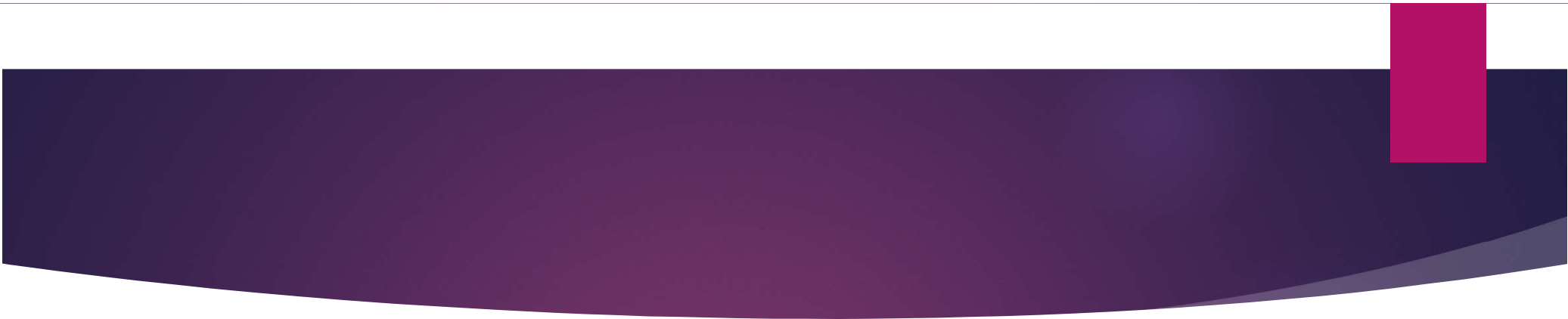


Kidney physiology



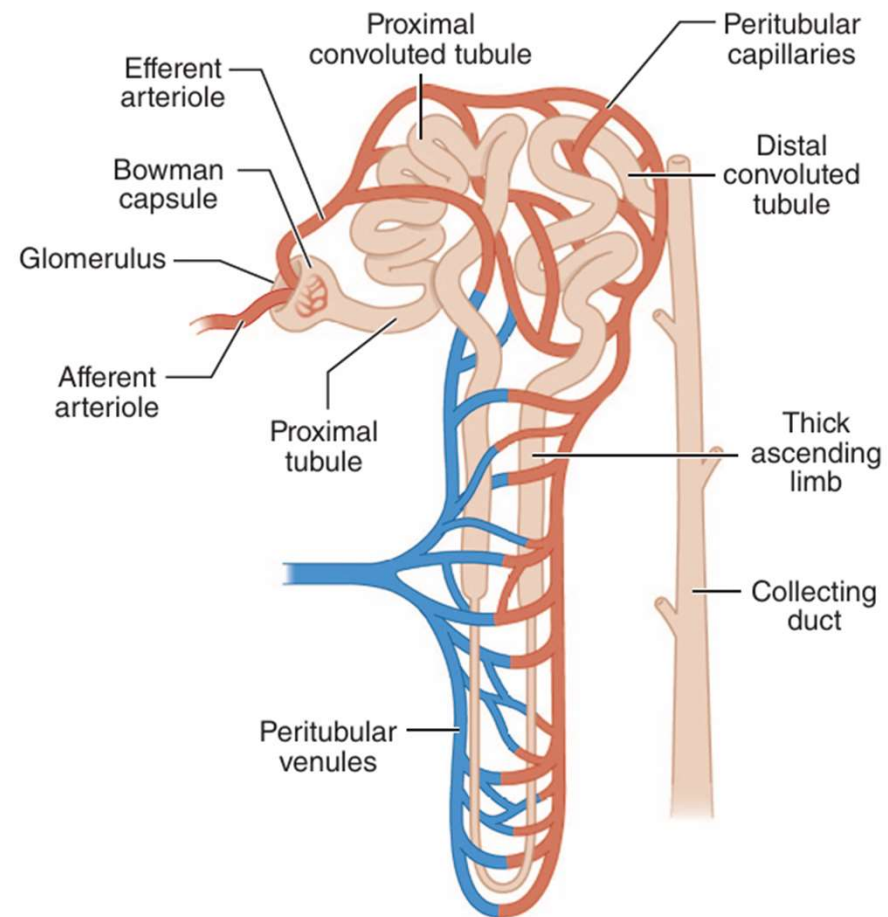
- 
- ▶ There are ~900,000 glomeruli in each kidney in normal-birth-weight adults and as few as 225,000 in low-birth-weight adults, with the latter producing numerous comorbid risks.



DETERMINANTS AND REGULATION OF GLOMERULAR FILTRATION

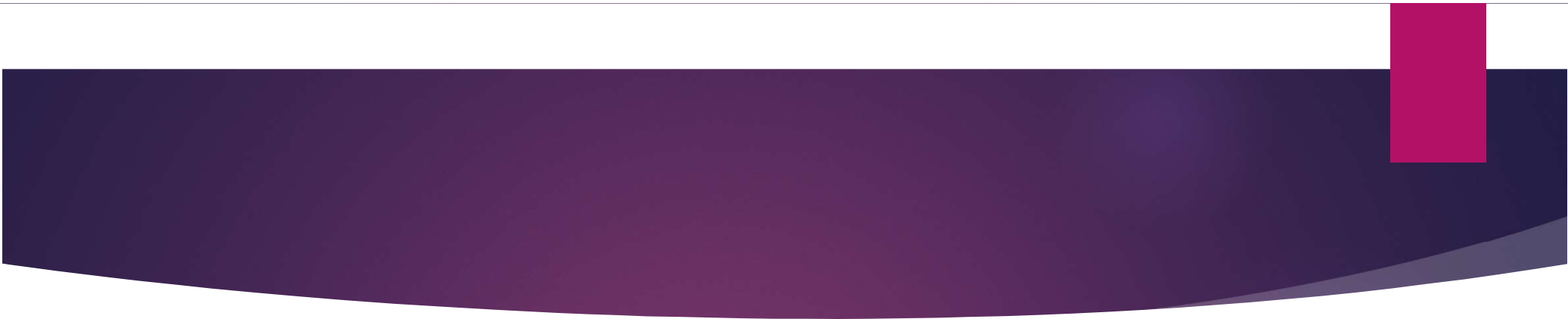
- ▶ Renal blood flow normally drains ~20% of the cardiac output, or 1000 mL/min. Blood reaches each nephron through the afferent arteriole leading into a glomerular capillary where ultrafiltration forms the tubular fluid. The distal ends of the glomerular capillaries coalesce to form an efferent arteriole leading to the first segment of a second capillary network (cortical peritubular capillaries or medullary vasa recta) surrounding the tubules



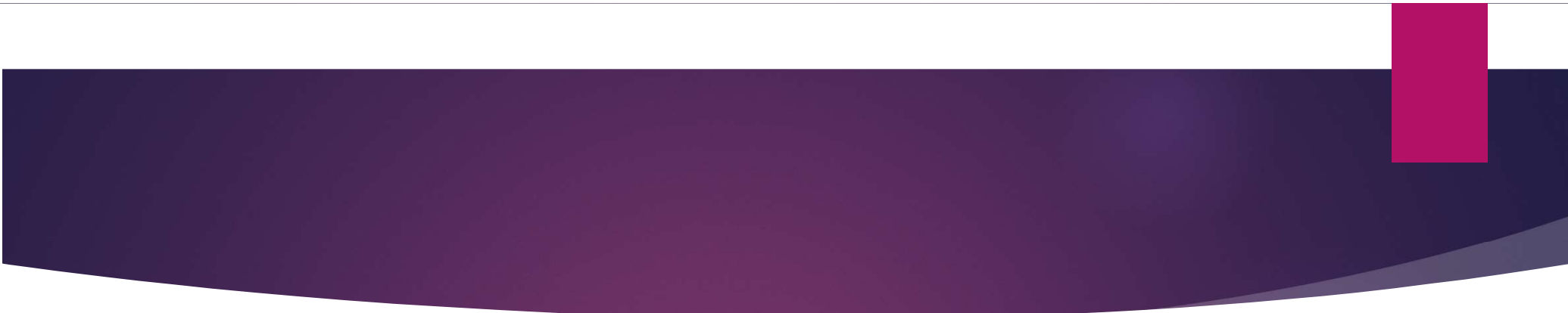


A

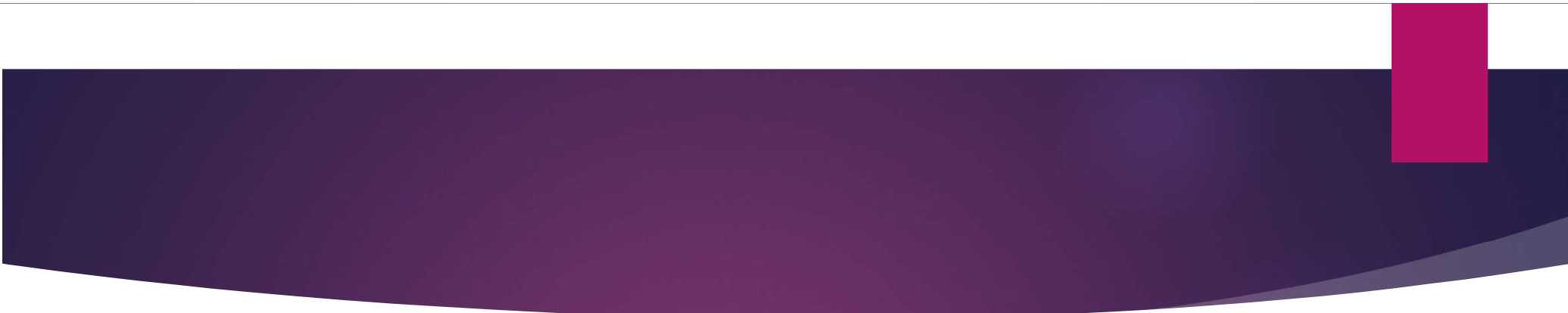


- 
- ▶ The hydrostatic pressure gradient across the glomerular capillary wall is the primary driving force for glomerular filtration. Oncotic pressure within the capillary lumen, determined by the concentration of unfiltered plasma proteins, partially offsets the hydrostatic pressure gradient and opposes filtration.

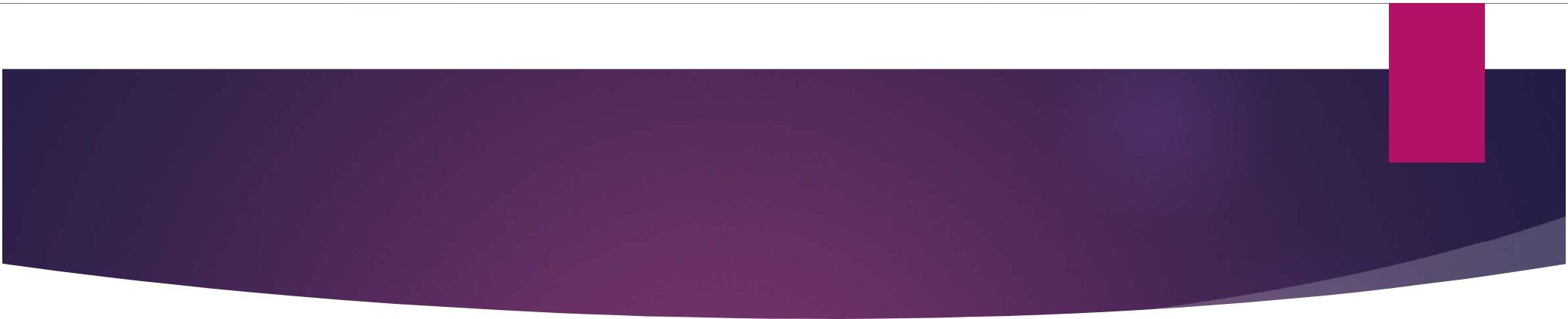


- 
- ▶ Although glomerular filtration is affected by renal artery pressure, this relationship is not linear across the range of physiologic blood pressures due to autoregulation of GFR.
 - ▶ Autoregulation of glomerular filtration is the result of three major factors that modulate either afferent or efferent arteriolar tone; these include
 - ▶ an autonomous vasoreactive (myogenic) reflex in the afferent arteriole,
 - ▶ tubuloglomerular feedback (TGF),
 - ▶ and angiotensin II-mediated vasoconstriction of the efferent arteriole.

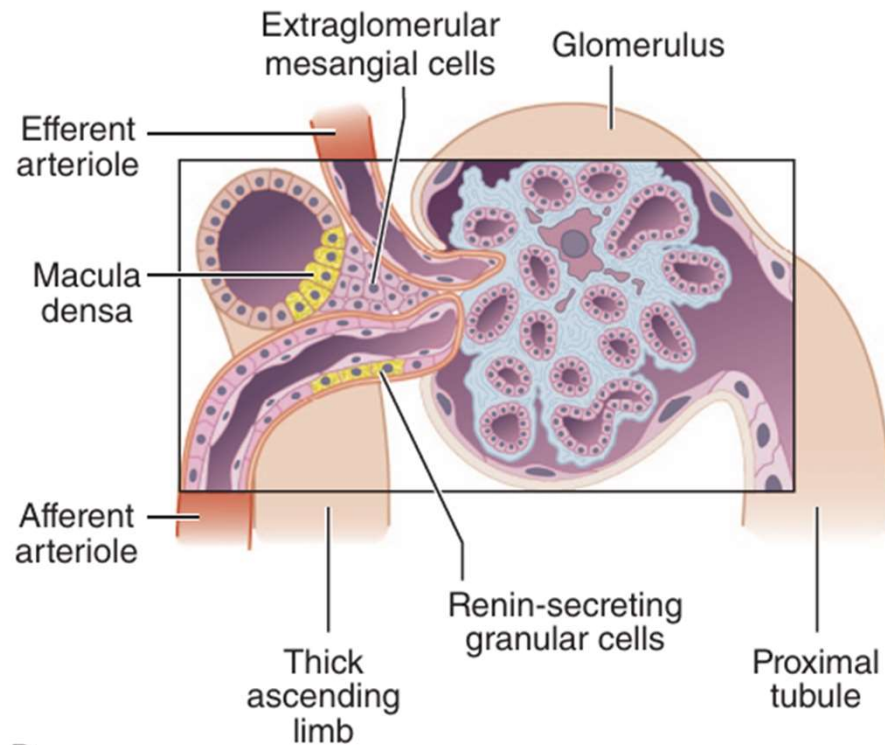


- 
- ▶ The myogenic reflex
 - ▶ is a first line of defense against fluctuations in renal blood flow. Acute changes in renal perfusion pressure evoke reflex constriction or dilatation of the afferent arteriole in response to rising or falling pressure, respectively.
 - ▶ This phenomenon helps protect the glomerular capillary from sudden changes in systolic pressure.



- 
- ▶ TGF changes the rate of filtration and tubular flow by reflex vasoconstriction or dilatation of the afferent arteriole. TGF is mediated by specialized cells in the thick ascending limb of the loop of Henle called the macula densa that act as sensors of solute concentration and tubular fluid flow rate.
 - ▶ With high tubular flow rates, a proxy for an inappropriately high filtration rate, greater solute delivery to the macula densa evokes vasoconstriction of the afferent arteriole, causing GFR to return toward normal.





B

2365

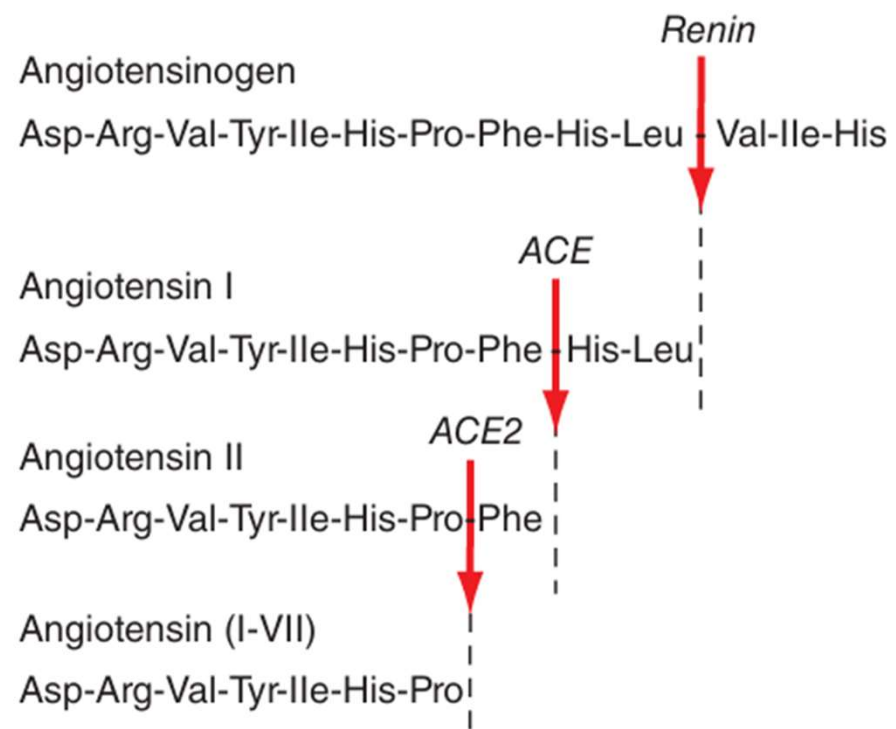
One component of the soluble signal from the macula densa is adenosine triphosphate (ATP) released by the cells during increased NaCl reabsorption. ATP is metabolized in the extracellular space to generate adenosine, a potent vasoconstrictor of the afferent arteriole. During conditions associated with a fall in filtration rate, a lower rate of solute delivery to the macula densa attenuates TGF, allowing afferent arteriolar dilatation and restoring GFR to normal levels.



angiotensin II

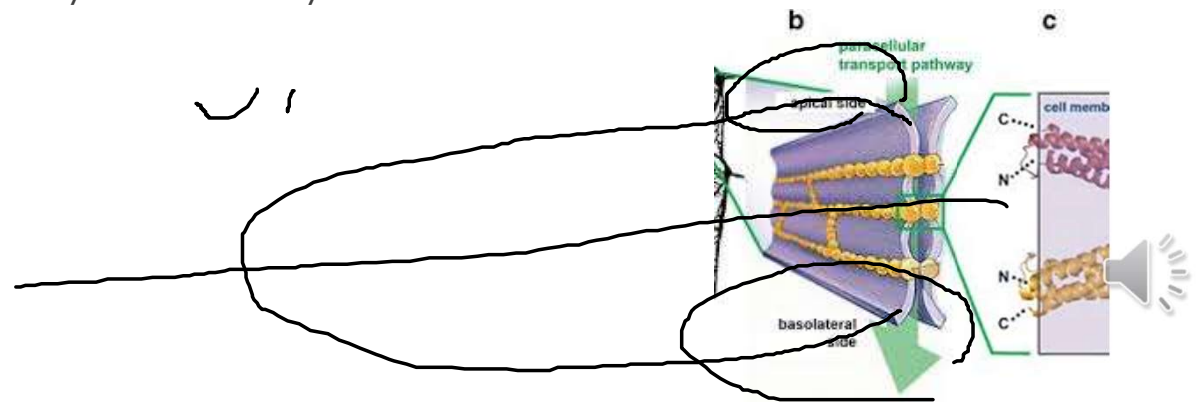
- ▶ During states of reduced renal blood flow, renin is released from granular cells within the wall of the afferent arteriole near the macula densa in a region called the juxtaglomerular apparatus .
- ▶ Renin, a proteolytic enzyme, catalyzes the conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE) .
- ▶ Angiotensin II evokes vasoconstriction of the efferent arteriole, and the resulting increased glomerular hydrostatic pressure elevates GFR to normal levels.





MECHANISMS OF RENAL TUBULAR TRANSPORT

- Tight junctions form an occlusive barrier that separates the lumen of the tubule from the interstitial spaces surrounding the tubule and also apportions the cell membrane into discrete domains: the apical membrane facing the tubular lumen and the basolateral membrane facing the interstitium. This regionalization allows cells to allocate membrane proteins and lipids asymmetrically.



EPITHELIAL SOLUTE TRANSPORT

- ▶ cellular transport
- ▶ paracellular transport:
- ▶ some epithelial cell layers allow rather robust paracellular transport to occur (leaky epithelia), whereas other epithelia have more restrictive tight junctions (tight epithelia)
- ▶ The proximal tubule contains leaky epithelia, whereas distal nephron segments, such as the collecting duct, contain tight epithelia.



■ MEMBRANE TRANSPORT

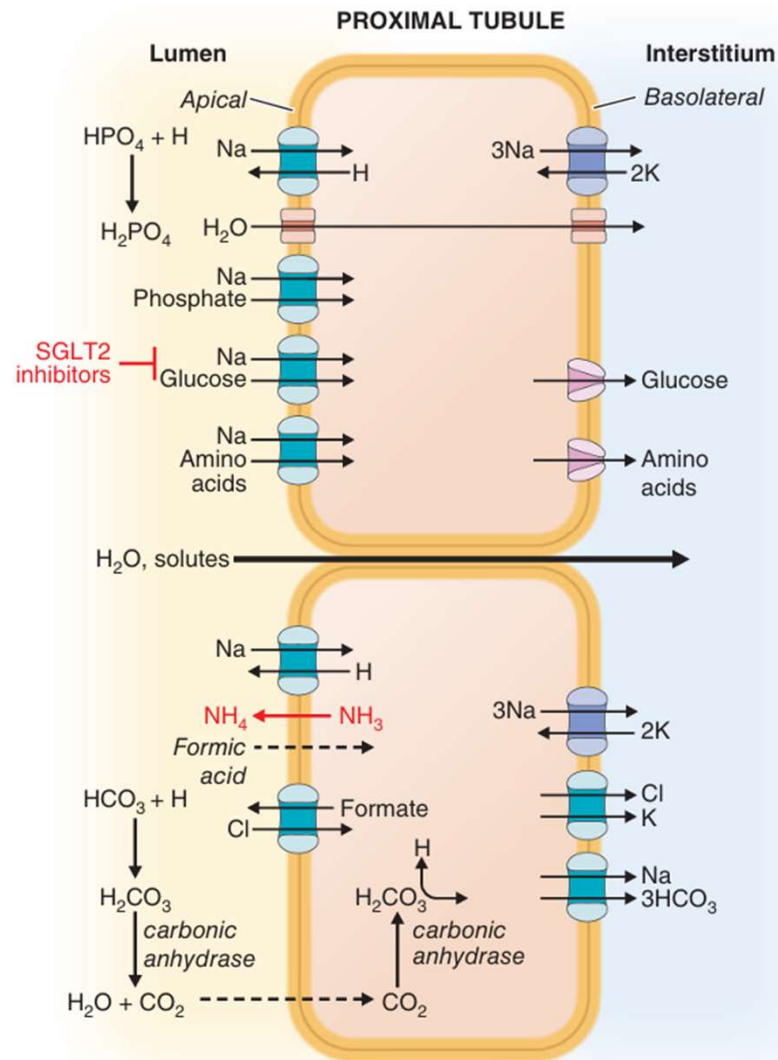
- ▶ These different mechanisms mediate specific types of transport activities, including
- ▶ active transport (pumps),
- ▶ passive transport (channels),
- ▶ facilitated diffusion (transporters),
- ▶ and secondary active transport (cotransporters).



PROXIMAL TUBULE

- ▶ The proximal tubule is responsible for reabsorbing ~60% of filtered NaCl and water, as well as ~90% of filtered bicarbonate and most critical nutrients such as glucose and amino acids.
- ▶ The proximal tubule uses both cellular and paracellular transport mechanisms. The apical membrane of proximal tubular cells has an expanded surface area available for reabsorption created by a dense array of microvilli called the brush border, and leaky tight junctions enable high-capacity fluid reabsorption.

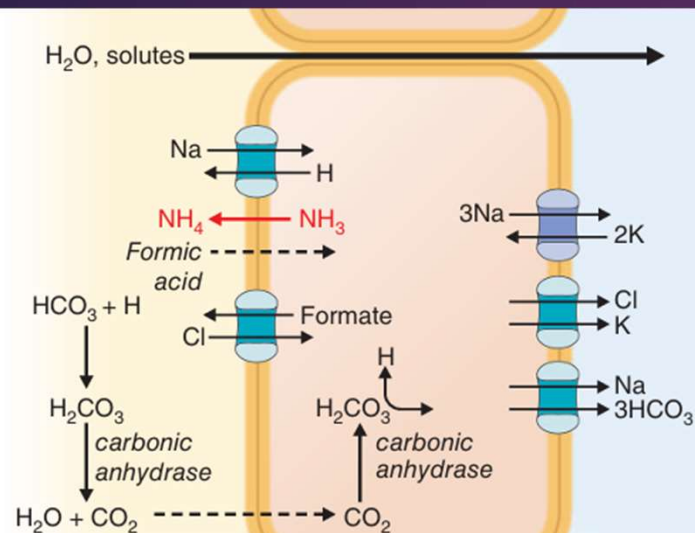




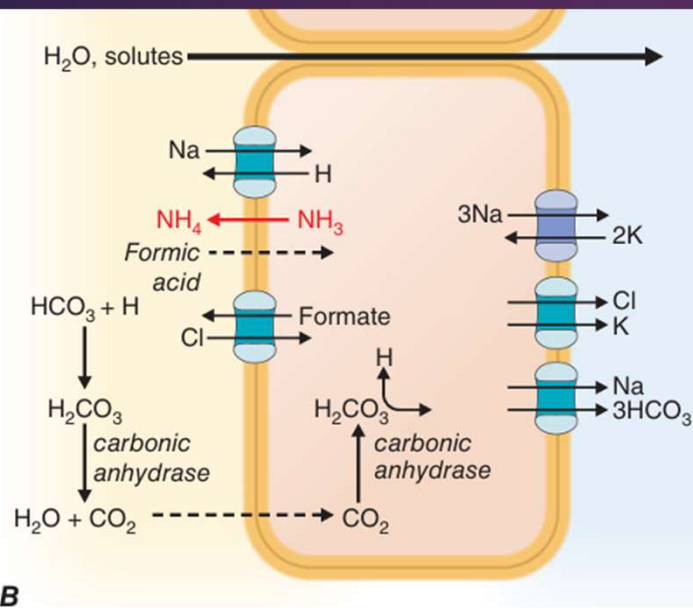
B

Cellular transport of most solutes by the proximal tubule is coupled to the Na⁺ concentration gradient established by the activity of a basolateral Na⁺/K⁺-ATPase. This active transport mechanism maintains a steep Na⁺ gradient by keeping intracellular Na⁺ concentrations low. Solute reabsorption from the tubular lumen is coupled to the Na⁺ gradient by Na⁺-dependent transporters such as Na⁺-glucose and Na⁺-phosphate cotransporters present in apical membranes.



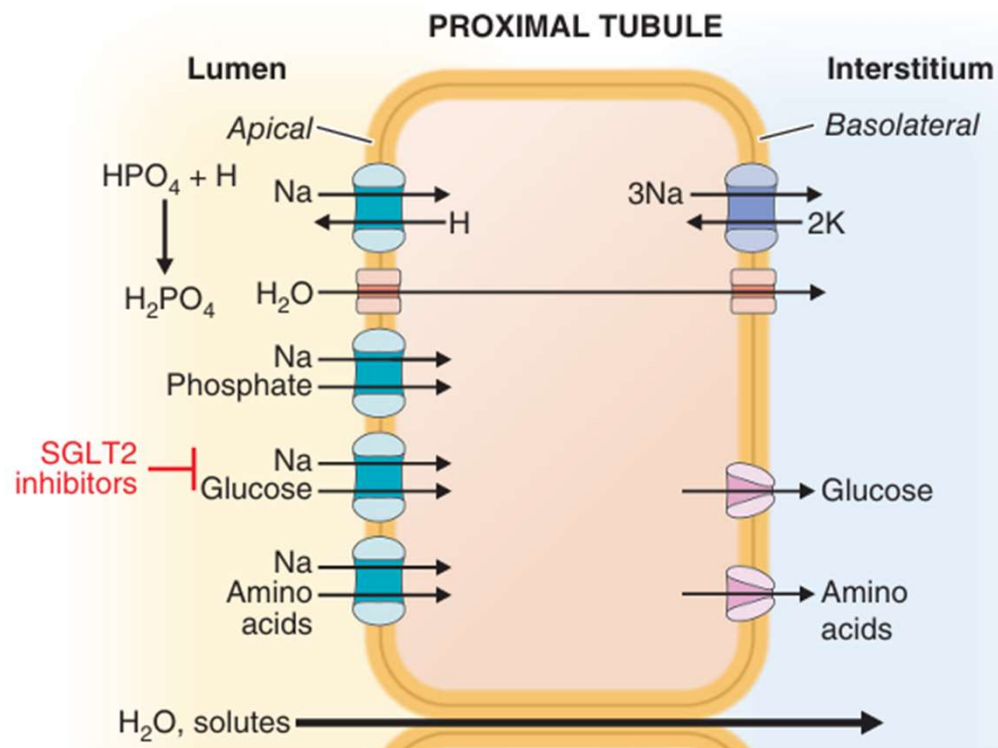


Filtered bicarbonate is first titrated by protons delivered to the lumen mainly by apical membrane Na^+/H^+ exchange. The resulting carbonic acid (H_2CO_3) is metabolized by brush border carbonic anhydrase to water and carbon dioxide. Dissolved carbon dioxide then diffuses into the cell, where it is enzymatically hydrated by cytoplasmic carbonic anhydrase to re-form carbonic acid. Finally, intracellular carbonic acid dissociates into free protons and bicarbonate anions, and bicarbonate exits the cell through a basolateral $\text{Na}^+/\text{HCO}_3^-$ cotransporter. This process is saturable, which can result in renal bicarbonate excretion when plasma levels exceed the physiologically normal range (24–26 meq/L). Carbonic anhydrase inhibitors such as acetazolamide block proximal tubule bicarbonate reabsorption and are useful for alkalinizing the urine.



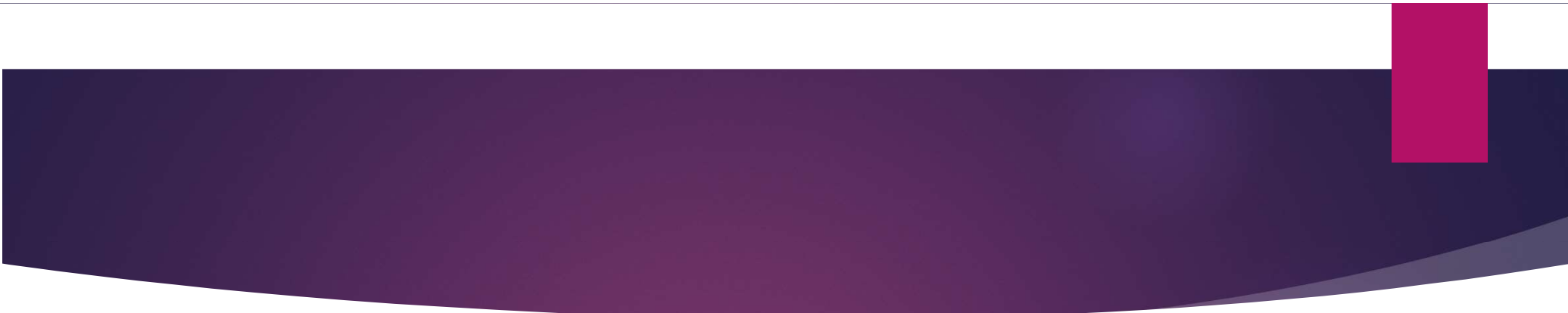
The proximal tubule contributes to acid secretion by two mechanisms involving the titration of the urinary buffers ammonia (NH_3) and phosphate. Renal NH_3 is produced by glutamine metabolism in the proximal tubule. Subsequent diffusion of NH_3 out of the proximal tubular cell enables trapping of H^+ , which is secreted by apical Na^+/H^+ exchange, in the lumen as ammonium ion (NH_4^+)





- Reabsorption of glucose is nearly complete by the end of the proximal tubule. Cellular transport of glucose is mediated by apical Na⁺ glucose cotransport coupled with basolateral, facilitated diffusion by a glucose transporter. This process is also saturable, leading to glycosuria when plasma levels exceed 180–200 mg/dL, as seen in untreated diabetes mellitus. Inhibitors of the Na⁺-glucose cotransporter SGLT2 in proximal tubules block glucose reabsorption and lower blood glucose, which has therapeutic benefits in diabetes mellitus and chronic diabetic kidney disease.



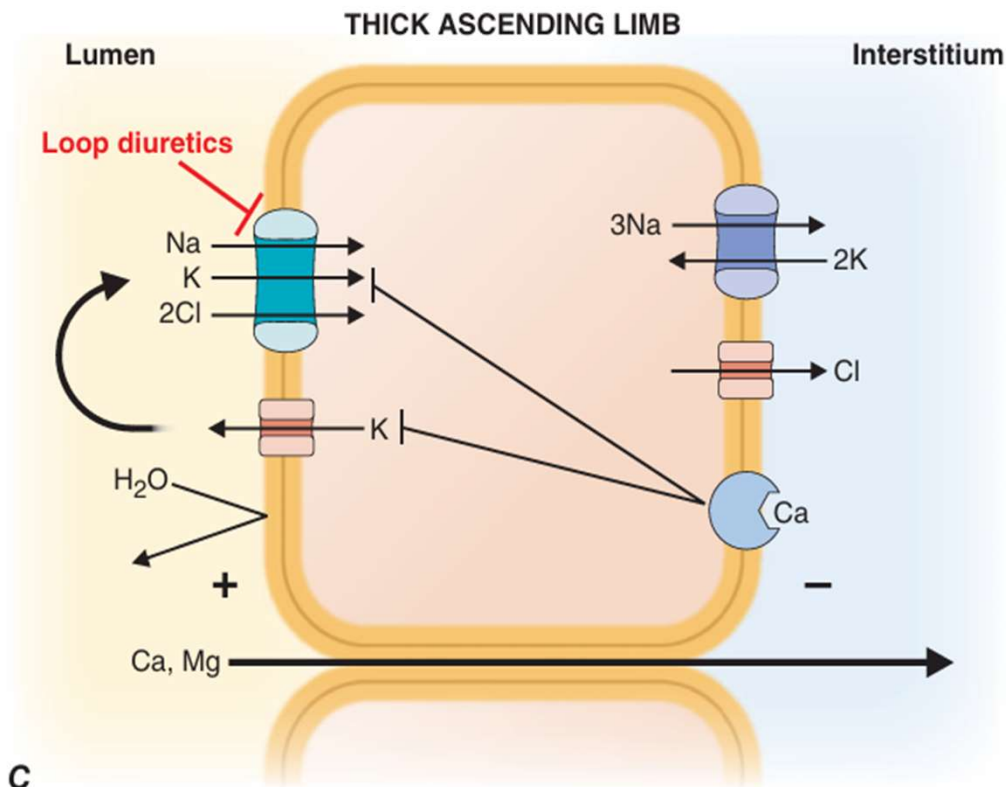
- 
- ▶ Circulating 25-hydroxy vitamin D (calcidiol) is bioactivated by proximal tubular 1 α -hydroxylase to produce 1,25-di-hydroxy vitamin D (calcitriol), the most active form of the hormone, which acts on the small intestine to promote calcium absorption. Phosphate balance is affected by circulating fibroblast growth hormone 23 (FGF23), a bone-derived hormone that interacts with its receptor (FGFR1) and co-receptor (Klotho) on proximal tubular cells to suppress sodium phosphate cotransport and promote renal phosphate excretion. PTH stimulates proximal tubular 1 α -hydroxylation of vitamin D, whereas it suppresses sodium-phosphate cotransport.



LOOP OF HENLE

- ▶ Approximately 15–25% of filtered NaCl is reabsorbed in the loop of Henle, mainly by the thick ascending limb. The loop of Henle has an important role in urinary concentration by contributing to the generation of a hypertonic medullary interstitium in a process called countercurrent multiplication. The loop of Henle is the site of action for the most potent class of diuretic agents (loop diuretics) and also contributes to reabsorption of calcium and magnesium ions.

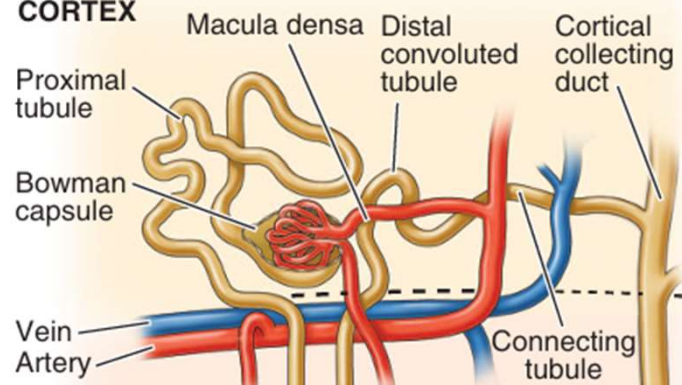




The descending thin limb is highly water permeable owing to dense expression of constitutively active aquaporin-1 water channels. By contrast, water permeability is negligible in the ascending thin and thick limbs. In the thick ascending limb, there is a high level of secondary active NaCl transport enabled by the Na⁺/K⁺/2Cl⁻ cotransporter on the apical membrane in series with basolateral Cl⁻ channels and Na⁺/K⁺-ATPase

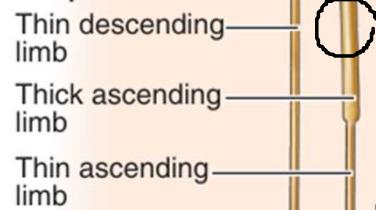


CORTEX



MEDULLA

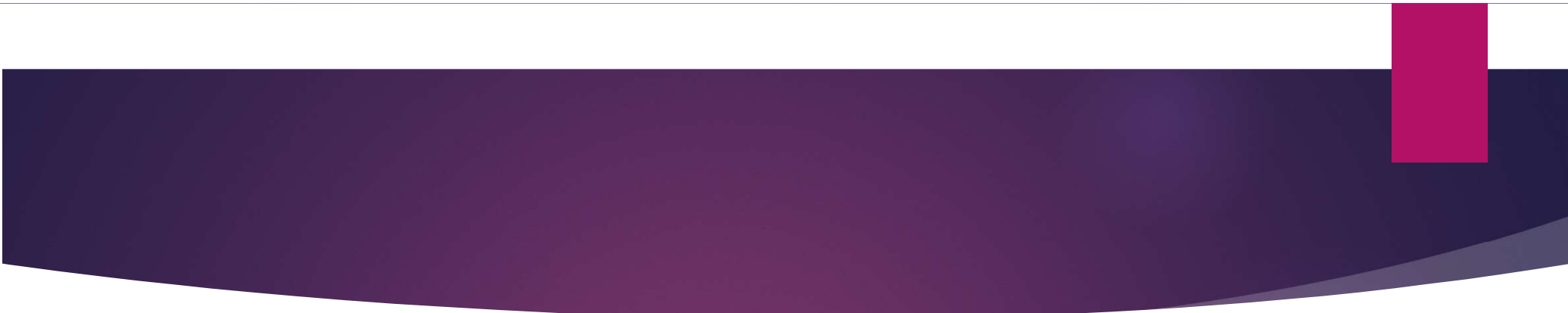
Loop of Henle:



Inner medullary collecting duct

A



- 
- ▶ The $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter is the molecular target for loop diuretics. Tubular fluid K^+ is the limiting substrate for this cotransporter (tubular concentration of K^+ is similar to plasma, $\sim 4 \text{ meq/L}$), but transporter activity is maintained by K^+ recycling through an apical potassium channel. The cotransporter also enables reabsorption of NH_4^+ in lieu of K^+ , and this leads to accumulation of both NH_4^+ and NH_3 in the medullary interstitium.



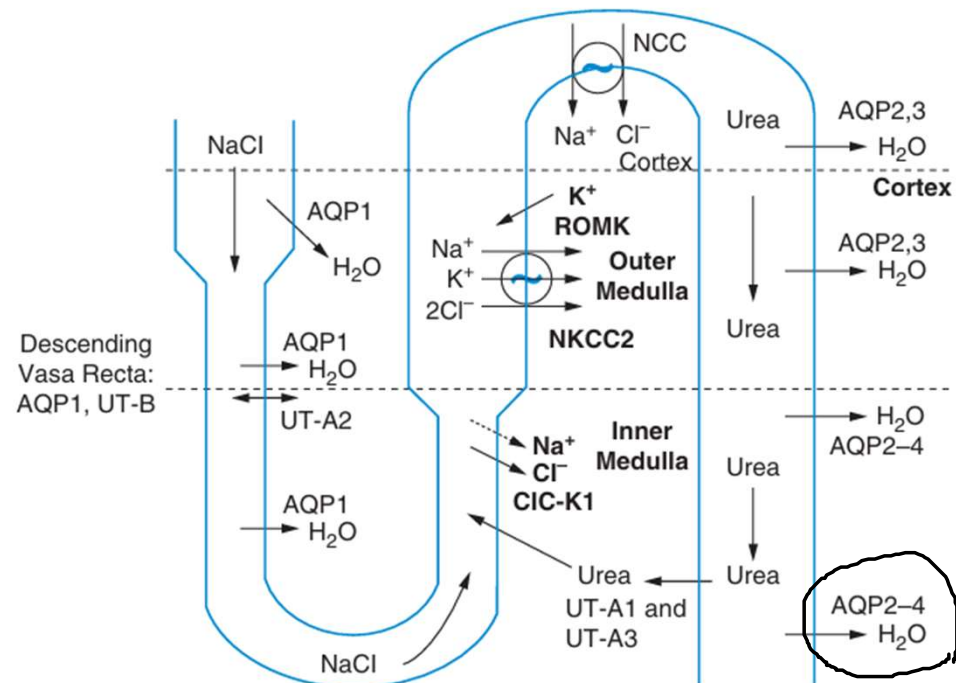


FIGURE 56-2 The renal concentrating mechanism. Water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism (see text for details). Diagram showing the location of the major transport proteins involved; a loop of Henle is depicted on the *left*, collecting duct on the *right*. AQP, aquaporin; CLC-K1, chloride channel; NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary K⁺ channel; UT, urea transporter. (Reproduced with permission from JM Sands: *Molecular approaches to urea transporters*. *J Am Soc Nephro* 13(11):2795, 2002.)

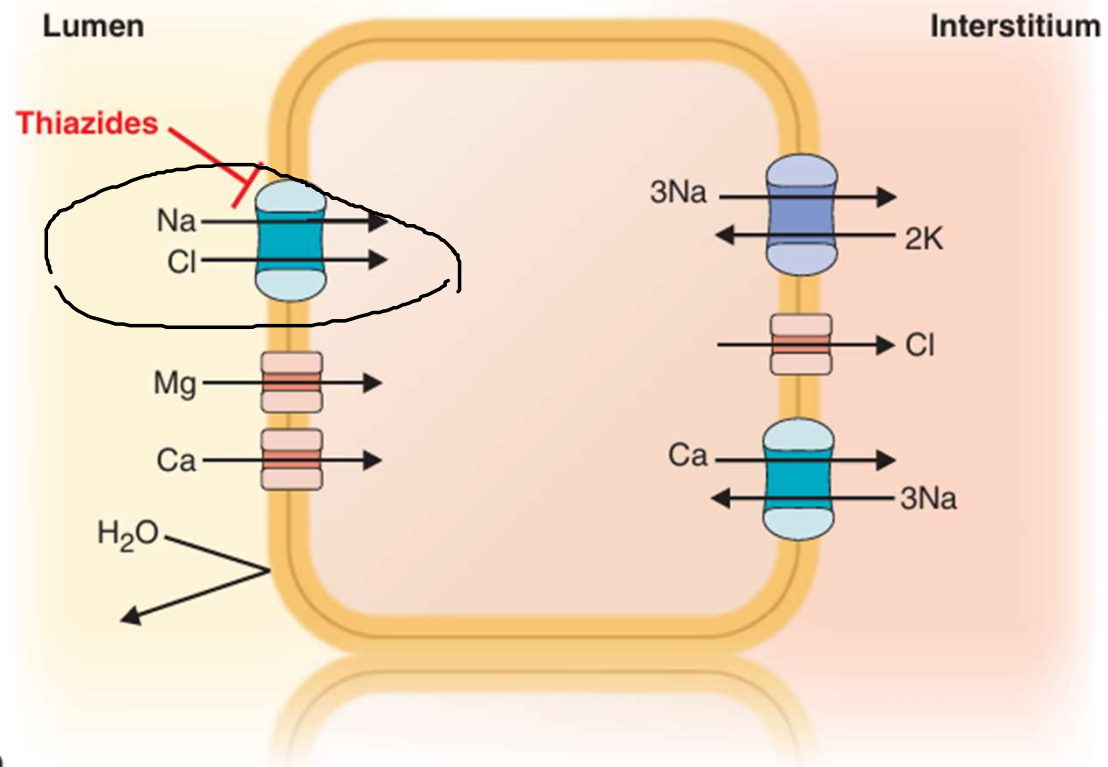


DISTAL CONVOLUTED TUBULE

- ▶ The distal convoluted tubule reabsorbs ~5% of filtered NaCl. This segment is composed of a tight epithelium with little water permeability. The major NaCl-transporting pathway uses an apical membrane, electroneutral thiazide-sensitive Na^+/Cl^- cotransporter in tandem with basolateral Na^+/K^+ -ATPase and Cl^- channels



DISTAL CONVOLUTED TUBULE



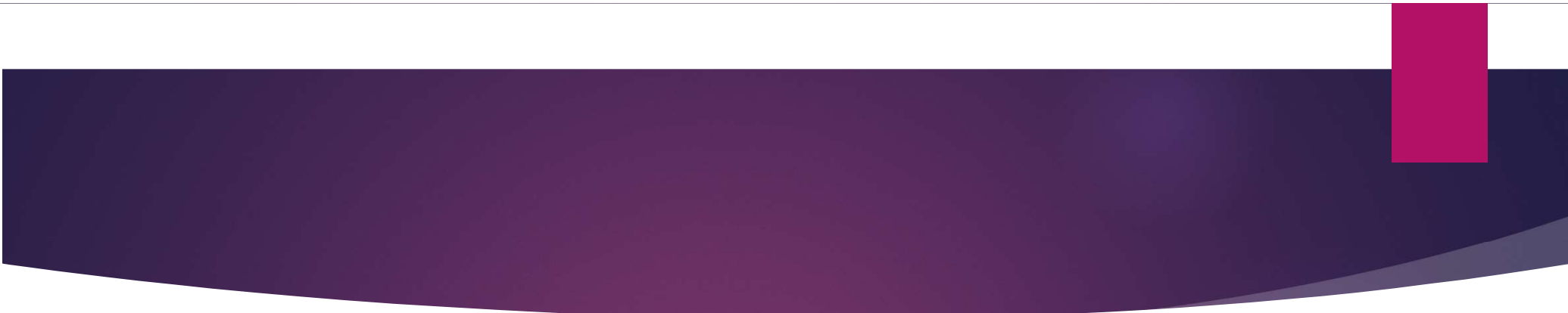
D



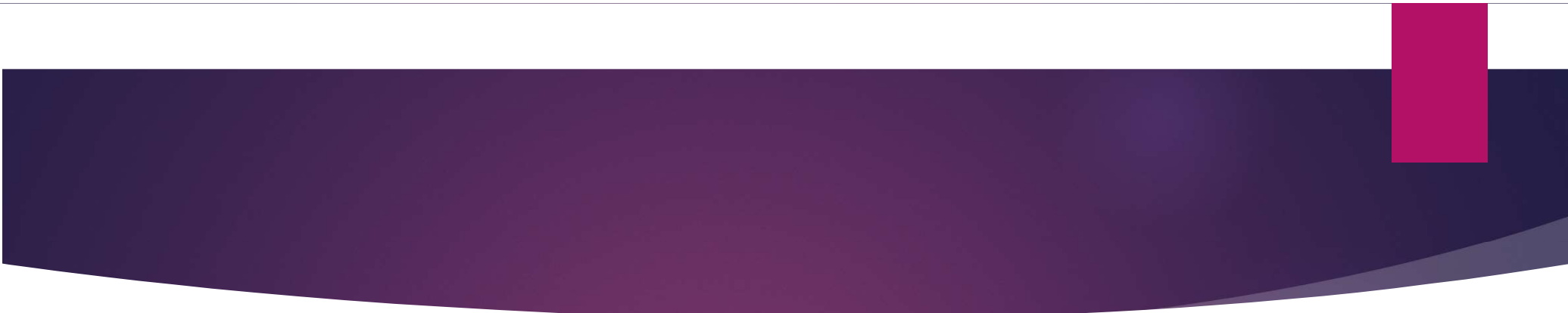
COLLECTING DUCT

- ▶ The collecting duct modulates the final composition of urine. The two major divisions, the cortical collecting duct and inner medullary collecting duct, contribute to reabsorbing ~4–5% of filtered Na^+ and are important for hormonal regulation of salt and water balance



- 
- ▶ Cells in both segments of the collecting duct express vasopressin-regulated water channels (aquaporin-2 on the apical membrane, aquaporin-3 and -4 on the basolateral membrane). The antidiuretic hormone vasopressin binds to the V2 receptor on the basolateral membrane and triggers an intracellular signaling cascade. This signaling cascade stimulates the insertion of water channels into the apical membrane of collecting duct cells to promote water permeability, water reabsorption, and production of concentrated urine
 - ▶ In the absence of vasopressin, collecting duct cells are water impermeable, and urine remains dilute



- 
- ▶ The cortical collecting duct contains high-resistance epithelia with two cell types. Principal cells are the main water-reabsorbing, Na⁺-reabsorbing, and K⁺-secreting cells, and the site of action of aldosterone, K⁺-sparing diuretics, and mineralocorticoid receptor antagonists such as spironolactone and eplerenone.
 - ▶ The other cells are type A and B intercalated cells. Type A intercalated cells mediate acid secretion and bicarbonate reabsorption also under the influence of aldosterone. Type B intercalated cells mediate bicarbonate secretion and acid reabsorption.



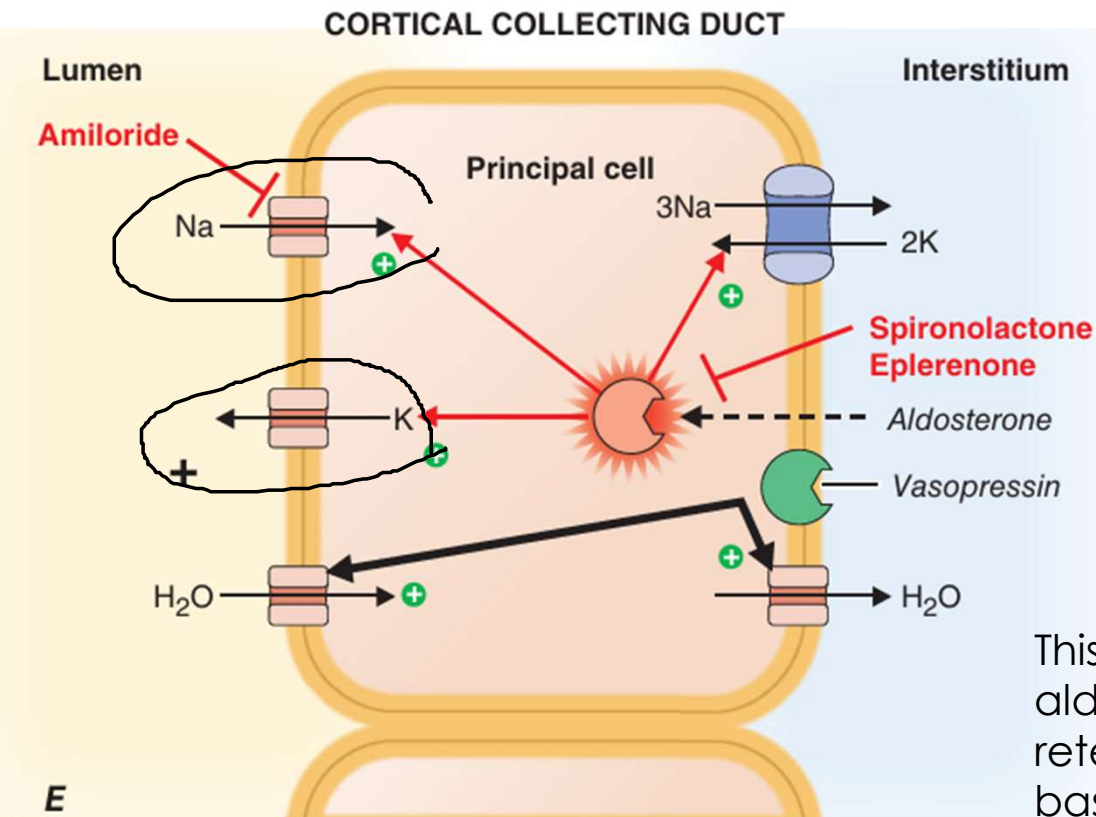
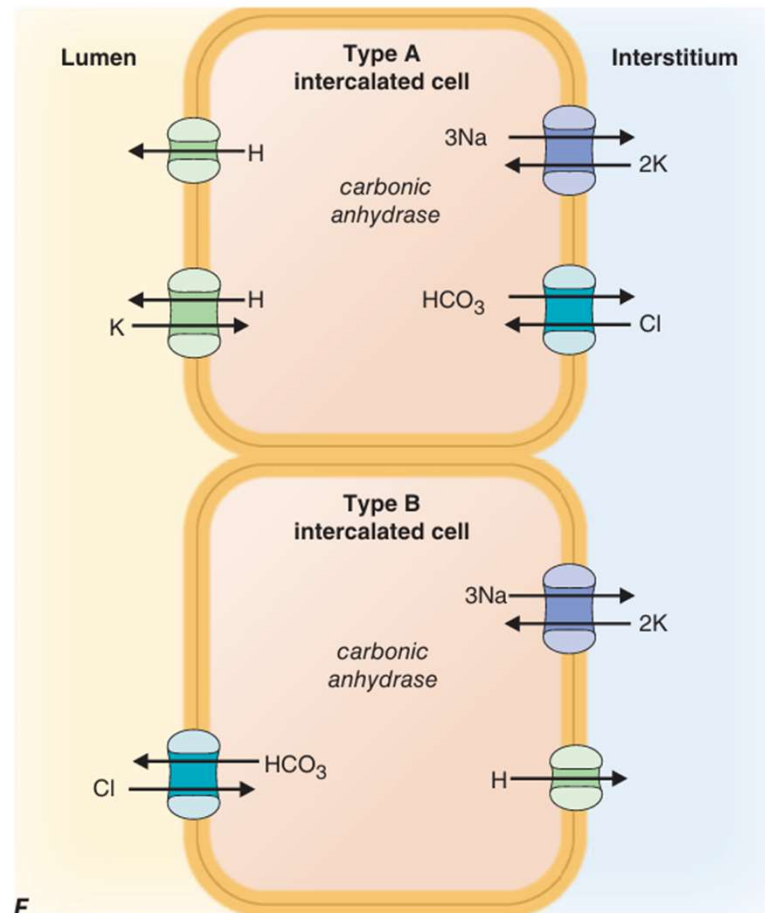
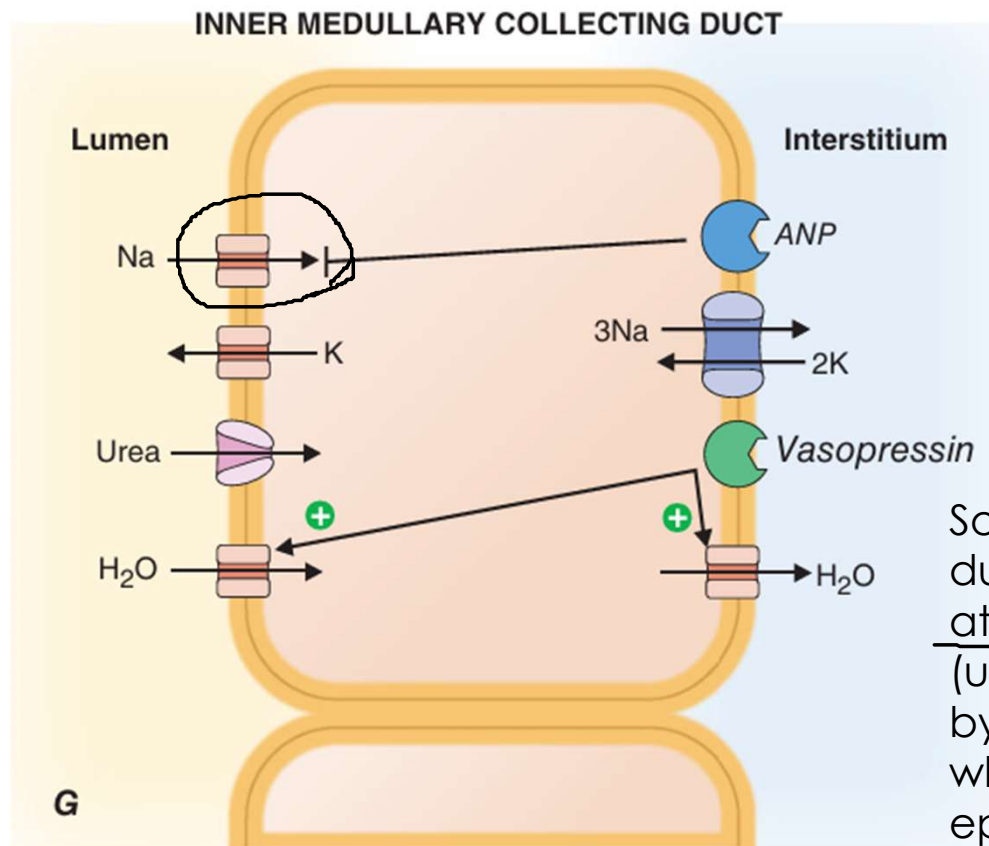


FIGURE 320-3 (Continued)

This Na⁺ reabsorptive process is tightly regulated by aldosterone, activates ENaC, leading to Na⁺ retention. Aldosterone enters the cell across the basolateral membrane, binds to a cytoplasmic mineralocorticoid receptor, and then translocates into the nucleus, where it modulates gene transcription, which potentiates Na⁺ reabsorption and K⁺ secretion. The potassium-sparing diuretics amiloride and triamterene block ENaC, resulting in lower Na⁺ reabsorption.

CORTICAL COLLECTING DUCT





Sodium reabsorption by inner medullary collecting duct cells is also inhibited by the natriuretic peptides atrial natriuretic peptide or renal natriuretic peptide (urodilatin). Atrial natriuretic peptides are secreted by atrial myocytes in response to volume expansion, whereas urodilatin is secreted by renal tubular epithelia. Natriuretic peptides interact with either apical (urodilatin) or basolateral (atrial natriuretic peptides) receptors on inner medullary collecting duct cells. This effect in turn reduces the activity of the apical Na⁺ channel in these cells and attenuates net Na⁺ reabsorption, producing natriuresis.

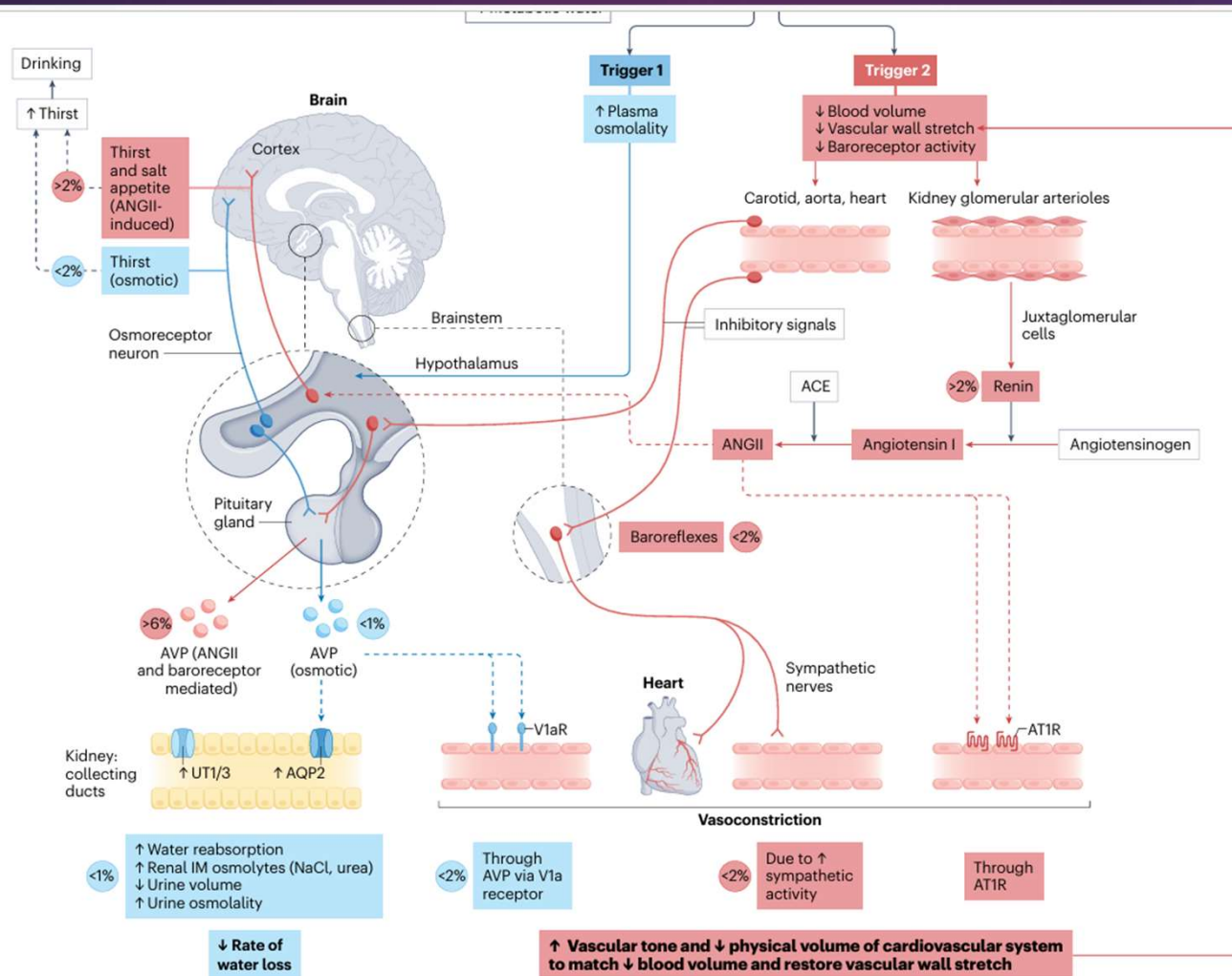


Fig. 1 | Overview of the core response to a decrease in body water content.

through the V1aR together with baroreceptor responses help to maintain