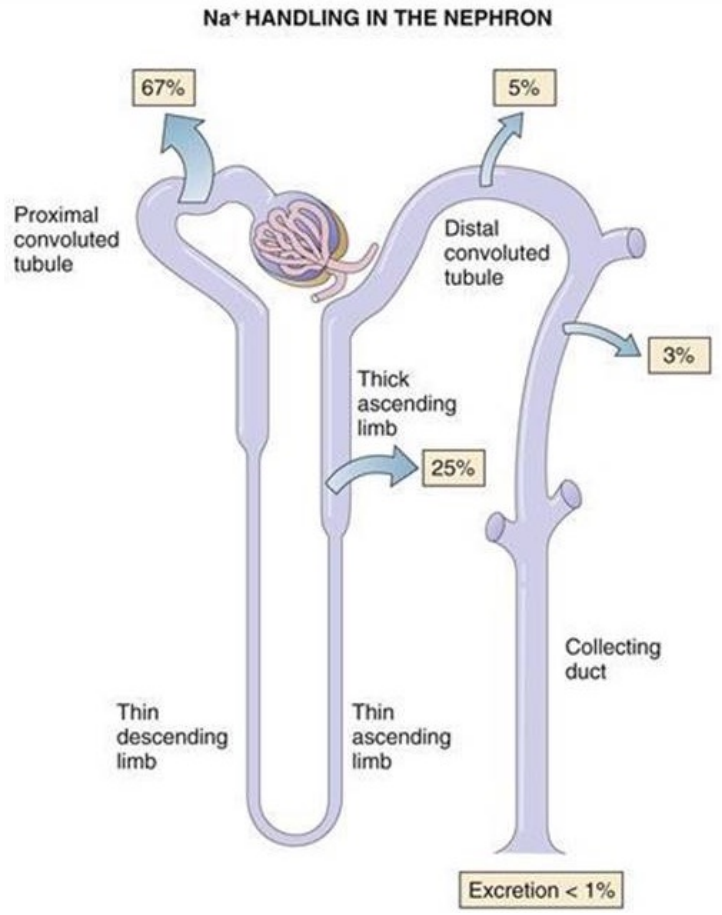
- Water reabsorption occurs in the PCT (65%), descending LOH (10%) and collecting duct system (variable)
  - PCT and descending LOH have **high water permeability**
  - The ascending LOH and DCT are **impermeable** to water
  - Water permeability in CD is intrinsically low but can be marked increased if needed
- The amount of Na+ reabsorbed is always much higher than water and it occurs in different segments of LOH -- "separating salt from water"
  - Na+ reabsorbed in ascending LOH and DCT

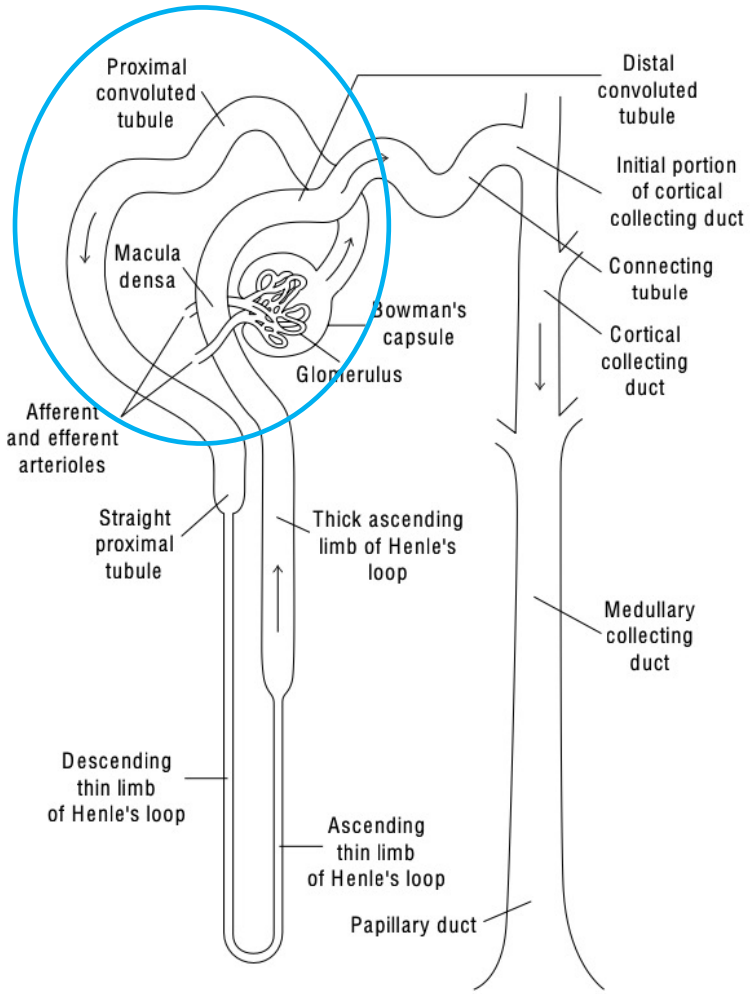
MOVEMENT OF WATER

- Water movement is largely dictated by the osmotic gradient
- The luminal membrane is not naturally permeable to water and water can move via:
  - Simple net diffusion through lipid bilayer
  - Through aquaporins in the plasma membrane of tubular cells
  - Through tight junctions in between tubular cells
- Basolateral membrane is also permeable to water due to presence of aquaporins

SODIUM HANDLING IN THE KIDNEYS

- Sodium reabsorption occurs in various locations
  - 65% in PCT
  - 25% in thin + thick ascending loop of Henle (LOH)
  - 5% in DCT
  - 5% in collecting duct
- Final urine contains <1% of total filtered Na
- Na+ reabsorption is driven by Na/K ATPase located on basolateral membrane
  - The pumps keep the intracellular [Na+] lower than the interstitium
  - Together with tubular epithelial cells having a negative charge, luminal Na+ ions enter the cells passively down their electrochemical gradient



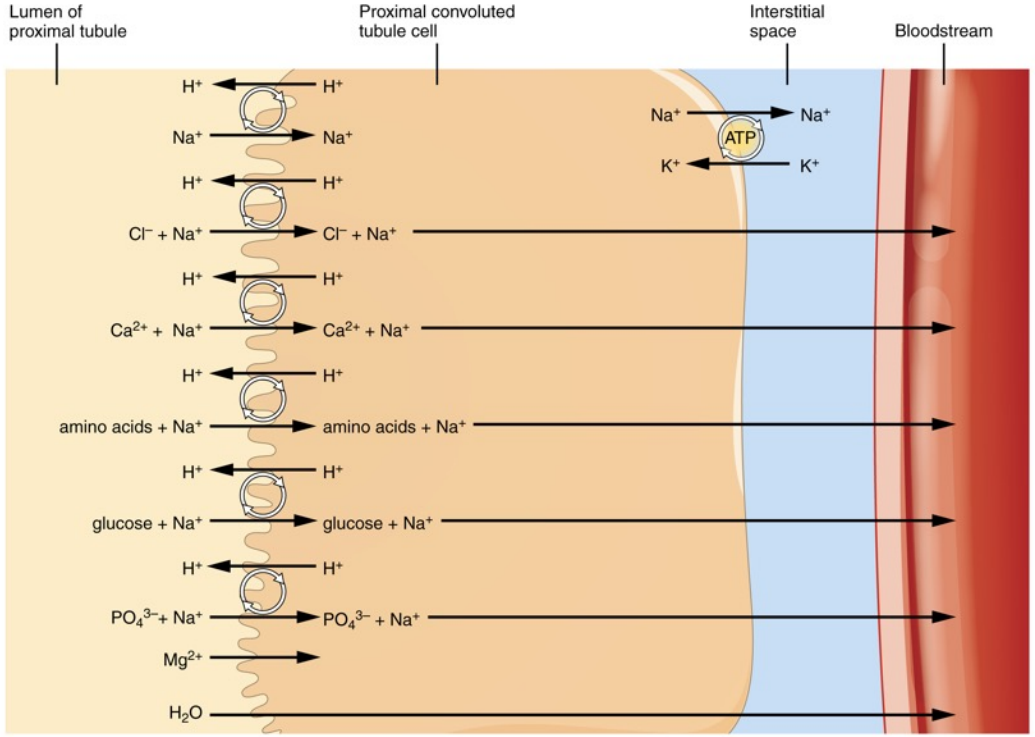


PROXIMAL CONVOLUTED TUBULE (PCT)

REABSORPTION IN PCT

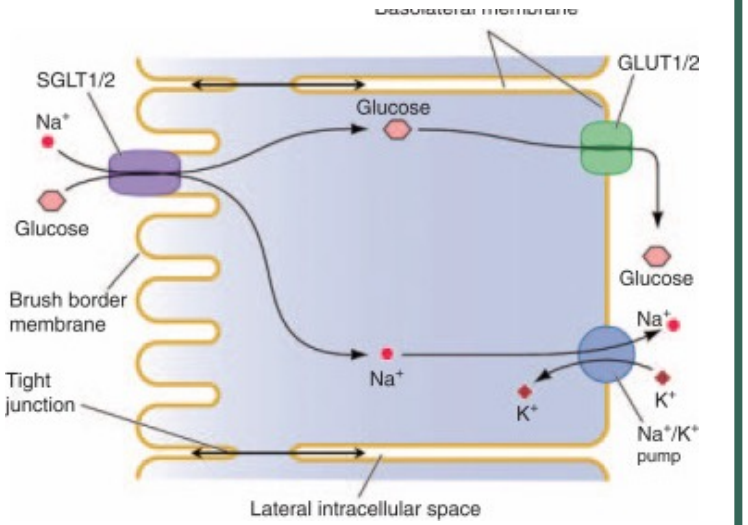
- Proximal tubules is the main site for reabsorption of organic nutrients
- 3 characteristics to aid in massive absorption:
  - Luminal membrane contains microvilli to increase surface area
  - PCT cells contain large number of mitochondria to supply ATP for active transport
  - Contains tight junctions that are permeable to small solutes and water, allowing diffusion by paracellular transport
- Reabsorption via active transport with the "uphill" step being across the luminal membrane, against the electrochemical gradient
  - Symporters and antiporters (exchangers) are often coupled with sodium
  - Manifest a degree of specificity – a transporter selectively takes up one or few substances only

REABSORPTION IN PCT



- Glucose, sodium, chloride, HCO3-, phosphate, urea, amino acids, water-soluble vitamins, lactate, and ketoacids (acetate, acetoacetate, beta-hydroxybutyrate) are all absorbed in PCT
  - PCT reabsorbs virtually all of amino acids and glucose
- Urea reabsorbed paracellularly
- Transporters located on luminal side
  - Symporters exist for Na/glucose, Na/amino acids, Na/phosphate, and Na/lactate
  - Na/H exchanger is the only antiporter

GLUCOSE REABSORPTION IN PCT



- Glucose is freely filtered at glomerulus → reaches the proximal tubule
- PCT reabsorption involves **sodium-dependent glucose symporters (SGLT)** across the apical membrane → glucose enters tubular cells → exits apical membrane into the interstitium via **glucose transporters (GLUT 1, 2)**
  - Utilizes Na+ movement down electrochemical gradient to the "uphill" reabsorption of glucose
  - SGLT-2 in early PCT and SLGT-1 in late PCT
    - SGLT2 is low affinity, high-capacity whereas SGLT1 is high affinity, low-capacity → scavenge residual glucose molecules
- Tm-limited system
  - Glucosuria occurs when the renal threshold is exceeded OR if tubular injury occurs
  - Renal threshold = the plasma level at which the glucose first appears in the urine more than normal amount (Dogs: 180-200 mg/dL. Cats: 280-290 mg/dL)

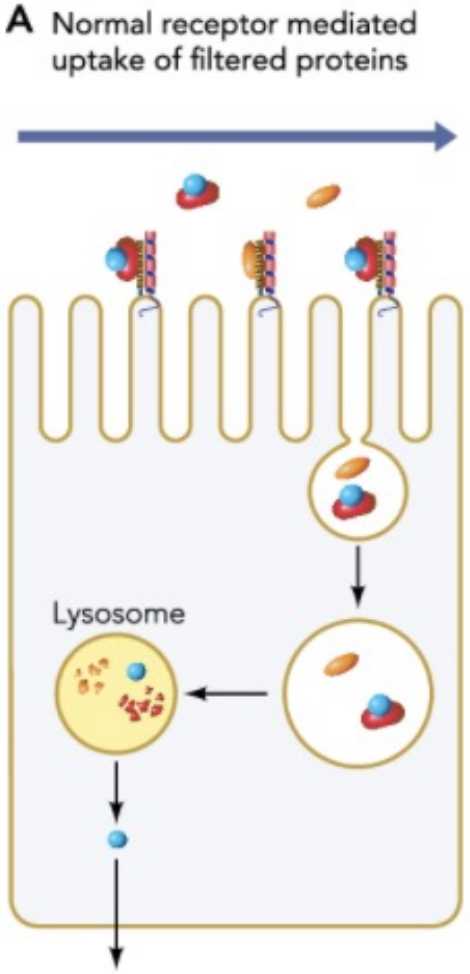
TRANSPORT MAXIMUM (TM)

- The point at which increase in concentration of a substance does not result in an increase in movement of a substance across a cell membrane
  - Certain molecules can reach an upper limit to the speed at which they transport (e.g. glucose, ketoacids, PAH)
  - Once Tm is exceeded, the amount can't be reabsorbed anymore and spills over into tubular fluid (e.g. Hyperglycemia leading to glucosuria)

PROTEIN UPTAKE IN PCT

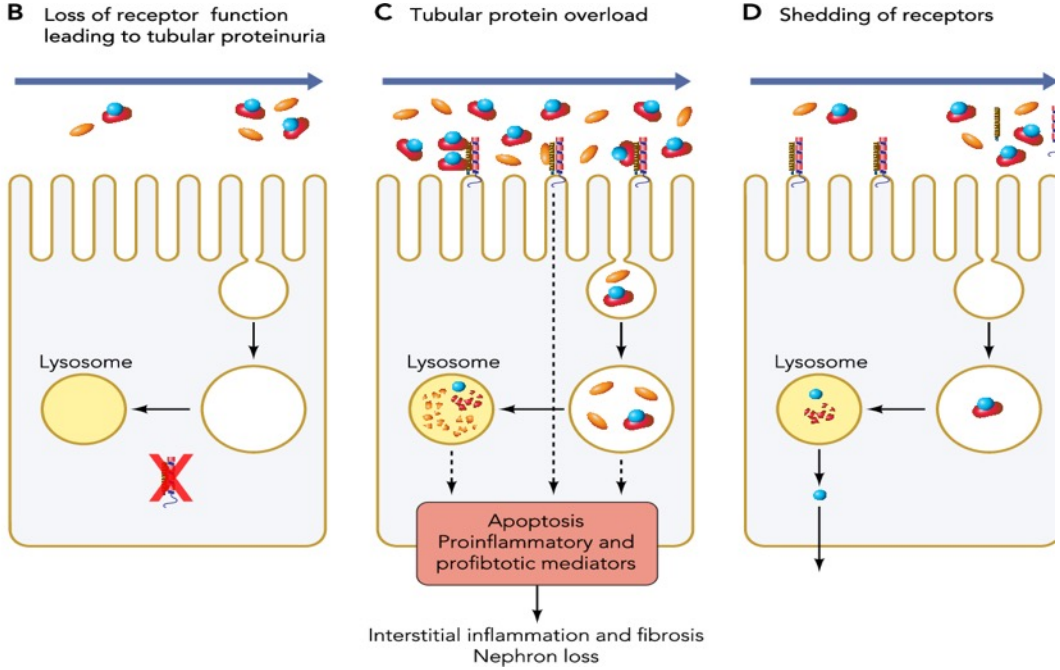
- Small and medium-sized proteins (e.g. angiotensin, insulin) are filtered through glomerulus and reach proximal tubules
- Even a small amount of albumin (0.02% of plasma albumin) crosses the glomerulus
  - However, the amount is negligible due to the relatively huge volume of fluid filtered per day
- Uptake, rather than absorption, is used to describe their transport from lumen into epithelial cells as they are transported **intact**
  - Subsequently degraded into constituent amino acids prior to being transported into cortical interstitium

LARGE PROTEIN UPTAKE IN PCT



- Protein uptake occurs via endocytosis at the luminal membrane
  - Active process
  - Triggered by binding of protein molecules to specific receptors
- Once endocytosed, pinched-off intracellular vesicles merge with lysosomes → lysosomes degrade protein to low-molecular-weight fragments (I.e. amino acids)
  - Rate of endocytosis parallels the concentration of the protein in glomerular filtrate until maximal rate of vesicle formation occurs
- Amino acids exit the cells across basolateral membrane into interstitial fluids → peritubular capillaries

DEVELOPMENT OF PROTEINURIA

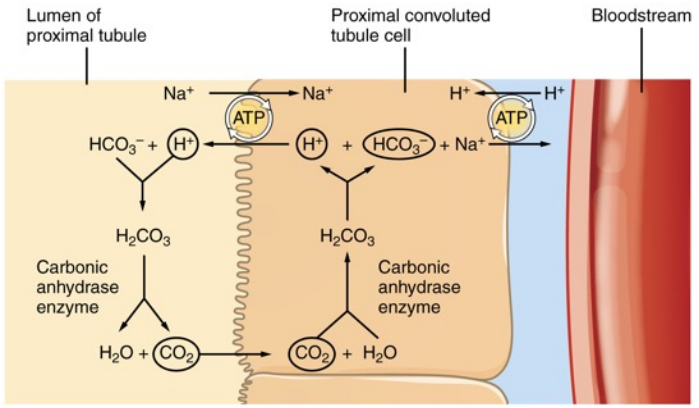


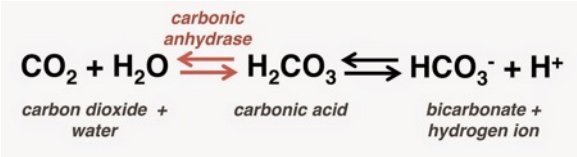
- As discussed, protein uptake is a receptor-mediated process
- Once the tubules' function reaches maximum capacity (I.e. all receptors are bound with protein overload), the remaining proteins in the filtrate pass through into the urine
- Disease state (e.g. loss of receptor function [genetic] or shedding of receptors [in diabetes]) can also occur
- Recommend reading: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3354822/

SMALLER PROTEIN UPTAKE IN PCT

- E.g. very small peptides (e.g. angiotensin II)
- Freely filtered at glomerulus and catabolized into amino acids in PCT lumen via peptidases (on luminal membrane)
- Amino acids are then reabsorbed via Na/amino acid symporters

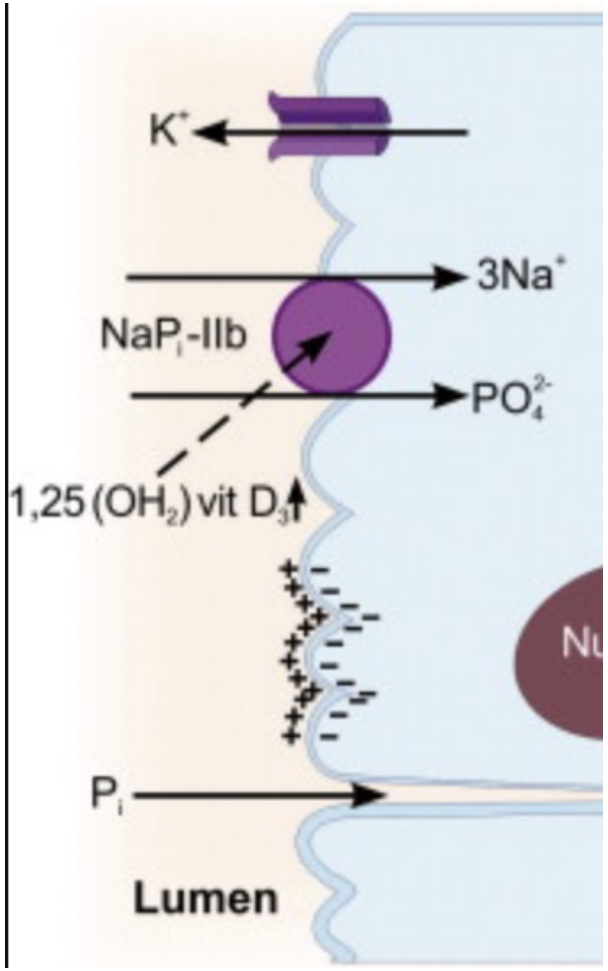
BICARBONATE REABSORPTION IN PCT





- Renal carbonic anhydrases (CA) are mostly located intracellularly, but some are present on the brush border
- In the lumen, HCO3- combines with H+ to form carbonic acid (H2CO3)
  - Na+/H+ exchanger (NHE) moves Na+ into cell and H+ out of cells to maintain H+ pool
- 2CO3 catalyzed by CA into H2O and CO2
  - Both diffuse across the apical membrane into cells
- Within the cell, the reverse rx occurs to produce HCO3-
- HCO3- transported via Na/HCO3- cotransporter across basolateral membrane into the interstitium
  - Na/K ATPase maintains the Na+ gradient
  - H+ is recycled via NHE

PHOSPHATE REABSORPTION IN PCT



- Phosphate is freely filtered in the glomerulus
- Predominantly reabsorbed in the PCT
- **Sodium-phosphate cotransporter, NaPi-IIa** are located on the apical membrane → travels w/ Na+ down its electrochemical gradient
  - Incr PTH can reduce # of NaPi-IIa cotransporter in PCT → reduce PCT phosphate reabsorption → phosphate wasting

ANION AND CATION SECRETION IN PCT

- Both cations and anions are actively secreted in PCT
- Many of anions are filtered at glomerulus and secreted in PCT
  - Actively transported out of basolateral membrane (rate-limiting step) and out of the apical membrane via facilitate diffusion on various uniporters or sodium-dependent antiporters (organic anion transporters, OATs)
    - OATs are specific to anions but not specific ones
  - Anions are not very permeable through tight junctions
  - Tm limitation
  - Urate is another important anions
    - Freely filtered through glomerulus and almost all filtered urate is reabsorbed in early PCT
    - Active tubular secretion also occurs later in PCT → reabsorbed again in straight portion of PCT
    - Reabsorption is always greater than secretion and homeostatically balanced to maintain consistent plasma [urate]

ANION AND CATION SECRETION IN PCT

- Cations transport is similar to anions
- Moves across basolateral membrane via uniporters (organic cation transporters, OCT) → into lumen → exit via antiporter that exchanges a proton for the organic cation
- Tm limitation
- Many of them are not protein bound → undergo glomerular filtration + tubular secretion
- Some undergo passive reabsorption

ANION AND CATION SECRETION IN PCT

Anions

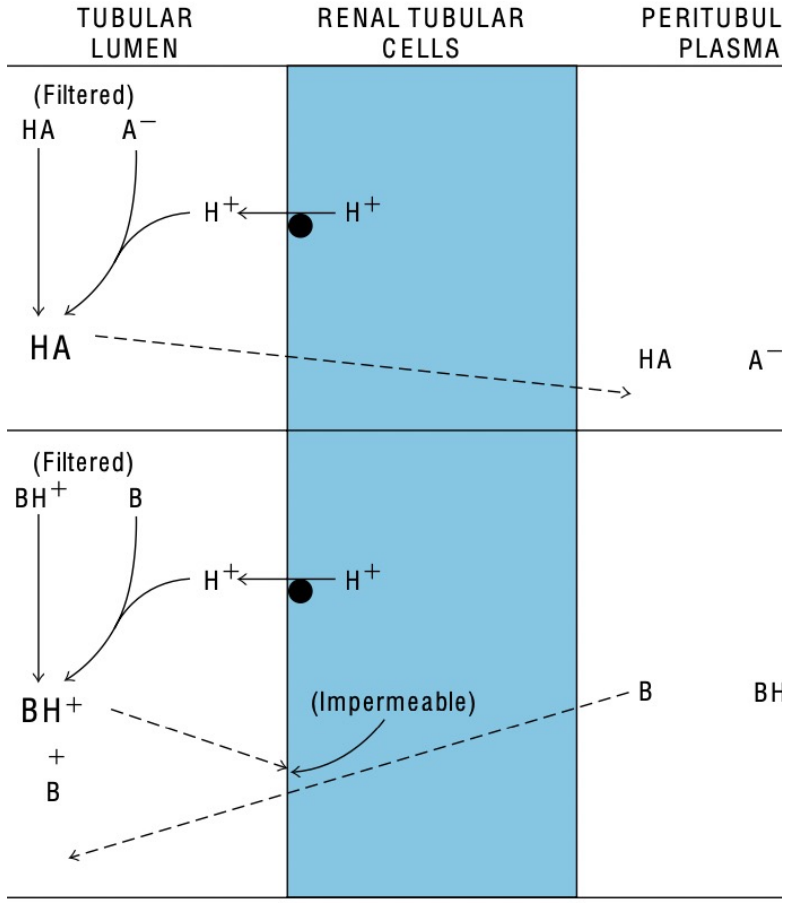
Endogenous substances	Drugs
Bile salts	Acetazolamide
Fatty acids	Chlorothiazide
Hippurates	Furosemide
Hydroxybenzoates	Penicillin
Oxalates	Salicylates
Prostaglandins	Sulfonamides
urate	

Cations

Endogenous substances	Drugs
Acetylcholine	Atropine
Choline	Isoproterenol
Creatinine	Cimetidine
Dopamine	Morphine
Epinephrine	Procaine
Histamine	Quinine
Serotonin	Tetraethyl ammonium
Norepinephrine	
Thiamine	

INFLUENCE OF pH ON REABSORPTION/SECRETION

- Many substances handled by kidneys are either weak acids or bases
  - Weak acids and bases are only partially ionized in their solutions
- Weak acids remain as acid at low pH and dissociate into an anion and a protein at high pH
  - Opposite is true for weak bases
- In general, neutral forms of acids or bases are more permeable in lipid membranes than ionized forms
  - Neutral form can diffuse into or out of the tubular lumen down concentration gradient
  - Ionized forms are trapped in the lumen
- Acidic urine therefore promotes neutral forms of acids and dissociation of bases
  - Weak acids are reabsorbed and less of them excreted whereas the bases are trapped in the lumen
- This concept is relevant when considering altering urine pH to enhance/reduce drug excretion



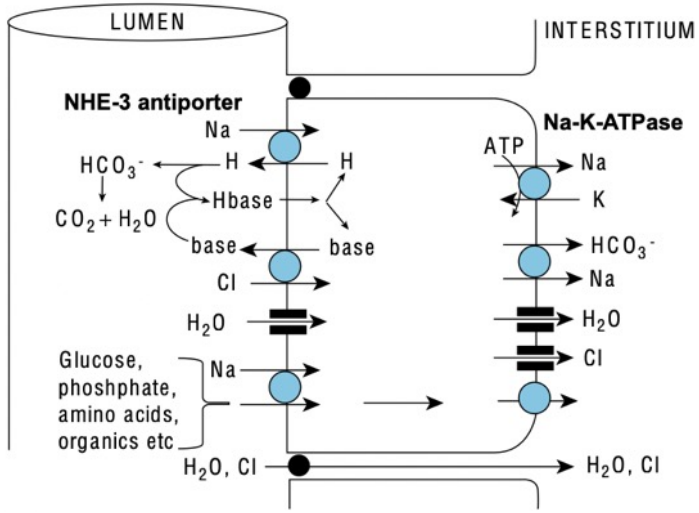
SODIUM AND CHLORIDE HANDLING

- Sodium and chloride are both freely filtered at glomerulus
- More than 99% are reabsorbed and normally NO tubular secretion occurs
- 2 general "rule of thumb":
  - Reabsorption of Na+ is almost always **active, transcellular** driven by the sodium-potassium-adenosine triphosphatase (Na/K ATPase)
  - Reabsorption of Cl- is both **passive via paracellular diffusion** and **active (transcellular)** and **always coupled with sodium** (directly or indirectly)

SODIUM REABSORPTION IN PCT

- 65% of Na+ reabsorbed in PCT
- Filtered Na+ enters cells across luminal membrane via antiporters or symporters
- Driven by Na/K ATPase on basolateral membrane

CHLORIDE REABSORPTION IN PCT



- Cl- always goes with Na+ due to law of electroneutrality
  - Any finite volume of fluid reabsorbed must contain equal amounts of anion and cation equivalent
- Cl- reabsorption via luminal membrane via:
  - Active transport – Cl/base exchangers
  - Passive – paracellular route
- Cl/base exchangers work along with NHE
  - In the cell, there is dissociation of acids into a proton and a base
  - The protons are transported out of the cell via NHE
  - In the lumen, the proton + base recombine back into an acids (neutral molecule)
  - The neutral acid then diffuses across the luminal membrane back into cell to continue the cycle

CHLORIDE REABSORPTION IN PCT

- However, majority of Cl- reabsorption occurs via paracellular diffusion and mainly takes place in distal PCT
  - Concentration of [Cl-] in Bowmans' capsule is the same as plasma.
  - Along early PCT, the reabsorption of H2O causes the [Cl-] to rise above that of the peritubular capillaries
  - This generates a chemical gradient towards distal PCT that allows paracellular Cl- movement for Cl- reabsorption
- Cl- exits epithelial cells into interstitium paracellularly or via Cl- channels on the basolateral membrane

WATER REABSORPTION IN PCT

- 65% of water is reabsorbed in PCT
- PCT is highly permeable to water so minimal changes in osmolality (<1 mOsm/kg) can drive reabsorption of large quantities of water
- Water moves from lumen into interstitium via aquaporins and tight junctions across the plasma membrane, driven by the osmotic gradient
  - Aquaporins-1 (AQP-1) located at booth basolateral and apical membranes and are not regulated by ADH

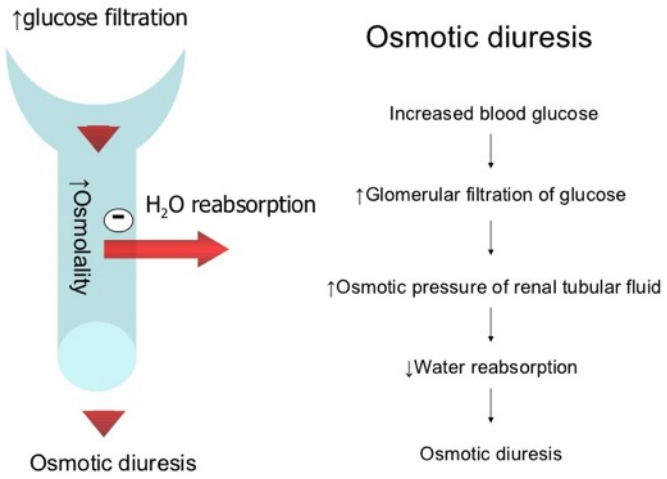
END RESULTS OF PCT REABSORPTION

- Iso-osmotic volume reabsorption occurs in PCT
  - The % of filtered sodium and water that are reabsorbed in PCT are the same
  - [Na+] and osmolality remain unchanged during fluid passage through the PCT
- The filtrate at the end of PCT is therefore iso-osmotic to plasma

DRUGS ACTING IN PCT

- Osmotic diuretics
- Carbonic anhydrase inhibitors: Acetazolamide

OSMOTIC DIURETICS



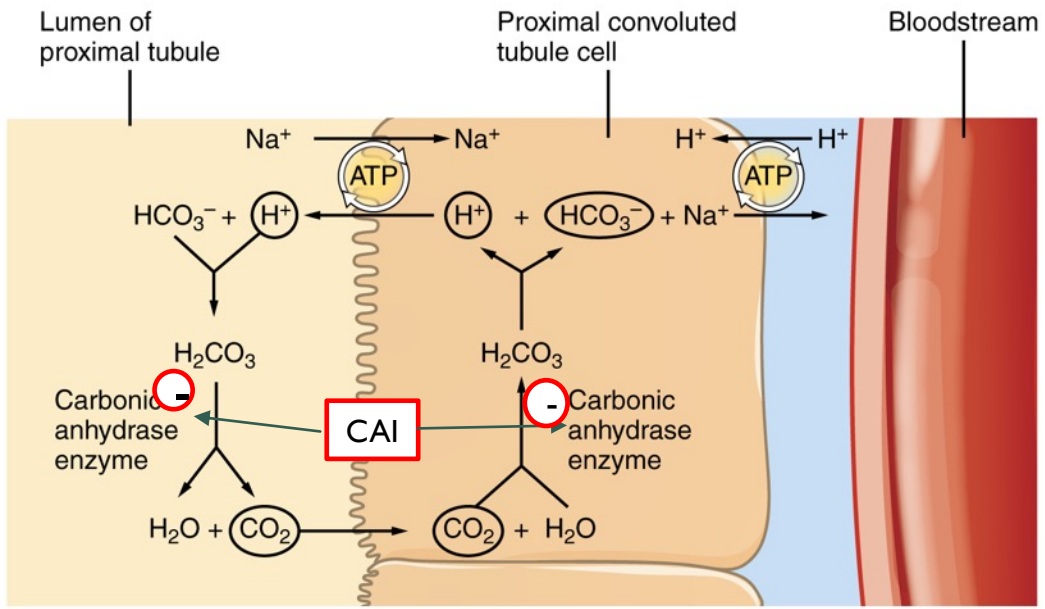
- Osmotic diuresis
  - The condition where increased urine flow develops due to presence of abnormally high amount of a substance in glomerular filtrate that is either incompletely reabsorbed/not absorbed by the PCT
  - As water reabsorption begins secondary to sodium reabsorption, the concentration of the unabsorbed solute increases, and its osmotic presence prevents further reabsorption of water
  - The failure of water reabsorption causes [Na+] to fall in in PCT compared to interstitium, which drives passive diffusion of Na+ across leaky tight junctions back into the lumen → more Na+ is presented to LOH
  - As a result of increased [Na+] in PCT + LOH, urine volume increases
  - Increased urine flow also decreases contact time between filtrate and interstitium, reducing Na+ reabsorption and water reabsorption → less Na+ loss = hypernatremia
- Physiological osmotic diuresis can occur during marked hyperglycemia or in DKA with increased ketoacids
- Pharmacological osmotic diuresis caused by mannitol

OSMOTIC DIURETICS

Mannitol

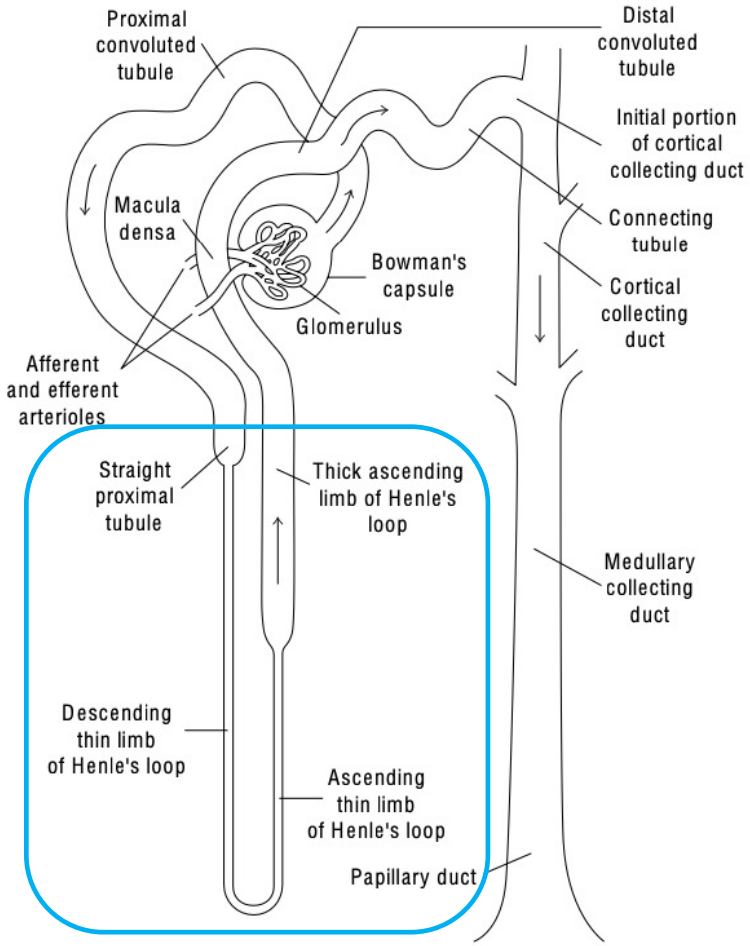
- Pharmacologically inert
- Filtered in glomerulus but not reabsorbed by nephron → allows water retention and promotes water diuresis
- Use: Reduced intracranial pressure and to promote excretion of nephrotoxins
  - Reduced ICP via 2 mechanisms:
    - 1) Rheological: Reduces blood viscosity and promotes plasma expansion and cerebral DO2
    - 2) Creating osmotic gradient across BBB → favours movement of water from parenchyma into intravascular space
  - Nephroprotective – prevents nephrotoxins from accumulating in the tubular fluid and minimize renal tubular swelling (osmotic draw)
  - Free radical scavenging properties
- Adverse effects: Fluid (volume depletion, volume overload in oliguric patients), electrolyte (hypernatremia, hypokalemia, pseudo-hyponatremia), and acid-base (metabolic acidosis)

CARBONIC ANHYDRASE INHIBITORS (CAI)



- Acetazolamide, dorzolamide etc.
- Mainly used in veterinary medicine for glaucoma

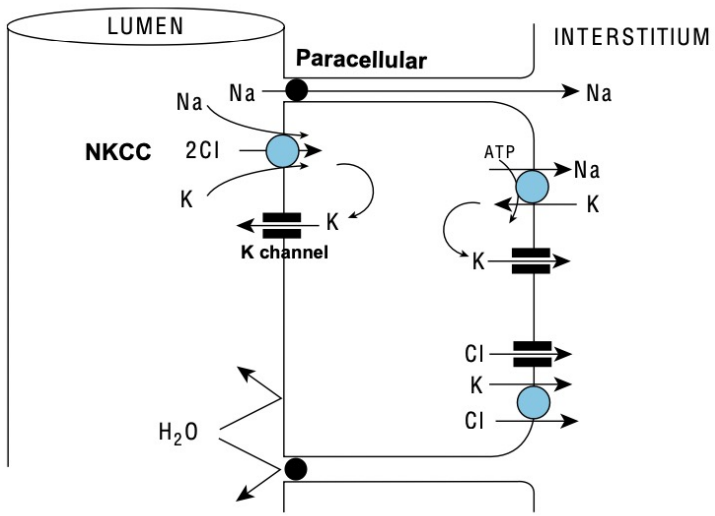
LOOP OF HENLE (LOH)



LOOP OF HENLE

- Divided into descending LOH, thin and thick ascending LOH
- Descending LOH
  - Doesn't reabsorb much of NaCl (Few mitochondria and little Na/K ATPase)
  - Cells express a lot of AQ-1 = Extremely permeable to water
  - Located deep in the renal medulla and uses countercurrent exchange to drive reabsorption
- Ascending LOH
  - Reabsorbs NaCl
    - High density of Na/K ATPase along basolateral membrane to drive particle resorption → highly prone to injury during renal hypoperfusion or hypoxia
  - Impermeable to water
- LOH overall reabsorbs more NaCl (25%) relative to water (10%) – called the "diluting segment"
- Fluid leaving the LOH is hypo-osmotic relative to plasma

SODIUM AND CHLORIDE REABSORPTION IN LOH



- Mainly occurs in ascending LOH
- Passive (50%) in the thin portion and active (50%) in the thick portion
- Descending LOH concentrates the luminal Na+ and creates a gradient that favors passive Na+ reabsorption
  - The gradient is what facilitates passive paracellular Na+ reabsorption in thin ascending LOH
- As filtrates reach the thick ascending LOH, the main luminal transporter used is the Na-K-2Cl cotransporter (NKCC) and the Na/H antiporter
  - Na+ is moved into interstitium via Na/K ATPase
  - K+ recycled back into lumen and into interstitium via K+ channels (ROMK)
  - Cl- moves into interstitium via Cl- channels
  - Cl- is the rate limiting factor in the NKCCmcotransporter's activity

DRUGS ACTING IN LOH: LOOP DIURETICS

- Furosemide, torsemide
  - Torsemide 10x more potent than furosemide
- MoA: Inhibit the Na-K-2Cl cotransporter (specifically the Cl- binding site) to induce diuresis
  - Increases renal excretion of water, Na+, K+, Cl-, Ca2+, Mg2+, H+ ion, ammonium and HCO3-
  - Excretion of K+ is much less than Na+
  - Renal venodilation and transiently increases GFR
- Adverse effects: Pre-renal azotemia, hyperglycemia, electrolytes (hyponatremia, hypocalcemia, hypokalemia, hypomagnesemia), metabolic alkalosis, high dose cause ototoxicity (cats > dogs), GI signs, ulcerative lesion @ injection site (SQ)

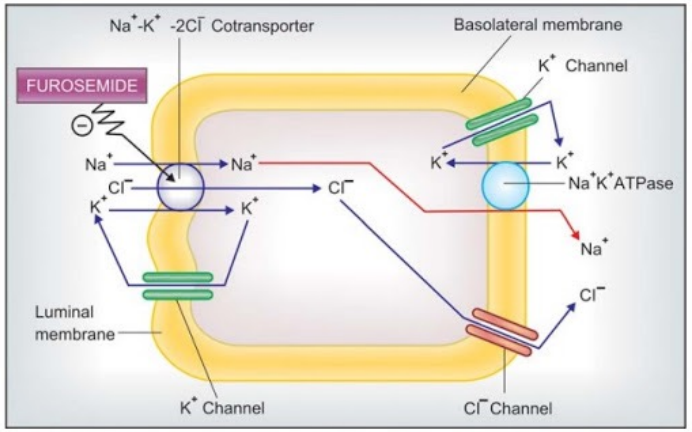
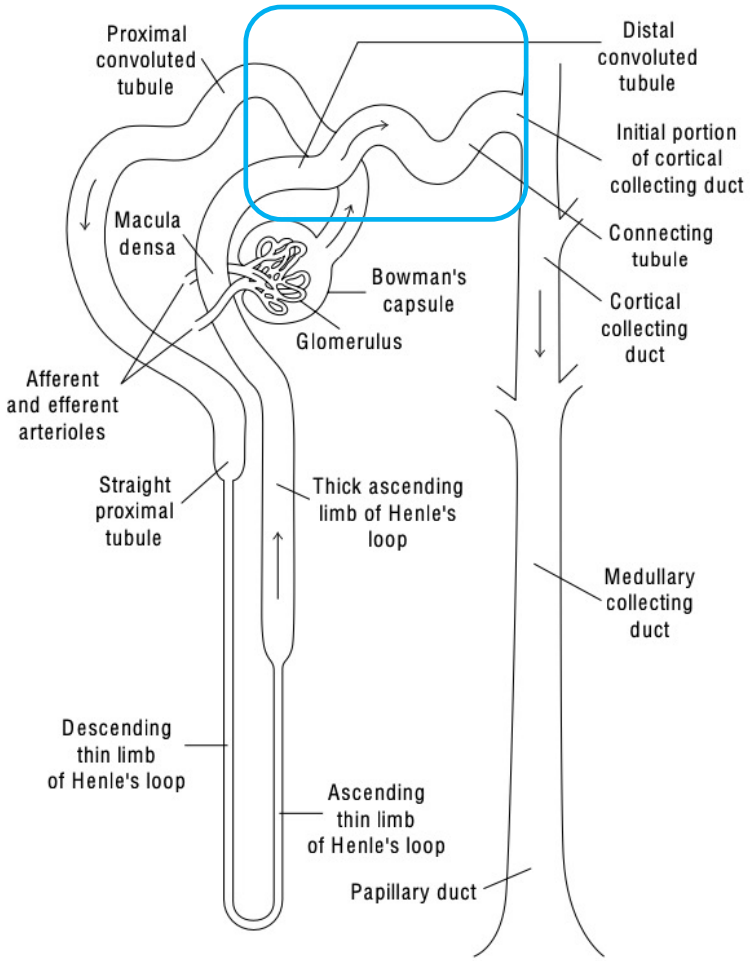


Fig. 41.1: Mechanism of salt reabsorption in the thick ascending limb of loop of Henle (AscLH) cell, and site of action of furosemide on the Na^+-K^+-$2Cl^-$ cotransporter

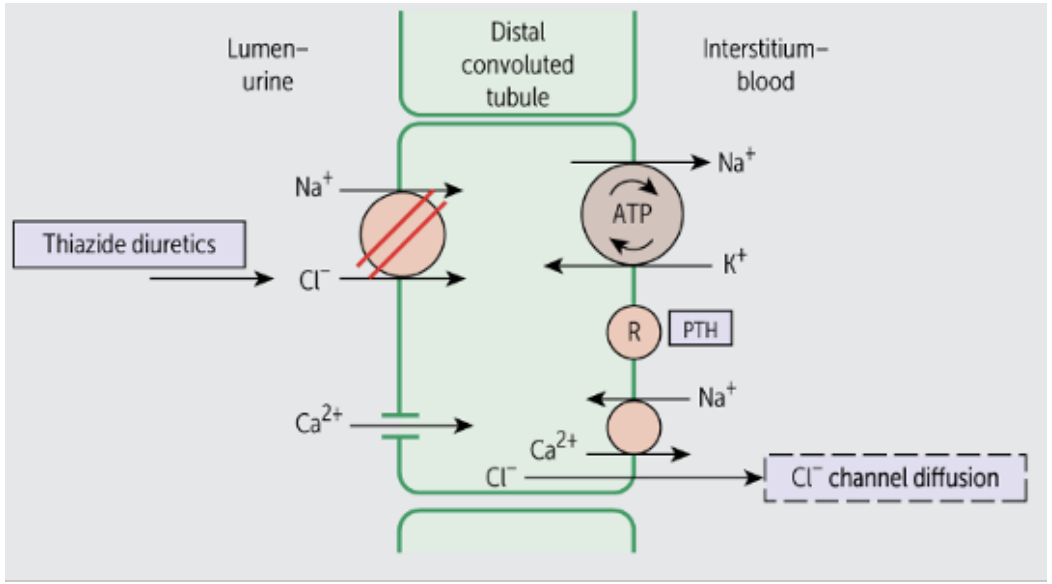
DIURETIC RESISTANCE

- Diuretic resistance = failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic
- Causes:
  - Poor adherence to drug therapy
  - Altered pharmacokinetics – e.g. poor oral absorption in GI disease, inhibited secretion from PCT in CKD
  - Insufficient kidney response to drug - e.g. low GFR, activation of RAAS, nephron adaption (upregulation of unbound Na+ transporters), concurrent use of NSAID



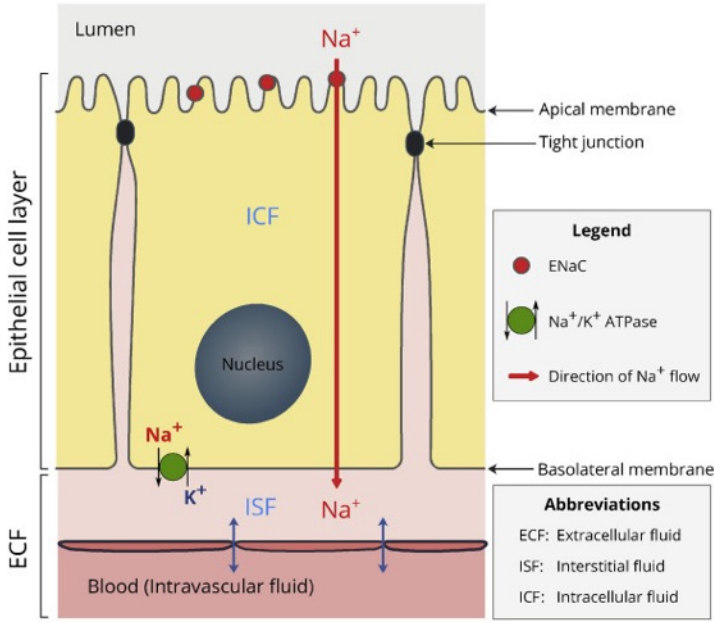
DISTAL CONVOLUTED TUBULE (DCT)

REABSORPTION AND SECRETION IN DCT



- Mostly impermeable to water
- Reabsorbs some Na+ (5-8%), Cl- and Ca2+
  - Na+ via Na/Cl cotransporter and ENaC
  - Cl- via basolateral Cl- channels (diffusion)
  - Ca+ via channels
- Secretes K+ and H+
- Receptors on basolateral membrane
  - Na/Ca2+ antiporter
    - Brings Na+ in cell, Ca2+ out of cell into interstitium
  - PTH-receptors on basolateral membrane
- Urine becomes fully dilute (hypotonic)

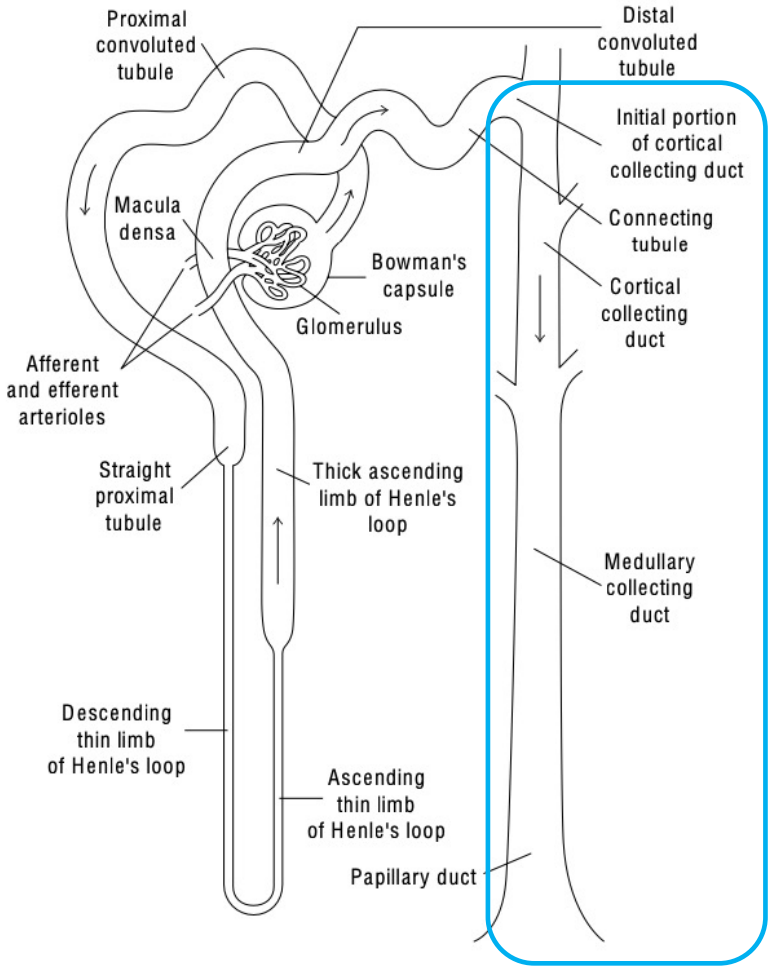
EPITHELIAL SODIUM CHANNEL (ENAC)



- Membrane-bound ion channel that is selectively permeable to Na+
- Present in DCT and principal cells of the collecting ducts
- Activity modulated by aldosterone
- Inhibited by ANP and diuretics (amiloride) which causes natriuresis and diuresis

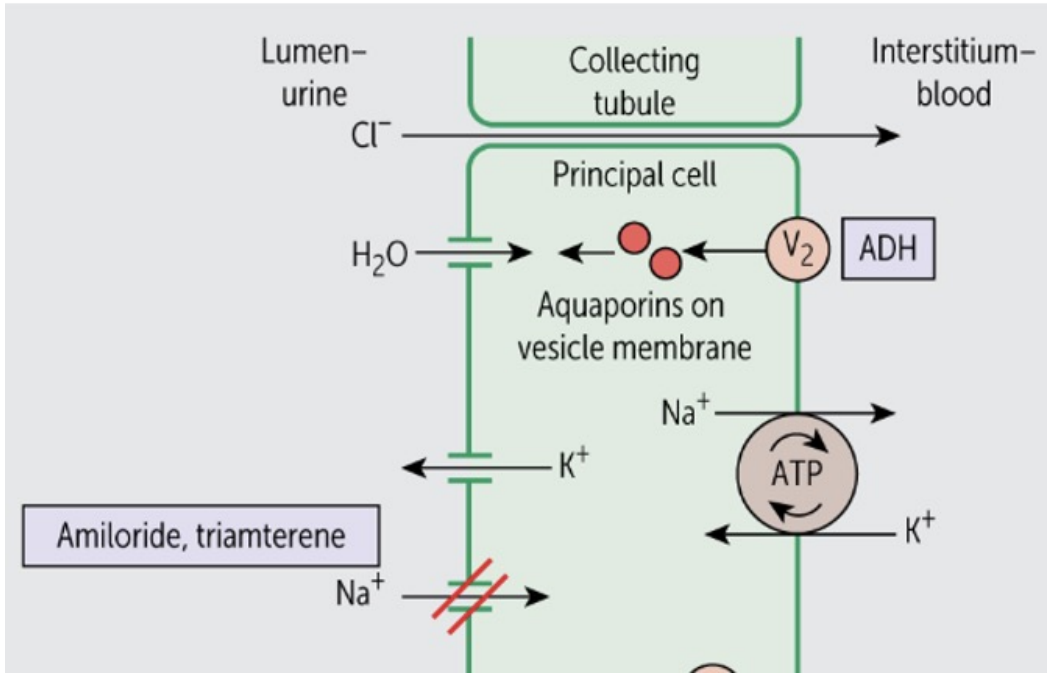
DRUGS ACTING IN DCT: THIAZIDE DIURETICS

- Hydrochlorothiazide
- MoA: Blocks the Na/Cl symporter on DCT
  - Increased excretion of Na+, Cl-, water, K+, Mg2+, phosphate, iodide, bromide
  - Decreases GFR
- Used in CHF, nephrogenic DI, and idiopathic hypertension (people)
- Adverse effects: GI signs, hypokalemia, dilution hyponatremia + hypomagnesemia, hyperuricemia



COLLECTING DUCTS

COLLECTING DUCTS: PRINCIPAL CELLS

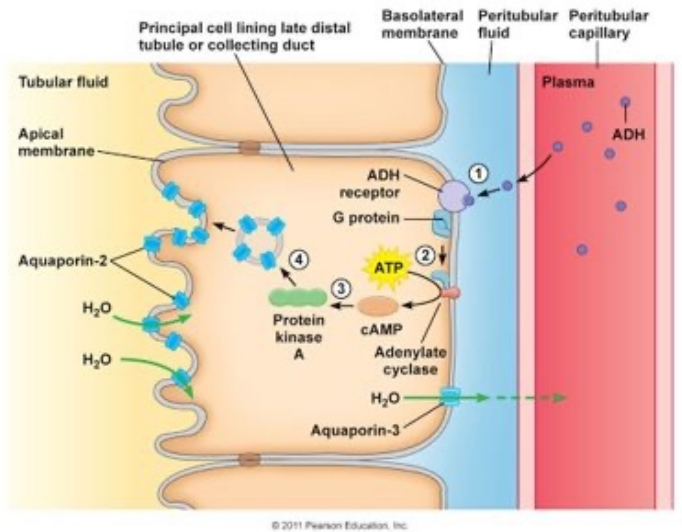


- Principal cells make up 70% of cells
- Reabsorbs NaCl and H2O, secretes K+
  - 3% Na reabsorbed via ENaC located on the apical membrane (passive)
  - Reabsorption of Cl- via paracellular pathways
  - Water is reabsorbed via AQP-2
- Na+ entry into cells creates a negative charge in the lumen
  - K+ secretion via apical channel stimulated by electrochemical gradient
  - Also enhances H+ secretion by intercalated cells later down
- Basolateral membrane contains mineralocorticoid receptors (aldosterone)

WATER HOMEOSTASIS IN COLLECTING DUCTS

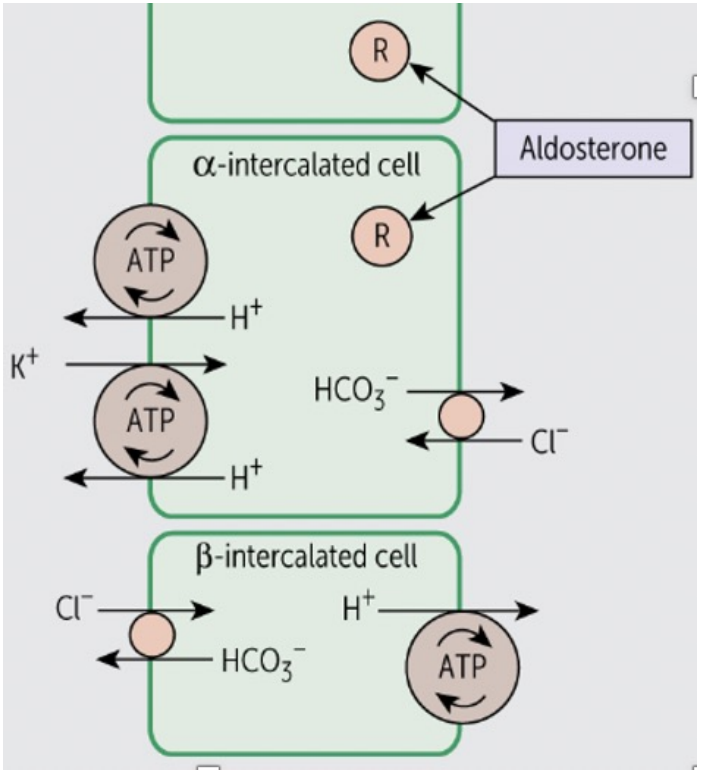
- The water permeability in CD is controlled by ADH
- With low permeability (I.e. ADH not activated), the filtrate will remain hypo-osmotic through the ducts
  - Once it reaches the medullary collecting duct, a huge osmotic gradient favoring reabsorption is present
  - Without ADH, this large volume of fluid will flow from CD into ureters and excreted
  - This is the concept of water diuresis
- With high permeability, water from the filtrate flowing through CD will be reabsorbed due to an osmotic gradient between the hypo-osmotic luminal fluid and the iso-osmotic interstitial fluid
  - Once osmolality of the luminal approaches the interstitial fluid, it will reabsorb equal proportions of solutes and water again
  - This results in urine that is iso-osmotic to plasma

AQUAPORINS AND WATER REABSORPTION



- Water permeability (and therefore reabsorption) is regulated by ADH
- The release of ADH is stimulated by hyperosmolality >> hypovolemia (discussed later)
- ADH binds to V2 receptors on the basolateral membrane of principal cells
  - Activation of adenylate cyclase, catalyzing the production of cAMP
  - CAMP induces migration of intracellular vesicles and fusion to the luminal membrane → AQPs-2 inserted into luminal membrane
- Without ADH, AQP-2 are withdrawn via endocytosis

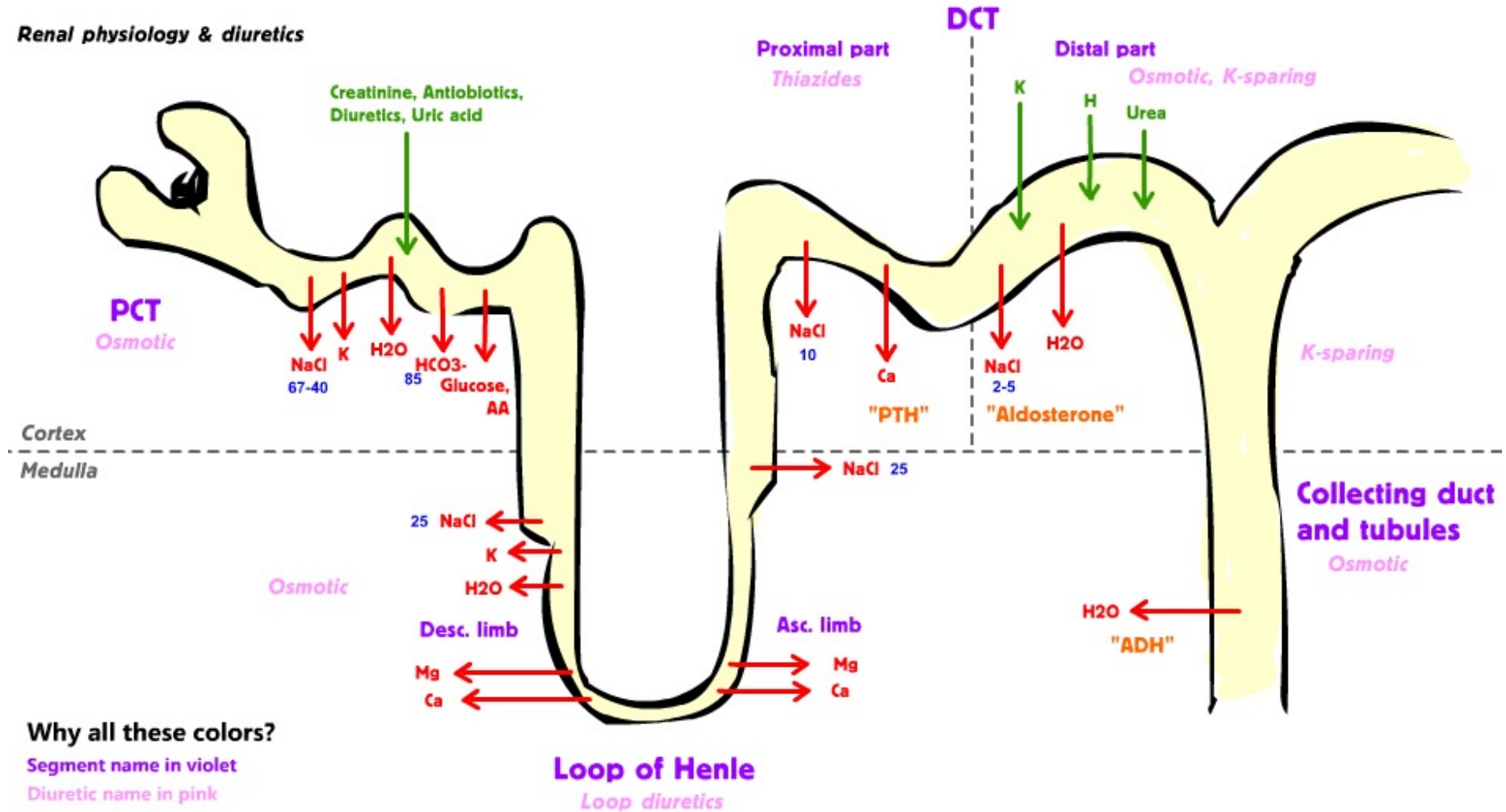
COLLECTING DUCTS: INTERCALATED CELLS



- Make up 30% of cells – divided into alpha and beta intercalated cells
- Regulates acid-base
- Alpha-intercalated cells
  - Secretes H+ and reabsorbs HCO3-
  - Apical H+ ATPase secretes H+
  - Apical H/K ATPAse secretes H+ and reabsorbs K+
  - Basolateral HCO3/Cl- antiporter moves Cl- intracellular and HCO3- into interstitium
  - Basolateral membrane contains mineralocorticoid receptors (aldosterone)
- Beta-intercalated cells
  - Apical HCO3/Cl antiporter secretes HCO3- and reabsorbs Cl-
  - Cl- exits cells via Cl- channel
  - Basolateral H+ ATPase to reabsorb H+ into interstitium

DRUGS THAT IN COLLECTING DUCT: SPIRONOLACTONE

- Aldosterone antagonist, potassium-sparing diuretic
- MoA: Competitively inhibit aldosterone
  - Increased excretion of Na+, Cl- and water and decreased excretion of K+, ammonium, phosphate, and titratable acid
  - In CHF, role in reducing myocardial fibrosis, vascular remodeling, and endothelial dysfunction (unclear in vet med)
- Used in conjunction with other diuretics who act on PCT to reduce Na+ reabsorption
  - Used with loop or thiazide diuretic to maximize effects
- Adverse effects: GI signs, electrolytes (hyperK, hypoNa), dehydration


Renal physiology & diuretics
DCT
Proximal part
Thiazides
Distal part
Osmotic, K-sparing
Creatinine, Antiobiotics,
Diuretics, Uric acid
K
H
Urea
PCT
Osmotic
NaCl
67-40
K
H2O
HCO3-
85
Glucose,
AA
NaCl
10
Ca
"PTH"
NaCl
2-5
"Aldosterone"
H2O
K-sparing
Cortex
Medulla
NaCl 25
Collecting duct
and tubules
Osmotic
25 NaCl
K
H2O
Osmotic
Desc. limb
Asc. limb
Mg
Ca
Mg
Ca
H2O
"ADH"
Loop of Henle
Loop diuretics
Why all these colors?
Segment name in violet
Diuretic name in pink
Reabsorption in red
Secretion in green
Percentage in blue
Hormone in orange

Segment/Cell Type	Major Functions	Cellular Mechanisms	Hormone Actions	Diuretic Actions
Early Proximal Tubule	Isosmotic reabsorption of solute and water	Na^+-glucose, Na^+-amino acid, Na^+-phosphate cotransport	PTH inhibits Na^+-phosphate cotransport	Osmotic diuretics
		Na^+-H^+ exchange	Angiotensin II stimulates Na^+-H^+ exchange	Carbonic anhydrase inhibitors
Late Proximal Tubule	Isosmotic reabsorption of solute and water	NaCl reabsorption driven by Cl^- gradient	—	Osmotic diuretics
Thick Ascending Limb of the Loop of Henle	Reabsorption of NaCl without water Dilution of tubular fluid Single effect of countercurrent multiplication Reabsorption of Ca^{2+} and Mg^{2+} driven by lumen-positive potential	Na^+-K^+-$2Cl^-$ cotransport	ADH stimulates Na^+-K^+-$2Cl^-$ cotransport	Loop diuretics
Early Distal Tubule	Reabsorption of NaCl without water Dilution of tubular fluid	Na^+-Cl^- cotransport	PTH stimulates Ca^{2+} reabsorption	Thiazide diuretics
Late Distal Tubule and Collecting Ducts (principal cells)	Reabsorption of NaCl	Na^+ channels (ENaC)	Aldosterone stimulates Na^+ reabsorption	K^+-sparing diuretics
	K^+ secretion	K^+ channels	Aldosterone stimulates K^+ secretion	
	Variable water reabsorption	AQP2 water channels	ADH stimulates water reabsorption	
Late Distal Tubule and Collecting Ducts (α-intercalated cells)	Reabsorption of K^+ Secretion of H^+	H^+-K^+ ATPase H^+ ATPase	— Aldosterone simulates H^+ secretion	— K^+-sparing diuretics

ADH, Antidiuretic hormone; PTH, parathyroid hormone; ENaC, epithelial Na^+ channel; AQP2, aquaporin 2.

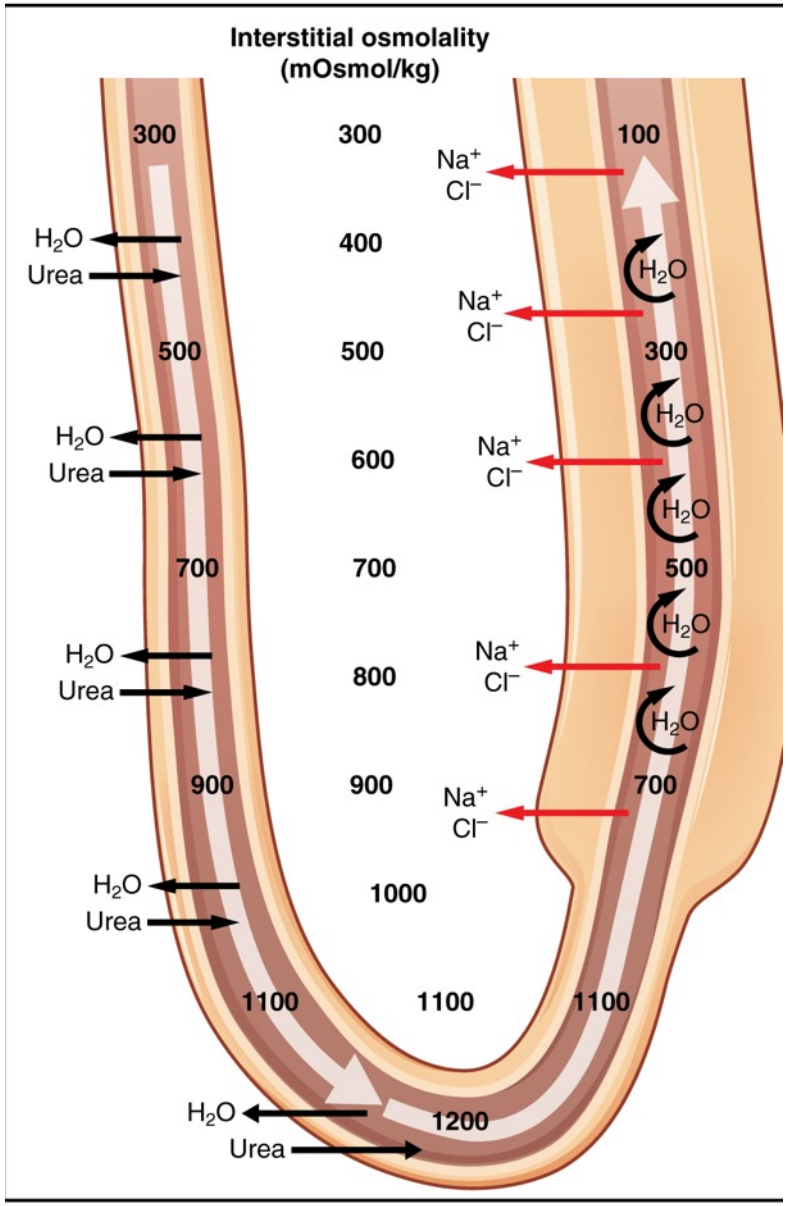
URINE CONCENTRATION

CONCENTRATING URINE

- Kidneys can produce hypo-, iso-, or hyper-osmotic urine
- Production of hypo-osmotic urine is via water diuresis (as discussed previously)
- Production of hyper-osmotic urine is also straightforward – it requires the reabsorption of water from the lumen into a hyperosmotic interstitium, concentrating the luminal fluid and allowing concentrated urine to be excreted
- The medullary osmotic gradient is the key as to how the kidneys can concentrate urine
  - This gradient increases from near iso-osmotic value at the corticomedullary border to a maximum of 1200 mOsm/kg at the papilla
  - Gradient highest during dehydration and can also be "washed out" during overhydration

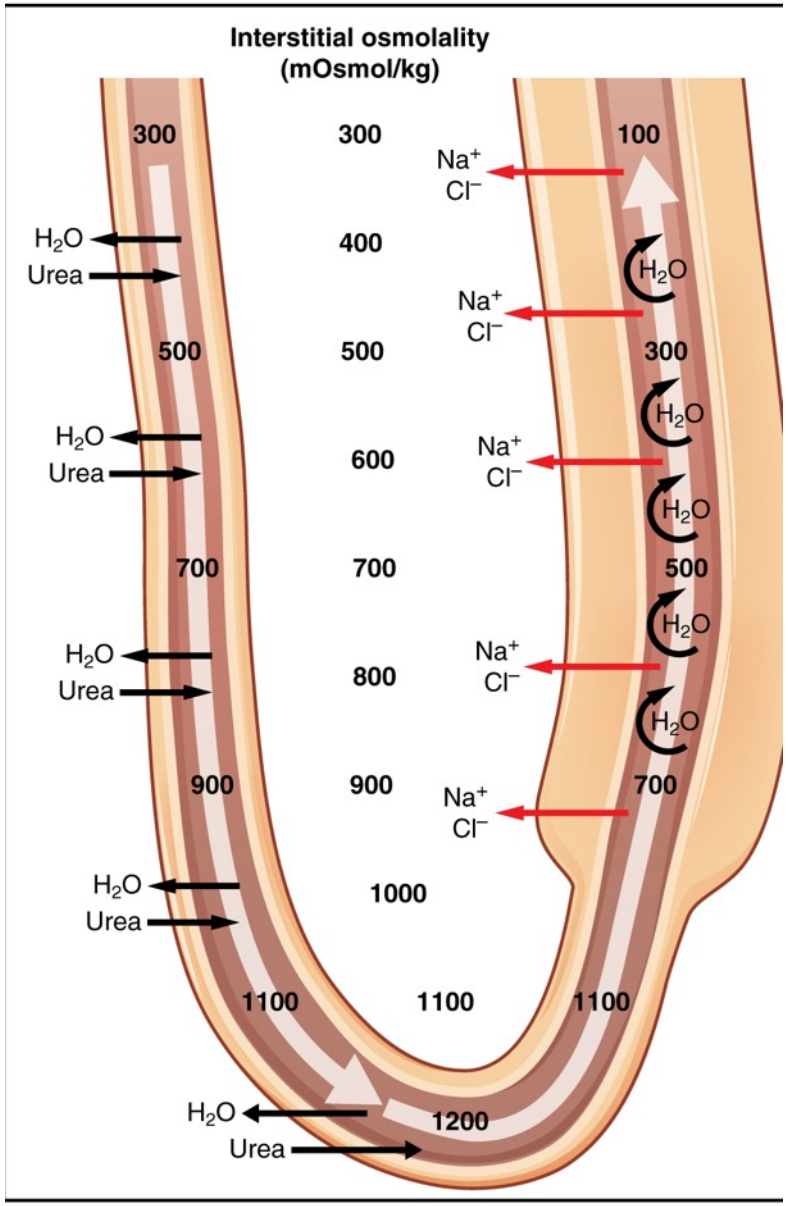
MEDULLARY OSMOTIC GRADIENT

- Juxtamedullary nephrons that penetrate deeply within the inner medulla
- Components that develop the medullary osmotic gradient:
  1) Active NaCl transport in thick ascending LOH (NKCC)
  2) Arrangement of blood vessels (vasa recta) and nephron in the medulla, with descending parts in close apposition to ascending parts
     - Vasa recta capillaries are long, hairpin-shaped blood vessels that run parallel to LOH
     - Harpin turns slow rate of BF and helps maintain osmotic gradient
  3) Recycling of urea between the medullary collecting ducts and deep portion of LOH



MEDULLARY OSMOTIC GRADIENT

- By arranging this in a hairpin loop, it allows particles to move in and water to move out of the descending limb, which can continue to build a more concentrated gradient.
- Together with hairpin arrangement, by altering solute and water permeability at different segments, the net effect is multiplied
  - Creates a much higher concentration generated along the duct's length and in the surrounding fluid compared to the concentration of the original fluid



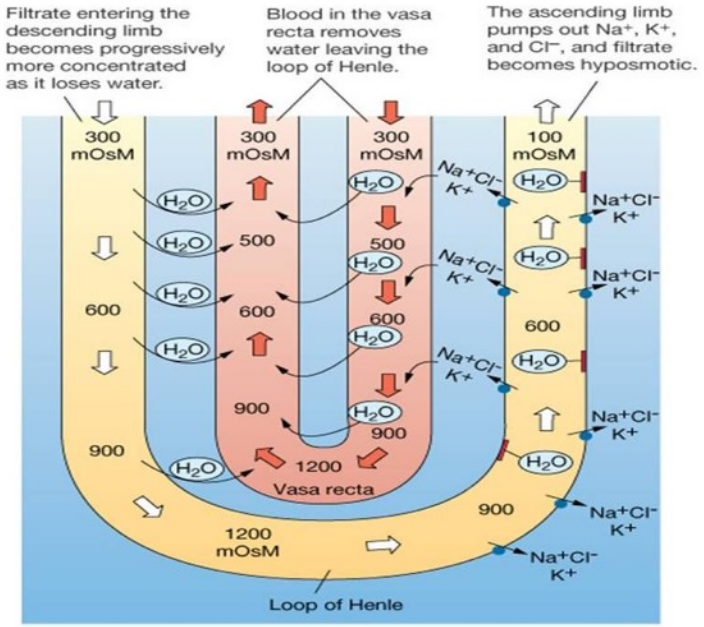
COUNTERCURRENT MULTIPLIER

- Countercurrent multiplication moves NaCl from the tubular fluid into the interstitial space deep within the kidneys.
- 1st: The single effect
  - Driven by active transport of NaCl out of the tubular fluid in the thick ascending limb via NKCC into the interstitial fluid → interstitium becomes hyperosmotic
    - Dilutes tubular fluid to ~50-100 mOsm/L
  - Water moves passively down its concentration gradient out of the tubular fluid in the descending limb via AQP-1 into the interstitial space, until it reaches equilibrium
    - The water is returned to circulation by vasa recta
- 2nd: Fluid flow
  - As urine is continually being produced, new tubular fluid enters the descending limb, which pushes the fluid at higher osmolarity down the tube and an osmotic gradient begins to develop

COUNTERCURRENT MULTIPLIER

- As filtrate continues to move through the LOH, these 2 steps are repeated over and over → osmotic gradient steadily multiple until it reaches a steady state
  - The bent of hairpin loop has osmolality of 1200 mOsm/kg compared to 300 mOsm/kg at the corticomedullary junction
- The longer the LOH, the greater the gradient
- Other components of urine concentrating mechanism:
  - ADH-dependent reabsorption of water in CD
  - Reabsorption of NaCl in ascending LOH generates a high [NaCl] in medullary interstitium which drives water reabsorption in CD
  - Urea accumulation in medullary interstitium drives urea excretion

COUNTERCURRENT EXCHANGE

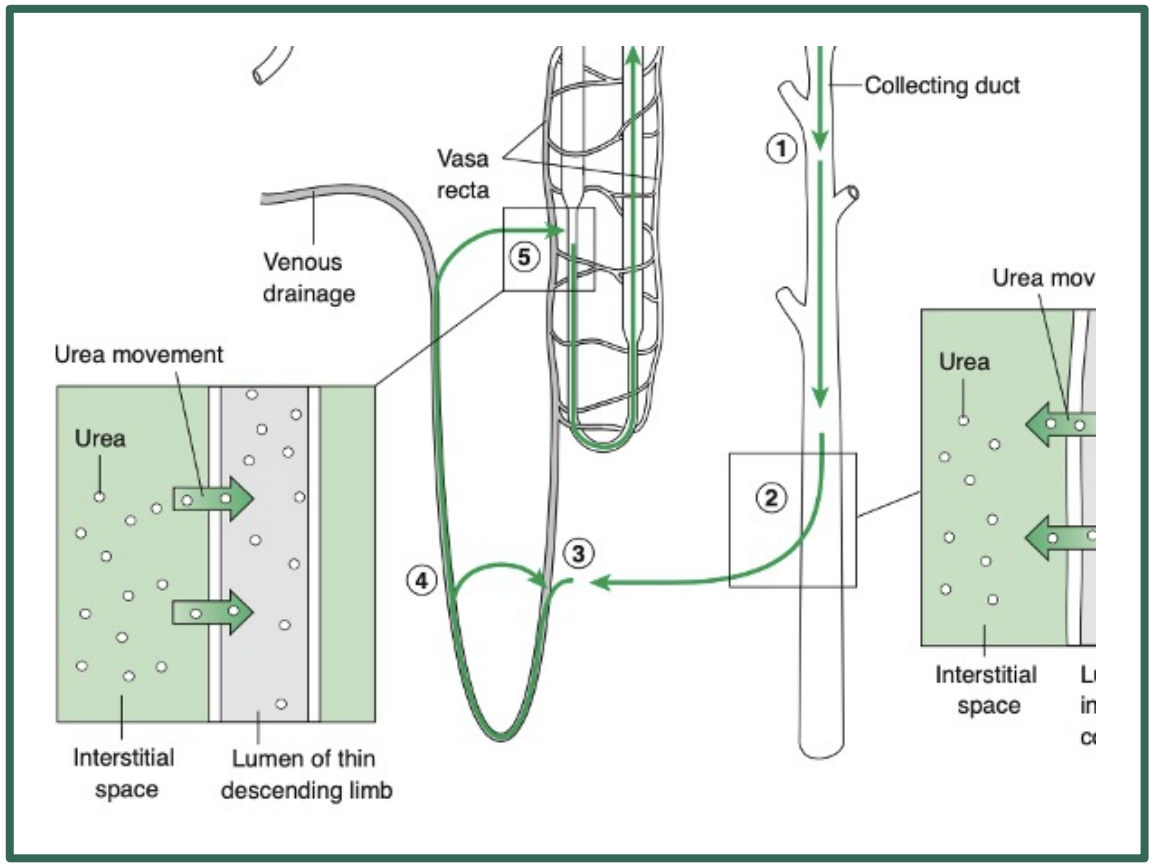


- Designed to prevent dilution of the medullary concentration gradient
- Blood in descending vessel is isotonic (300 mOsm/kg)
- As it descends into concentrated interstitium, water moves out and blood becomes concentrated
- At the hairpin turn (inner medulla), it reaches maximal concentration
- In the ascending limb the opposite cycle occurs: Water entering the blood vessels → dilutes out and becomes isotonic to serum again as vasa recta returns to the body
- Creates a circular loop of flow that maintains a high [particles] in the inner medulla to prevent dilution
- LOH establishes the gradient, and the vasa recta maintains the gradient

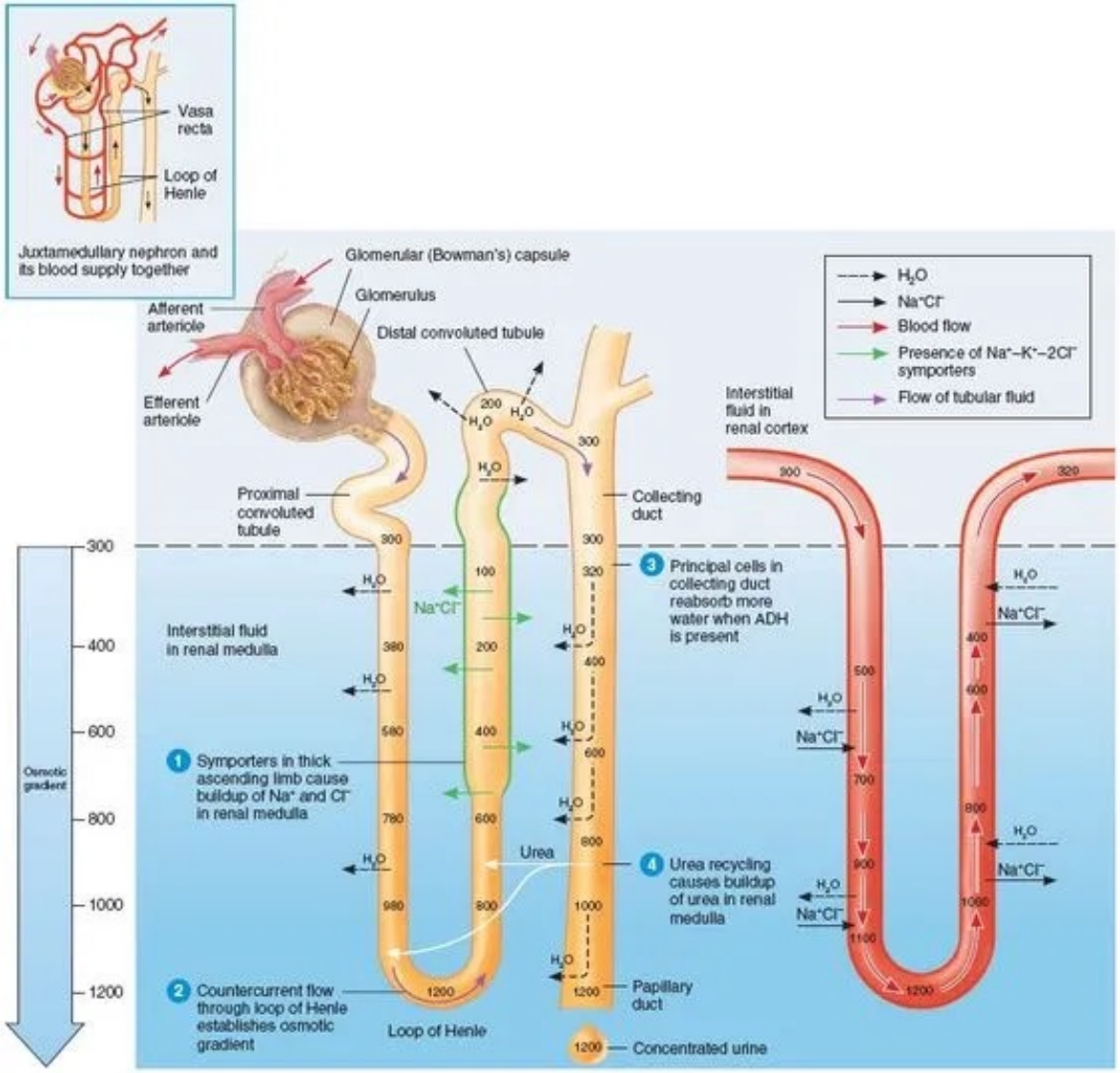
UREA RECYCLING

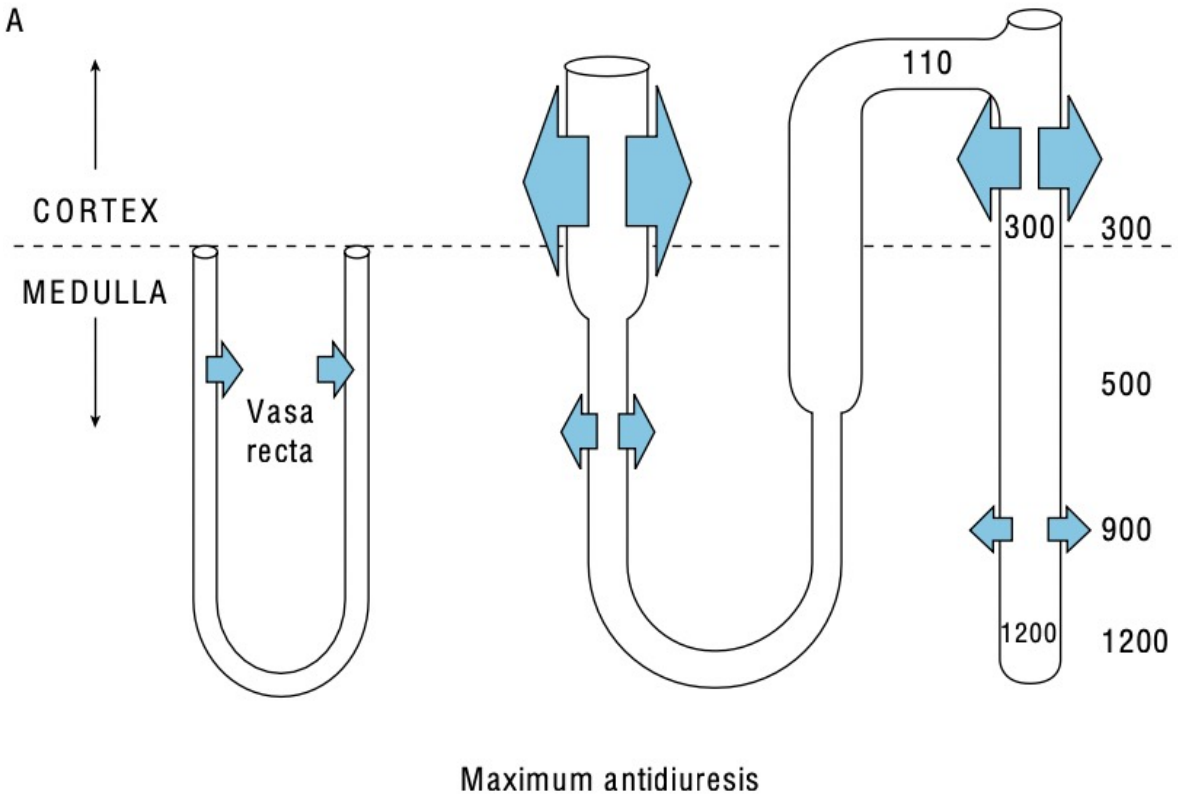
- Of the peak osmolality (1000 mOsm/kg) seen in the renal papilla, half is accounted for by NaCl and the rest is accounted for by urea
- Urea is freely filtered at glomerulus → 50% reabsorbed in PCT
- Urea is secreted in the thin portions of LOH driven by the high [urea] in the medullary interstitium
  - This restores the amount of reabsorbed urea back to filtrate
- Due to minimal urea transport between the end of thin limb to the beginning of collecting duct, the luminal [urea] increases 50x its plasma value
- Urea is reabsorbed by specialized transporters in the inner medullary ducts → this urea accumulates and raises the interstitial [urea]
- The combination of high urea + high NaCl brings medullary osmolality close to 1200 mOsm/kg

UREA RECYCLING



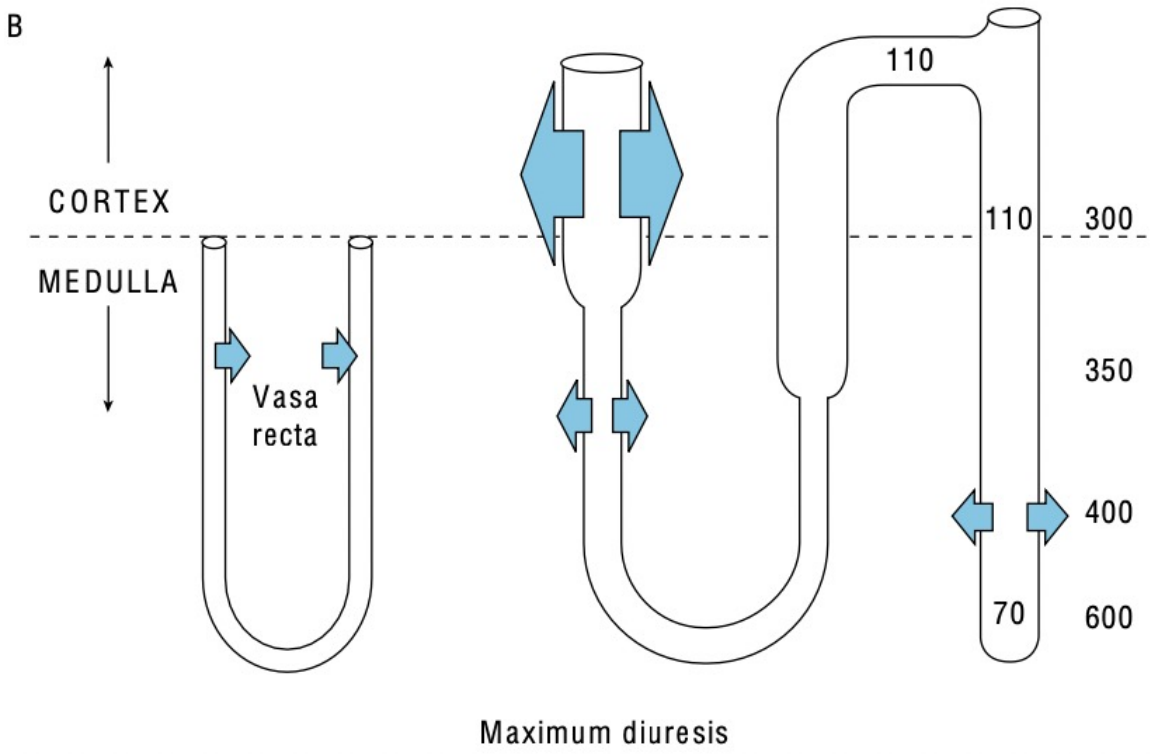
1. Water is drawn out of CD (osmotic gradient set up via Na/K ATPase and countercurrent multiplier mechanism) → luminal [urea] increases
2. Urea passes through urea transporters in distal CD → enters interstitium and generates a gradient
   - ADH-mediated urea transporters only in **inner** medulla
3. Urea then diffuses into the blood via permeable barrier of descending vasa recta → through hairpin loop → into ascending vasa recta
4. Majority of urea recycles back into descending limb of LOH as part of countercurrent exchange
5. In descending LOH, the urea transporters allow shuttling back of interstitium urea into the tubular lumen → prevents it from returning the systemic circulation


Vasa recta
Loop of Henle
Juxtamedullary nephron and its blood supply together
Glomerular (Bowman's) capsule
Glomerulus
Afferent arteriole
Efferent arteriole
Distal convoluted tubule
Proximal convoluted tubule
Collecting duct
Interstitial fluid in renal medulla
Interstitial fluid in renal cortex
H_2O
Na^+Cl^-
Blood flow
Presence of Na^+–K^+–$2Cl^-$ symporters
Flow of tubular fluid
Osmotic gradient
300
400
600
800
1000
1200
1 Symporters in thick ascending limb cause buildup of Na^+ and Cl^- in renal medulla
2 Countercurrent flow through loop of Henle establishes osmotic gradient
3 Principal cells in collecting duct reabsorb more water when ADH is present
4 Urea recycling causes buildup of urea in renal medulla
Urea
Loop of Henle
Papillary duct
Concentrated urine
(a) Reabsorption of Na^+, Cl^-, and water in long-loop juxtamedullary nephron
(b) Recycling of salts and urea in vasa recta



Maximum antidiuresis

During antidiuresis, ADH inserts AQP-2 in the cortical and medullary collecting tubules to allow water reabsorption.
End results = urine is concentrated and hyperosmotic (1200 mOsm).
The is increased urea permeability which assist in generating the medullary osmotic gradient.



Maximum diuresis

During diuresis, no water is reabsorbed in the cortical collecting tubule, but some water reabsorption can occur in the medullary portion independent of ADH.
However, since medullary solute reabsorption > water reabsorption, the urine is still dilute.

MEDULLARY WASHOUT

- During state if overhydration, although there is still substantial amounts of water being reabsorbed (due to a large osmotic gradient), even more water is not reabsorbed
  - Creates a large urine volume
- With this, not much urea is reabsorbed (due to lack of ADH)
- The low urea reabsorption + persistent amount of water reabsorbed; the inner medulla becomes partially diluted
  - Decreases from >1000 down to 500-600 mOsm/kg
- Another factor contributing to this is due to lack of ADH-mediated vasoconstriction → increases medullary blood flow
- Medullary washout results in impaired ability to concentrate urine which can last for days

MEDULLARY WASHOUT: CAUSES

Long-standing PU/PD
-Loss of medullary solutes (Na+)

Conditions that increased medullary blood flow (e.g. hypokalemia, hypercalcemia, chronic PU)

Severe renal disease with structural changes

Any condition leading hyponatremia (e.g. hypoadrenocorticism)

Low urea (e.g. severe liver disease/synthetic failure)

Lack of adequate physiologic stimuli for ADH release (e.g. chronic hypotonicity (PUPD), volume expansion (IVF))

Obligate diuresis (e.g. hyperglycemia, post-obstructive diuresis)

Iatrogenic factors: glucocorticoid, diuretics, IVF/SQF, nephrotoxins, high salt diet/treats

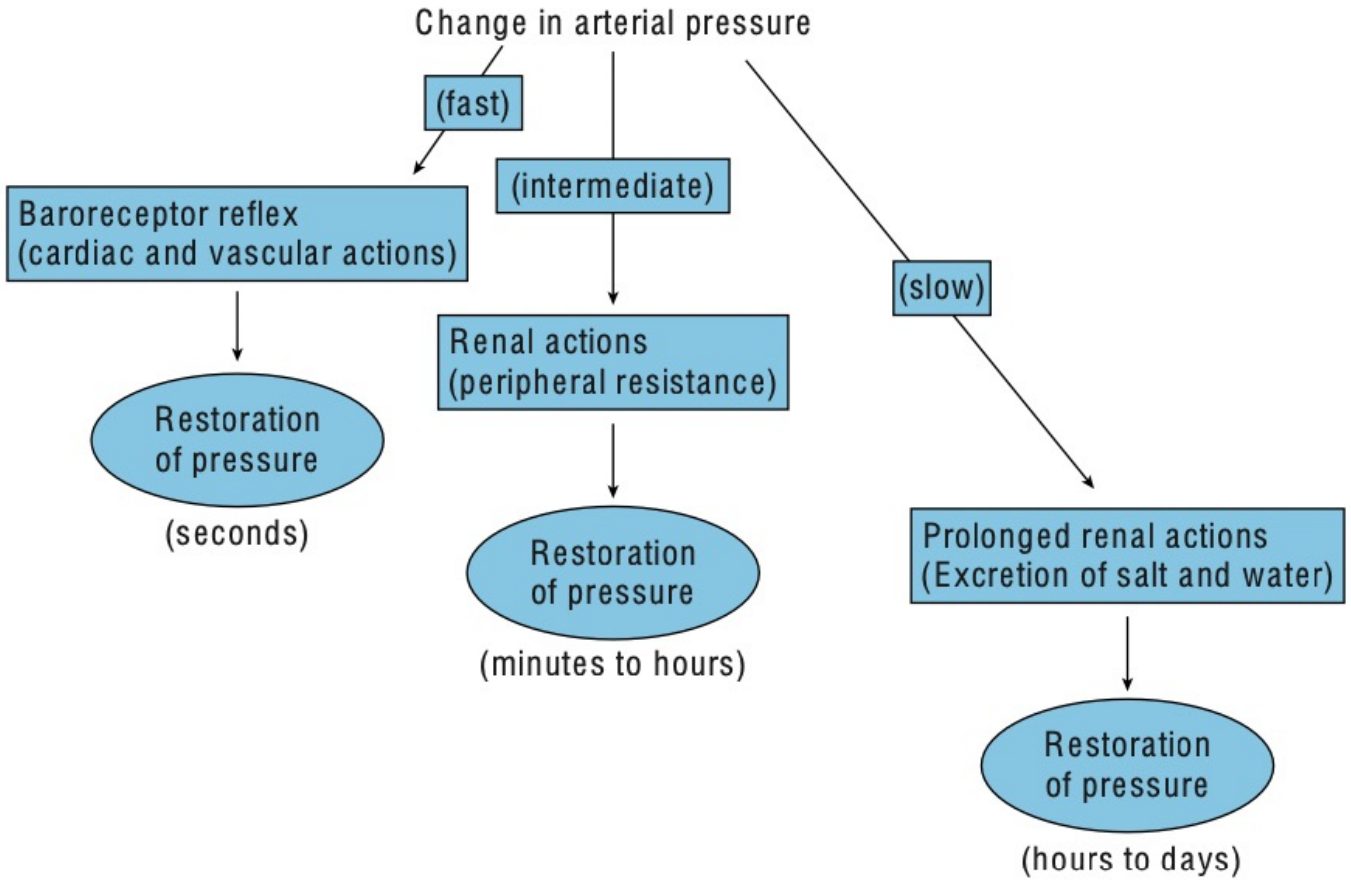
CONTROL OF BLOOD PRESSURE

BLOOD PRESSURE REGULATION

- Involves multiple body systems – brain, heart, kidney
- Closely linked to total body volume
- Sensors of volumes:
  - Baroreceptors (heart)
  - Flow receptors (kidneys)
  - Hepatic sensors → respond to pressure changes within the hepatic vasculature or changes in [Na+] in portal blood
  - CNS sensors → located in hypothalamus, response to [Na+] changes to modulate NaCl excretion

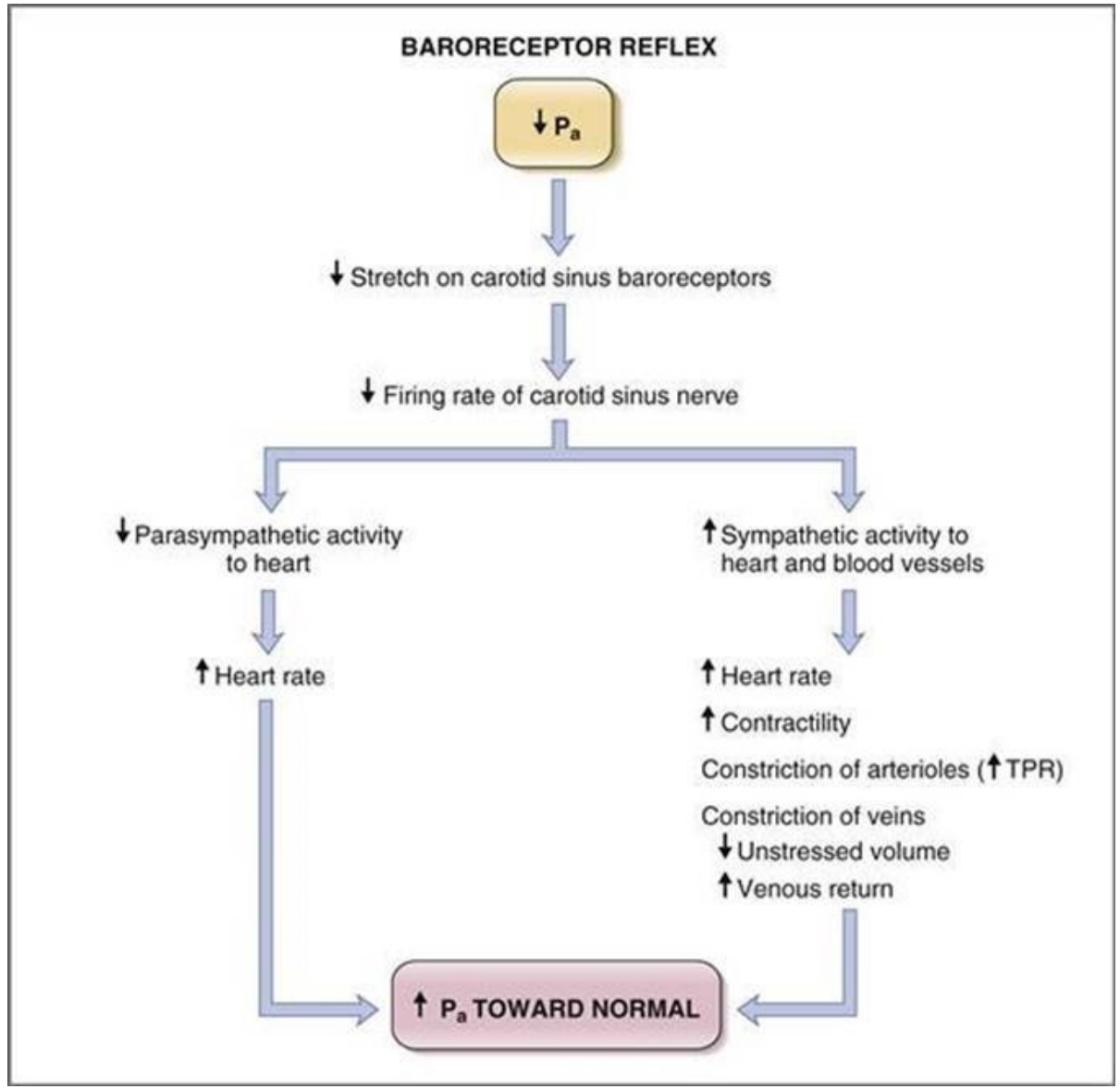
BLOOD PRESSURE REGULATION

1) Short-term (seconds): Cardiovascular reflexes
2) Intermediate-term (mins-hours): Renal control
3) Long-term (hours-days): Aldosterone
4) Other players:
   - Natriuretic peptides
   - Osmoreceptors → ADH
   - Other hormones



SHORT-TERM REGULATION

- Mediates the classic baroreceptor reflex
- High-pressure sensors (arterial): aortic arch, carotid sinus
  - Sense an increased intra-arterial pressure (mechanoreceptors) → increased firing
  - Signal travels to brainstem vasomotor region
  - Aortic arch →aortic nerve → afferent via glossopharyngeal + vagus nerve →NTS in brainstem vasomotor center
  - Carotid sinus→ glossopharyngeal nerve
- Low-pressure sensors (cardiopulmonary): In cardiac atria, RV, and large pulmonary vessels
  - Responds to distension of the structures where pressures are much lower than the arteries
  - Signals via afferent glossopharyngeal nerves and vagus → brainstem
- BOTH have the same efferent pathway: vasomotor center sends regulatory signals to heart, blood vessels, and kidneys (sympathetic outflow) → alter peripheral vascular resistance
  - Distension increase firing = vasodilation
  - Underloaded atria decrease firing = vasoconstriction

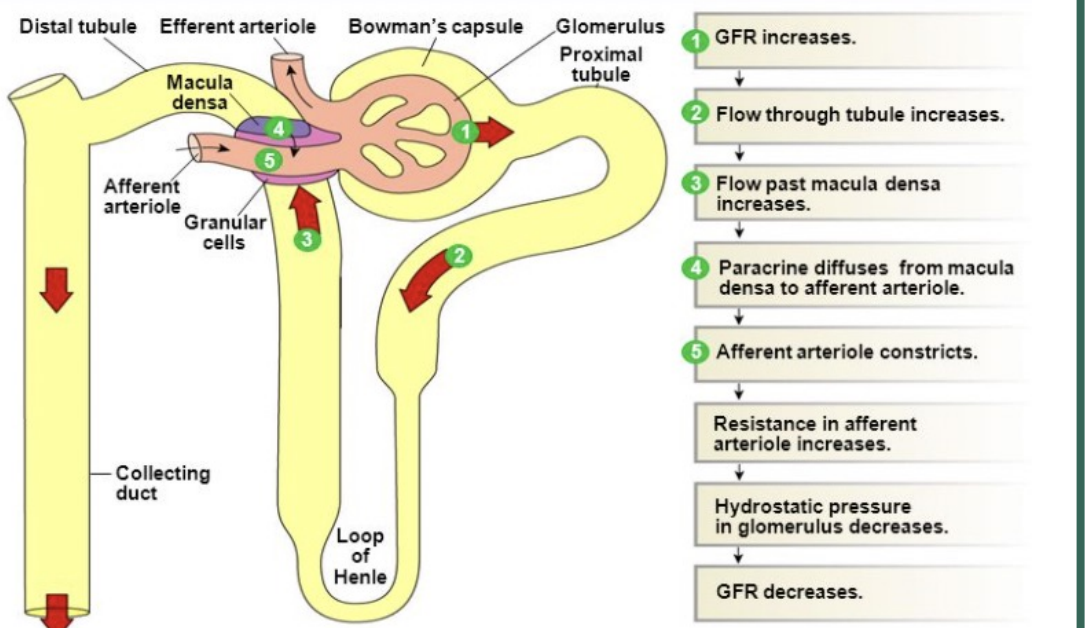

BARORECEPTOR REFLEX
↓ P_a
↓ Stretch on carotid sinus baroreceptors
↓ Firing rate of carotid sinus nerve
↓ Parasympathetic activity to heart
↑ Heart rate
↑ Sympathetic activity to heart and blood vessels
↑ Heart rate
↑ Contractility
Constriction of arterioles (↑ TPR)
Constriction of veins
↓ Unstressed volume
↑ Venous return
↑ P_a TOWARD NORMAL

INTERMEDIATE-TERM REGULATION

3 mechanisms:

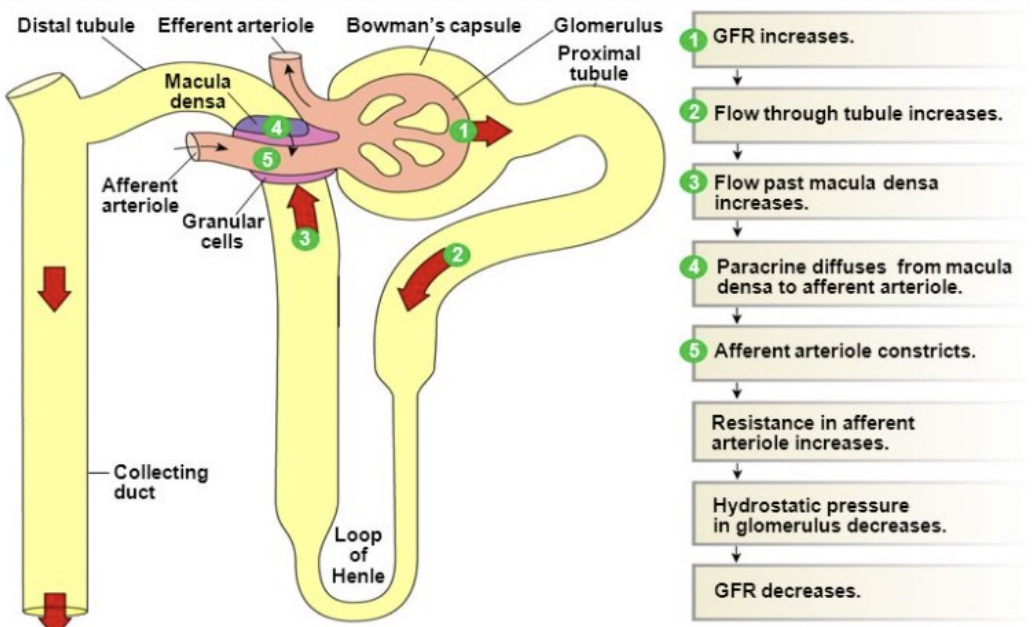
1. Renal sympathetic nerve stimulates renin secretion from granular cells (b1 adrenoreceptor-mediated)
2. Changes in SBP deforms granular cells membrane to stimulate release of renin (internal baroreceptor)
   - Renal (internal) baroreceptor located within the afferent arteriole (JGA) – detects change in pressure w/in the arteriole → act locally to stimulate granular cells to release renin
   - Do NOT send signal centrally
3. Tubuloglomerular feedback

TUBULOGLOMERULAR FEEDBACK



- Feedback loop in which [Cl] sensed at macula densa of JGA is converted into a signal that affect afferent arteriolar resistance and modulate blood flow and the amount of filtrate entering the tubule
- Sensor = macula densa
- Integrator = juxtaglomerular cells (granular cells)
- Effectors = Renal afferent and efferent arterioles

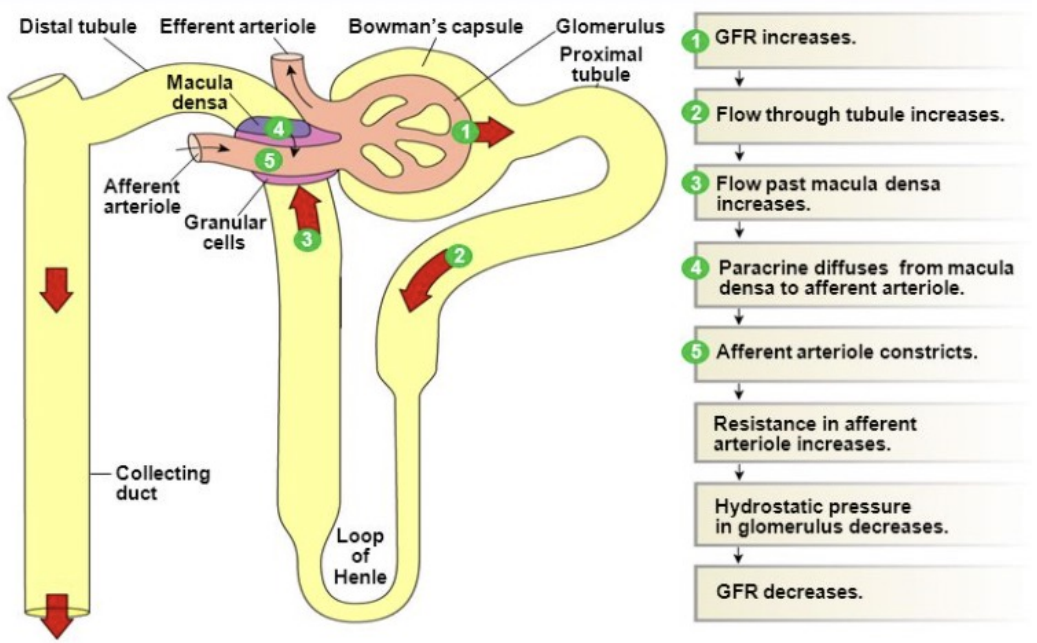
TUBULOGLOMERULAR FEEDBACK



<u>Response to increased GFR:</u>

- There is less time for NaCl to be reabsorbed in PCT → hyperosmotic filtrate
- Increased fluid movement and increased [Cl-] sensed by macula dense
  - Na, K, and Cl taken up by NKCC cotransporter
- Increased NaCl in lumen stimulate NHE → depolarize + activate macula densa cells
  - Depolarization allows Ca2+ entry
- Increased Ca2+:
  - Release ATP → stimulate purinergic P2 receptors on mesangial cells and afferent arteriolar smooth muscle cells → contraction of cells
  - Reduces renin secretion
  - ATP metabolized to adenosine → binds A1 receptor → afferent **vasoconstriction** and efferent vasodilation**
- This increases afferent resistance and decr RBF + GFR

TUBULOGLOMERULAR FEEDBACK



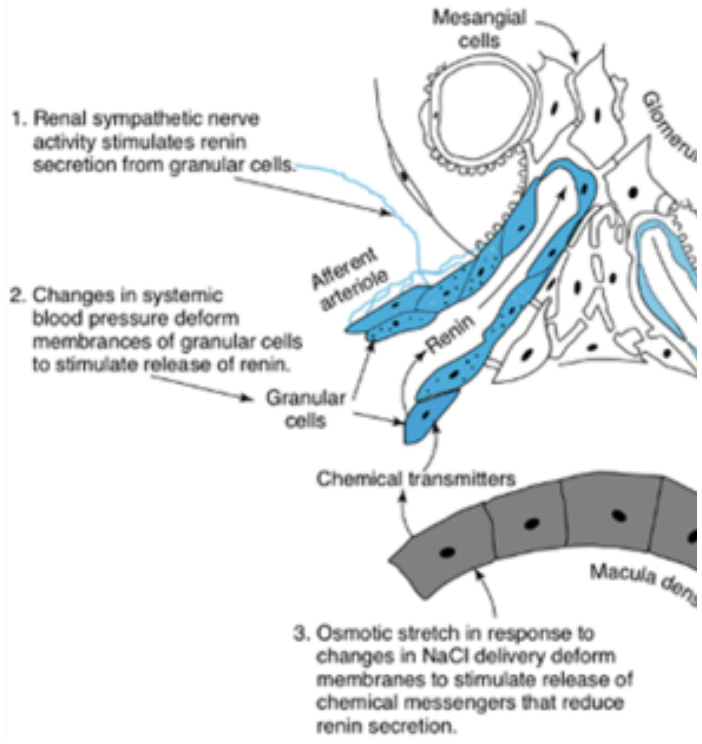
<u>Response to decreased GFR:</u>

- Less NaCl in DCT as most are reabsorbed in PCT → sensed by macula dense as decreased [Cl-]
- Less activation of JGA = less ATP and adenosine production
- JGA act directly on afferent arterioles → **afferent vasodilation**
- Released renin resulting in Ang II release → **efferent vasoconstriction**
- This results in increased glomerular capillary hydrostatic pressure = increased GFR

RENIN-ANGIOTENSIN ACTIVATION

- Renin converts angiotensinogen to Ang I
- Ang I to Ang II via ACE in pulmonary endothelium
- Ang II causes efferent arteriolar constriction
- RAS system is rapid acting, designed to deal with momentary fluctuations of GFR associated with BP changes
- With more sustained BP alterations, RAAS is activated

RENIN



- Produced as a pre-prorenin protein → trafficked, modified, and readied for secretion → secretory granules
- Released from the secretory granules of granular cells into renal interstitium and afferent arteriole
- Job: Converts angiotensinogen to Angiotensin I (Ang I)
- 3 factors stimulating renin release
  1. Hypotension and renal hypoperfusion --> sensed by internal baroreceptors (deforms granular cells) → triggers renin secretion
  2. Sympathetic nerve activity – beta-1 receptor stimulation incr renin secretion
     - cAMP and PKA-dependent process
  3. Reduced delivery of NaCl to MD via tubuloglomerular feedback
- Secretion decreased by
  - Incr NaCl reabsorption across macula densa (leads to osmotic swelling and decr renin secretion)
  - Incr afferent arteriolar pressure
  - Ang II and vasopressin

ANGIOTENSINOGEN

- Comes from the liver
- Levels increased by glucocorticoids, thyroid hormones, estrogen, cytokines
- No major role except to be converted into angiotensin I

ANGIOTENSIN CONVERTING ENZYME (ACE)

- Converts Angiotensin I to Angiotensin II
- Also inactivated bradykinin (vasodilator)
- ACE is expressed on all endothelium but highest % in pulmonary

ANGIOTENSIN II (ANG II)

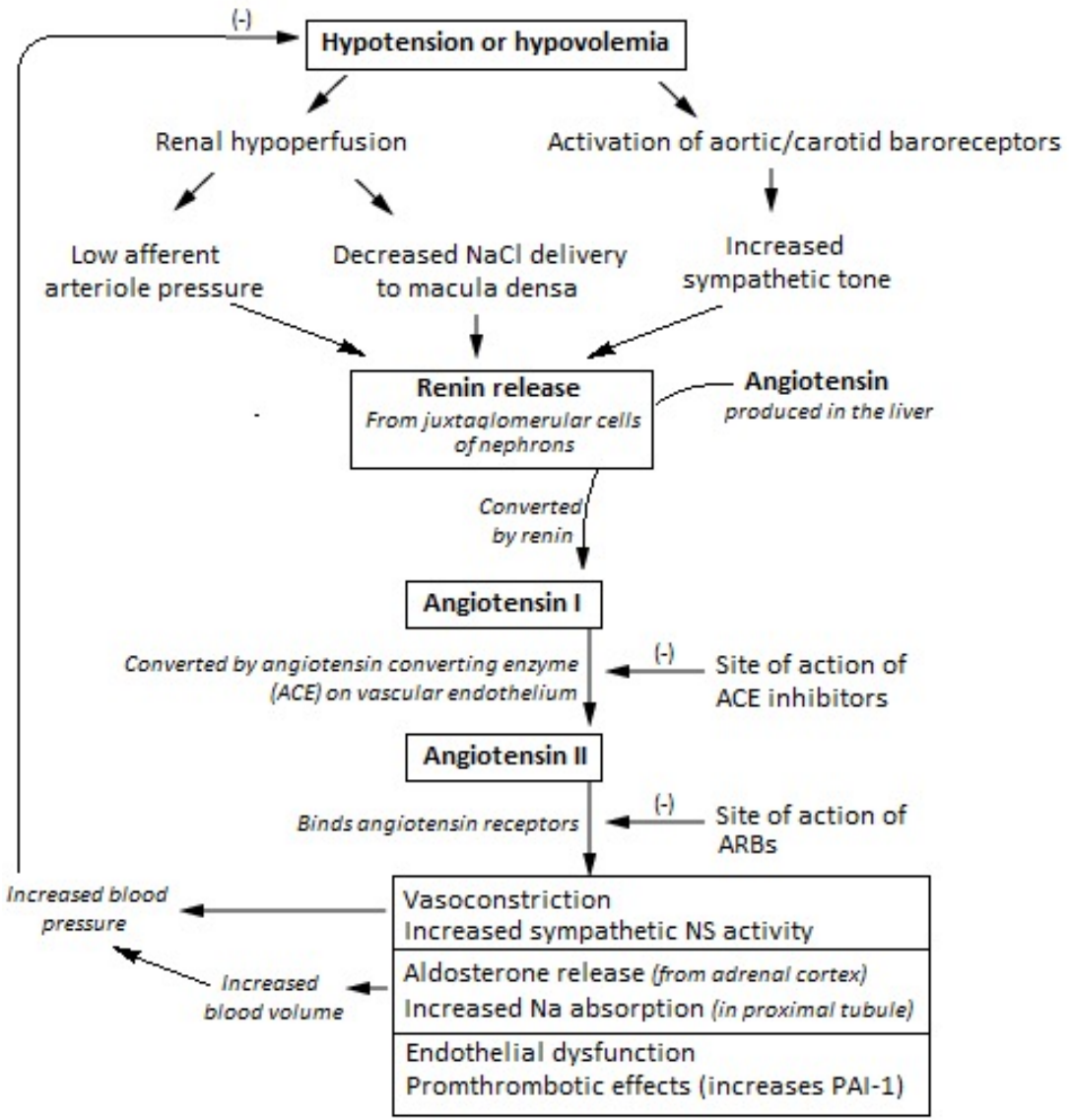
- Synthesized in the liver
- Effects of Ang II:
  - Arteriolar vasoconstriction (via PLC-IP3 pathway and Ca2+ mediated) via AT1 receptor
  - Increase Na+ reabsorption
    - Directly enhances Na/H exchanger in PCT = increase Na+ reabsorption
    - Stimulate adrenal zona glomerulosa → aldosterone secretion = Na+ reabsorption in CD
    - Stimulate contraction of mesangial cells → decr GFR = Incr Na+ retention
  - Increase sensitivity of baroreflex (brain) + promote norepi release → potentiates pressor effects
  - Stimulate hypothalamus to increase thirst
  - Increase ADH secretion
  - AT1-R mediated increased intracellular [Ca2+] to decrease renin secretion (-ve feedback)

ANGIOTENSIN II (ANG II)

- Removed from circulation via trapping mechanisms in the vascular bed of tissues other than the lungs
- Ang II increased by: incr sympathetic activity via renal nerves, incr circulating catecholamines (b1 receptor), prostaglandins
- Ang II decreased by: incr NaCl reabsorption across macula densa, incr afferent arteriolar pressure, Ang II, vasopressin
- Ang II receptors:
  - AT1: serpentine Gq protein coupled receptors to phospholipase C → incr Ca2+
    - AT1 mediates aldosterone production and its detrimental effects
  - AT2: G-protein coupled and act through various phosphatase → open K+ channels
    - Activation also increases NO production → incr cGMP
    - More plentiful in fetal and neonatal life
    - Renal and cardioprotective – systemic vasodilation, natriuresis, inhibition of renin release, and renal protection from inflammation, ischemia and fibrosis

ANGIOTENSIN III AND IV

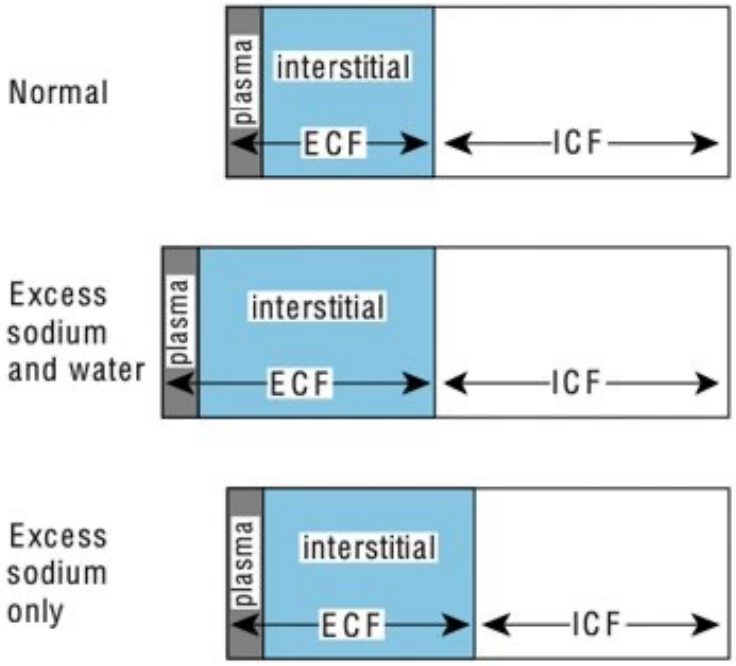
- Ang II is degraded into Ang III
- Ang III has 40% of vasopressor activity but 100% of aldosterone activity
- Ang IV's activity is mainly in CNS


(-)
Hypotension or hypovolemia
Renal hypoperfusion
Activation of aortic/carotid baroreceptors
Low afferent arteriole pressure
Decreased NaCl delivery to macula densa
Increased sympathetic tone
Renin release
From juxtaglomerular cells of nephrons
Angiotensin
produced in the liver
Converted by renin
Angiotensin I
Converted by angiotensin converting enzyme (ACE) on vascular endothelium
(-)
Site of action of ACE inhibitors
Angiotensin II
Binds angiotensin receptors
(-)
Site of action of ARBs
Increased blood pressure
Vasoconstriction
Increased sympathetic NS activity
Increased blood volume
Aldosterone release (from adrenal cortex)
Increased Na absorption (in proximal tubule)
Endothelial dysfunction
Promthrombotic effects (increases PAI-1)

LONG-TERM REGULATION: SODIUM CONTROL

- Baroreceptor reflex and RAS system are efficient at regulating vascular smooth muscle tone but aren't the ultimate determinants of BP
- The overall average BP is controlled by the kidneys, rather than the vasomotor center in the brainstem
- The kidneys do so by governing the amount of sodium (and therefore volume) on a long-term basis via the complete RAAS system
  - Blood volume is in turn determined by the total ECF volume
  - ECF volume is determined by the total osmotic content and osmolarity

RELATIONSHIP BETWEEN SODIUM AND ECF



- Total body water is divided into ICF and ECF
- ECF subdivided into interstitial and plasma volume
- Excess Na+ is **almost always** accompanied by water movement → excess Na+ causes ECF expansion
- If the osmolality remains the same, volume expansion is only in the ECF and ICF is unaffected (middle); total body water is increased
- However, if there is excess Na+ without excess water, water moves from ICF into ECF until osmolality equilibrates → ECF increases but ICF decreases with no change in total body water content

LONG-TERM REGULATION: SODIUM CONTROL

- The kidneys do not rely on plasma [Na+] but rather pressures in different part of the vasculature and in the kidneys
  - Pressure changes are interpreted as a change in total body [Na+]
- Various mechanisms come into play:
  - GFR
  - Glomerulotubular balance
  - RAAS → Ang II, pressure natriuresis (and diuresis), role of aldosterone***
  - Other mechanisms: natriuretic peptides, osmotic regulation (ADH), hormones

GFR

- Changing GFR is a mechanism for altering ECF volume and absorption of said volume
- Mediated by altering afferent and efferent arteriolar resistance via renal sympathetic activity and Ang II
  - Increased plasma volume will trigger decreased sympathetic activity → decrease renin secretion → decrease GFR and Na+ retention → decrease ECF volume
- An increase in either peritubular capillary hydrostatic pressure or interstitial pressure or decrease in peritubular capillary oncotic pressure will reduce net reabsorption and increase excretion = decrease volume
  - High interstitial pressure does more to oppose fluid efflux out of lumen than it does to promote fluid influx, as it causes a constant back-leak of reabsorbed fluid across tight junctions back into the lumen

CHANGES IN GFR

Changes that lower GFR

Occurs when there is fluid loss

1. Increased afferent and efferent arteriolar constriction (Ang II mediated)
2. Decreased arterial hydraulic pressure
3. Increased arterial oncotic pressure

- These 3 factors will decrease renal interstitial hydraulic pressure and increase Na+ reabsorption = preserve ECF volume

Changes that increase GFR

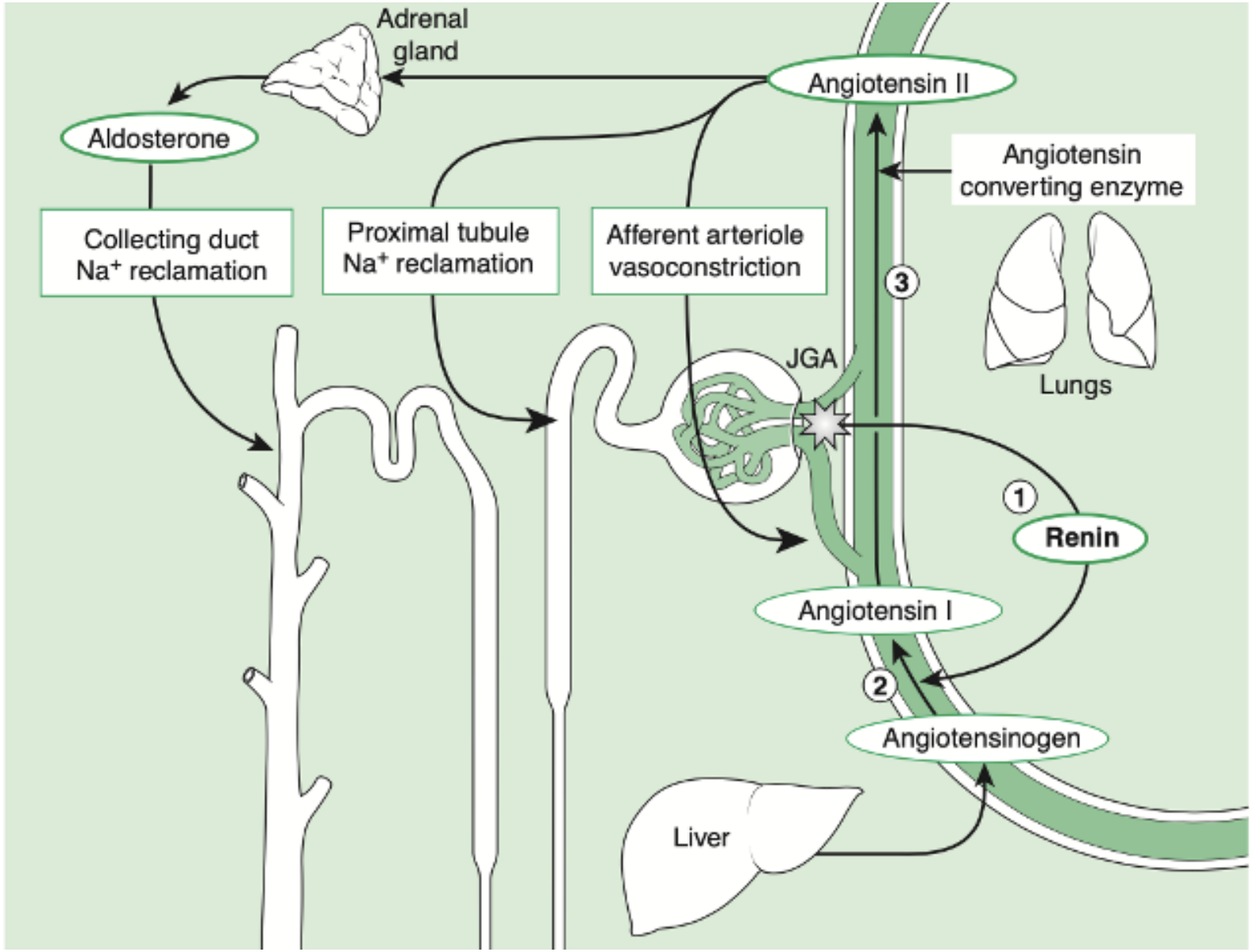
Resposnes to eliminate excess Na+

1. Decreased plasma oncotic pressure (dilutional)
2. Increased arterial pressure
3. Renal vasodilation (decreased sympathetic activity and Ang II)

- This results in increased GFR and interstitial pressures = reduce fluid reabsorption = reduce ECF volume

GLOMERULOTUBULAR BALANCE

- Mechanism to ensure a constant fraction of the filtered load of the nephron is resorbed across a range of GFR
  - I.e. The fraction of filtered Na+ remains constant in PCT, around 65%
  - If Na+ reabsorption is not around 65%, it means other mechanisms (not GFR) is at play
- Mechanism not completely clear – suspect changes in GFR result in Starling forces of the peritubular capillaries resulting in proportionally increased or decreased total nephronic resorption
- Completely intrarenal
- Protects distal segments of nephron from being overloaded during short-term increases in GFR
  - Distal segments of the nephron have a very limited capacity to increase tubular resorption of water and solutes
- A 2nd line protection for the nephron if tubuloglomerular feedback (1st line) were to fail

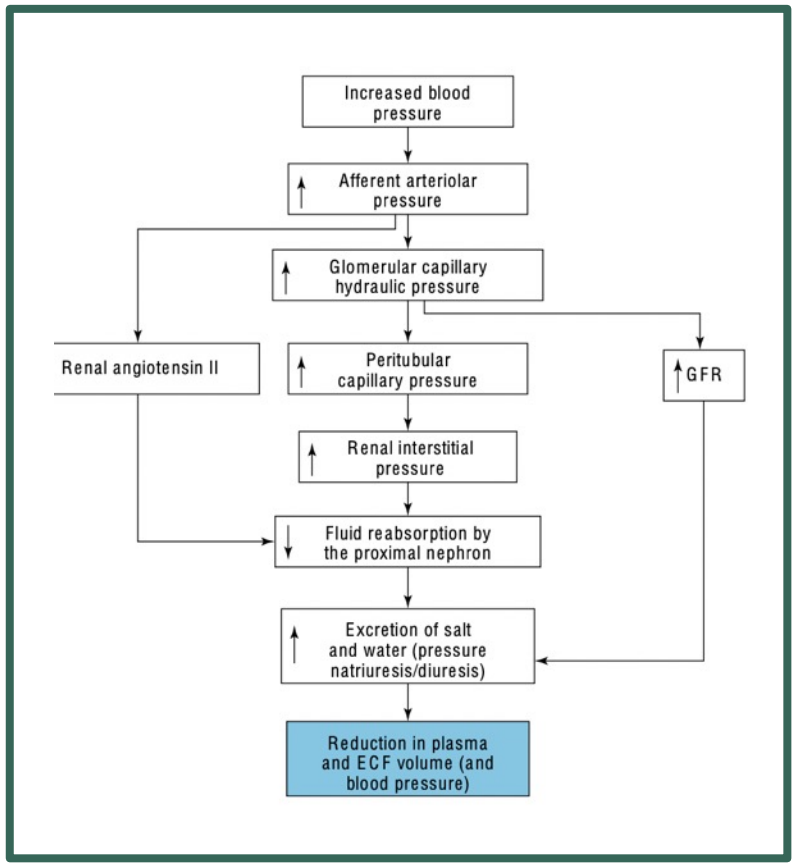


RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

RAAS: ANG II

1. Vasoconstrict renal arterioles → reduce RBF and GFR
2. Constrict glomerular mesangial cells → decreases SA and decr GFR
3. Stimulates Na+ reabsorption in PCT by stimulating NHE
4. Increase aldosterone release

PRESSURE NATRIURESIS AND DIURESIS

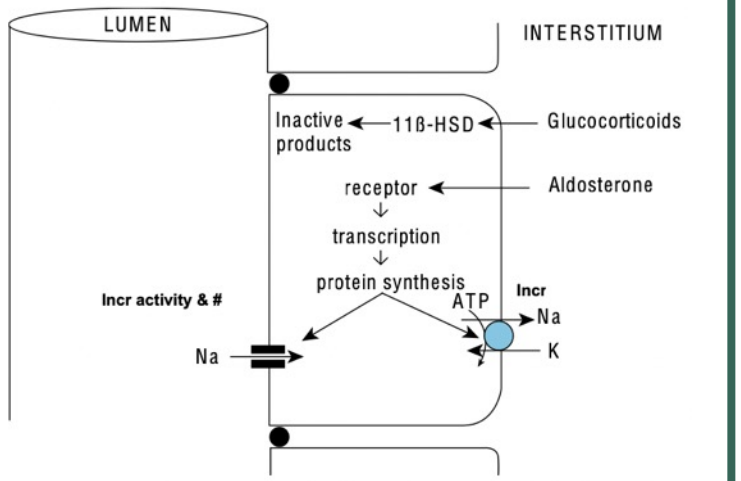


- Pressure natriuresis = increased renal Na+ excretion when incoming arterial pressure to the kidneys rises
  - Dominant physiological mechanism linking arterial BP to changes in total body [Na+]
  - Mediated by angiotensin II
- Completely within the kidneys without external neurohormonal influences
- Mechanism:
  - Increased arterial pressure increases the hydrostatic pressure within the peritubular capillaries
  - This reduces the Starling force for fluid reabsorption into the capillaries from renal interstitium → decreased proximal tubular reabsorption
    - High pressure reduce intrarenal Ang II → NHE withdrawn
  - With reduced reabsorption, water and Na+ appear to backleak into the tubule → enhanced urinary Na+ excretion

OPPOSITION TO ANG II

- Autoregulation of GFR, along with tubuloglomerular feedback, blunts excessive response to large changes in GFR or RBF
- Autoregulation of GFR involves prostaglandin production during massive vasoconstriction that can markedly reduce GFR and RBF (I.e. high Ang II and sympathetic stimulation)
  - Prostaglandins induce vasodilation of arterioles + relaxation of mesangial cells
  - RBF and GFR are still reduced but to a lesser extent

RAAS: ALDOSTERONE



- Long-term regulation of BP
- Produced by glomerulosa cells of adrenal cortex
- Act on mineralocorticoid receptors on principal cells of cortical collecting tubule + CD
  - Cross principal cells lipid membranes
  - Once bound, the receptor acts as transcription factor to promote gene expression and synthesis of mRNA
- "All purpose" stimulator of tubular Na+ retention
  - Stimulate ENaC on apical membrane (stabilizes ENaC protein to limit endocytotic return of protein to the cytoplasm)
  - Increased activity of basolateral Na-K-ATPase → incr electrostatic gradient to facilitate Na+ reabsorption
- Aldosterone influence 2% of total filtered Na+

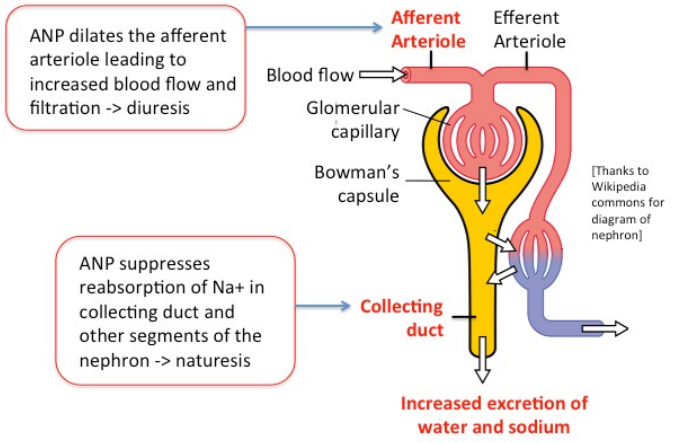
RAAS: ALDOSTERONE

- Overtime, even if BP normalized, Ang II will continue to stimulate adrenal cortex to produce aldosterone from initial hypotension → aldosterone targets distal nephron to incr Na+ resorption = restore total body Na+ and blood volume
- Aldosterone secretion is ultimately linked to what regulates renin secretion (internal baroreceptors, macula densa, renal sympathetic nerves)
  - Low plasma volume → renin secretion → incr ang II → incr aldosterone
- Aldosterone secretion controlled via:
  - Stimulated by Ang II and hyperkalemia
  - Inhibited by ANP

OTHER REGULATORS:

- Natriuretic peptides: Atrial (ANP) and brain (BNP)
- Osmoregulation: ADH
- Hormones
  - Enhance Na+ reabsorption: Cortisol, estrogen, GH, thyroid hormone and insulin
  - Decrease Na+ reabsorption: glucagon, progesterone, PTH

NATRIURETIC PEPTIDES



- Atrial and brain natriuretic peptides (ANP, BNP)
- Release stimulated by atrial distension during volume expansion
- Circulate and bind to high affinity receptors → cGMP-dependent signaling cascade → act on end organs: blood vessels, adrenal glands, kidneys
- Promote urinary Na+ excretion
  - Relax **afferent** arteriole (promotes filtration)
  - Inhibit release of renin
  - Inhibit action of Ang II
  - Act on ENaC in medullary collecting duct to inhibit Na+ reabsorption

ADH

- Increase osmolality stimulates ADH release from posterior pituitary
- Relevant ADH actions
  - Increase water permeability in CD via AQ 2-4 insertion
  - Increase Na+ reabsorption by cortical CD (synergistic w/ aldosterone)

OTHER HORMONES

Enhance Na+ reabsorption

- Cortisol, estrogen, GH, thyroid hormone and insulin

Decrease Na+ reabsorption:

- Glucagon, progesterone, PTH

TABLE 3-3 Effectors of Sodium Balance

Effector	Stimuli for Release	Inhibitors of Release	Major Effects
Aldosterone	Angiotensin II Hyperkalemia Adrenocorticotropic hormone	Dopamine ANP	Increased number and activity of luminal Na^+ channels and basolateral Na^+, K^+ ATPase in principal cells of cortical collecting ducts
Angiotensin II	↓ Renal perfusion pressure*	↑ Renal perfusion pressure*	Systemic vasoconstriction Glomerular arteriolar vasoconstriction (efferent > afferent) Stimulates proximal Na^+ reabsorption Stimulates aldosterone secretion
Atrial natriuretic peptide (ANP)	↑ Atrial stretch	↓ Atrial stretch	Inhibits Na^+ reabsorption in parts of the collecting duct Directly increases glomerular filtration rate
Catecholamines	↓ Effective circulating volume	↑ Effective circulating volume	Vasoconstriction Glomerular arteriolar vasoconstriction (efferent > afferent) Increase proximal tubular Na^+ reabsorption (α_1 effect) Stimulate renin release (β_1 effect)
Renin	↓ Perfusion pressure in juxtaglomerular apparatus Sympathetic nervous system activity Decreased Cl delivery to macula densa	Angiotensin II ANP Antidiuretic hormone	Not an "effector"—an enzyme that converts angiotensinogen to angiotensin I

*Via release and action of renin.

WATER EXCRETION

CONTROL OF WATER EXCRETION

- Water excretion is controlled by factors that govern intravascular volume status and osmolality
- 2 major components:
  - Proximal tubular reabsorption that occurs with Na+
    - Regulates ECF volume in response to change in BP
  - Distal tubular reabsorption that occurs independent of Na+
    - Regulates water resabosprtion by ADH
    - ADH release is stimulated by osmolality changes sensed by osmoreceptors

ADH/VASOPRESSIN

- Produced by hypothalamic neurons whose cell bodies are located in the supraoptic and paraventricular nuclei
- Axon terminates in posterior pituitary gland → ADH released from there into bloodstream
- Regulates water homeostasis via:
  - Regulating fast shuttling of AQ-2 to cell surface
  - Stimulating the synthesis of messenger RNA-encoding AQ-2
- Osmotic receptor trigger: 1-2% change in osmolality is enough to stimulate ADH release and thirst
  - Osmolality dropping to 290 mOsm/kg is sufficient
  - 10x more sensitive than hemodynamic system – 1-2% osmolality change stimulates the equivalent ADH release as 20-30% changes in BP

CONTROL OF ADH/VASOPRESSIN

Baroreceptor control

- Decreased ECF volume → aldosterone secretion
- Decreased ECF volume = hypovolemia → decreased baroreceptor firing → causes stimulation for ADH secretion

- Osmoreceptors = sensory receptor that detects changes in osmotic pressure (osmolality)
  - Present in the organum vasculosum of the laminae terminalis (OVLT), anterior + ventral to 3rd ventricle
  - OVLT has a unique fenestrated, leaky endothelium (not like BBB w/ tight junctions) and are not part of the CSF → exposed directly to the chemical environment of systemic circulation
- OVLT have membrane-bound cation channels sensitive to mechanical stimuli
- Activity inhibited by membrane stretch (hypotonic fluid → cells swell) and activated by membrane shrinkage (hypertonic fluid → cells shrink)

THIRST RESPONSE

- Thirst is stimulated by both reduced plasma volume and by increased osmolality
  - Thirst response is much less sensitive compared to ADH response
  - Ang II can also stimulate thirst

ALTERED Na+ EXCRETION IN CHF

- Neurohormonal drive to compensate for CHF includes catecholamine release and activation of RAAS (high levels of renin. Ang II and aldosterone) → increased effective circulating volume and fluid overload → congestive heart failure
- High fluid volume leads to elevated atrial pressure → should be perceived as increased firing = decreased ADH secretion + sympathetic drive
- However, baroreceptors are activated and kidney's setpoint is reset where normal Na+ excretion only occurs at the expense of excessive body fluid volume
  - If fluid volume is restored to normal, renal excretion of Na+ drops to very low
- ANP levels are also elevated during CHF due to high atrial pressures and partially counteracts the sodium-retaining signals to the kidneys
  - However, this doesn't restore Na+ output to normal level
- Persistent high circulating volume is deleterious to pulmonary function

ALTERED Na+ EXCRETION IN HYPERTENSION

- Hypertension is associated with a blood volume and total body [Na+] that is too high for the vascular tree
- This may be due to renal glomerular dz causing inappropriate renin release, tumour of adrenal cortex leading to excessive production of aldosterone, or abnormal genetic mutation that leads to excessive Na+ reabsorption

DRUGS ACTING ON RAAS SYSTEM

- Renin antagonists: Aliskiren– not used in vet med
- ACE inhibitors – benazepril, enalapril
- Angiotensin II – used in human medicine as vasopressor (ATHOS-3)
  - Angiotensin II for the Treatment of High-Output Shock: Evaluated the effectiveness of Ang II in patients with vasodilatory shock already receiving vasopressors (catecholamines >0.2 mcg/kg/min for ≥6 and ≤48h)
  - Found Ang II increased BP in patients with vasodilatory shock
- Angiotensin II receptor blockers (ARBs) - telmisartan

ACE INHIBITORS

- ACEi inhibitor acts to prevent ACE converting of angiotensin I to angiotensin II.
- Effects:
  - Reduce BP via inhibition of Ang II
  - Reduce proteinuria: Reduce intraglomerular hypertension by vasodilating efferent arterioles
  - Reduces glomerular capillary pressure while increasing renal plasma flow and preserve GFR
- Benazepril and Enalapril
  - Benazepril is cleared by both the kidneys and liver, whereas enalapril is only cleared by the kidneys

ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

- Acts on AT-1 receptor
- Licensed for systemic hypertension in cats (Telmisartan), indicated in certain types of heart failure in people
- In people, ARB is preferred over ACEi because
  - Lower incidence of cough and angioedema
  - Adverse effect stimulated by angiotensin II are blocked by ARBs
  - Reduce generation of pathogenic angiotensin II
  - AT-2 receptor that are not blocked can still respond to angiotensin II as a result of AT-1 blockade

TELMISARTAN

- MoA: selective blockade of AT1 receptor, aldosterone synthesis & secretion is reduced → vasodilation, decreased K+ and increased Na+ secretion
  - Does not interfere w/ substance P or bradykinin response
- Recent studies seem promising for its use in treatment of hypertension and proteinuria
- FDA approval only for tx of systemic hypertension in cats
- Adverse effects: GI upset, lethargy, dehydration, weight loss >>> hypotension, anemia, ELE, azotemia/renal insufficiency

REFERENCES

- Renal physiology texts: Danzinger, Koeppen & Staton, Vanders
- Plumbs


End of Presentation
ANY QUESTIONS?
Memecreator.org