RENAL PHYSIOLOGY

Jessica Sands, DVM
Emergency and Critical Care (ECC) Resident
May 10th, 2022

PLAN:

- Anatomy
  - Fluid Compartments
  - Renal
- Renal functions
  - Segments of nephron
    - Solute reabsorption
    - Water handling
- Micturition

FLUID COMPARTMENTS

60-40-20 RULE

- Total body water is 60% of body weight in animal with normal body condition
  - Higher if emaciated
  - Lower if over-conditioned
  - 2/3 (40% of total BW) is intracellular
  - 1/3 (20% of total BW) is extracellular
  - Further divided into interstitial and plasma volumes
- Movement between intra-extracellular spaces dictated by OSMOTIC PRESSURE
- Movement within extracellular space (interstitial-plasma) is dictated by STARLING'S FORCES

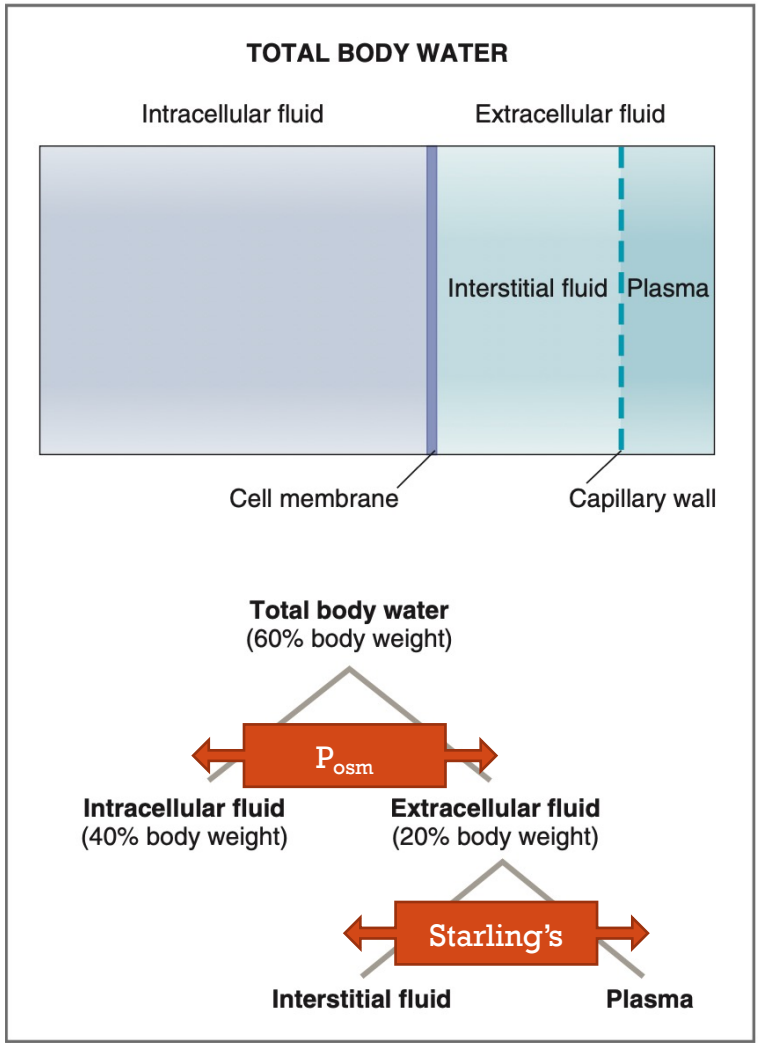


Fig. 6.4 Body fluid compartments. Total body water is distributed between intracellular fluid and extracellular fluid. Water as a percentage of body weight is indicated for the major compartments.

Which of the following volumes can be measured DIRECTLY (i.e NOT calculated values)

Total body water

Intracellular volume

Extracellular volume

Plasma volume

Interstitial fluid volume

MEASUREMENT OF FLUID COMPARTMENTS

- Injection of a known volume/concentration of solute with a predictable distribution between compartments
  - Total body water and extracellular water measured directly
  - Intracellular water is calculated value
- Volume can be calculated based on the indicator-dilution principal
  - Total amount of injected substance must remain the same
    - Amount= volume x concentration
    - $V_1C_1 = V_2C_2$
    - $V_1 = V_2C_2/C_1$

Table 25-3 Measurement of Body Fluid Volumes

Volume	Indicators
Total body water	^3H_2O, ^2H_2O, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as total body water – extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as blood volume = plasma volume/(1 – hematocrit)
Interstitial fluid	(Calculated as extracellular fluid volume – plasma volume)

NORMAL ION DISTRIBUTION

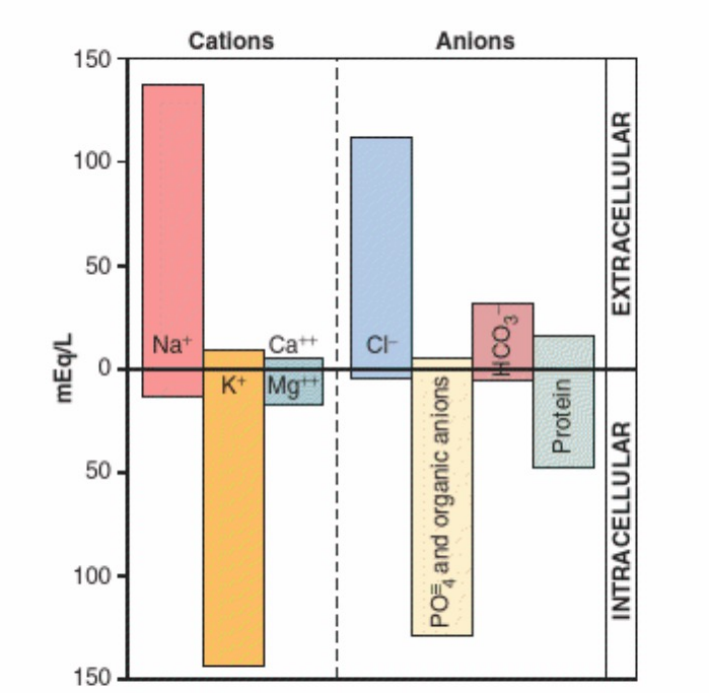


Figure 25-2. Major cations and anions of the intracellular and extracellular fluids. The concentrations of Ca^{++} and Mg^{++} represent the sum of these two ions. The concentrations shown represent the total of free ions and complexed ions.

- Osmolality: osmoles/kg H_2O
- Osmolarity: osmoles/L H_{2O}
- Osmolarity/osmolality can be used interchangeably because 1kg H_2O=1L H_2O
- Calculated osmolarity (mOsm/L):
  - $2[Na] + \frac{[BUN](mg/dL)}{2.8} + \frac{[BG](mg/dL)}{18}$
  - Normal osmolarity= 300mOsm/L
- Δ 1mOsm= 19.3mmHg osmotic pressure

RENAL ANATOMY AND GENERAL PHYSIO CONCEPTS

GROSS ANATOMY

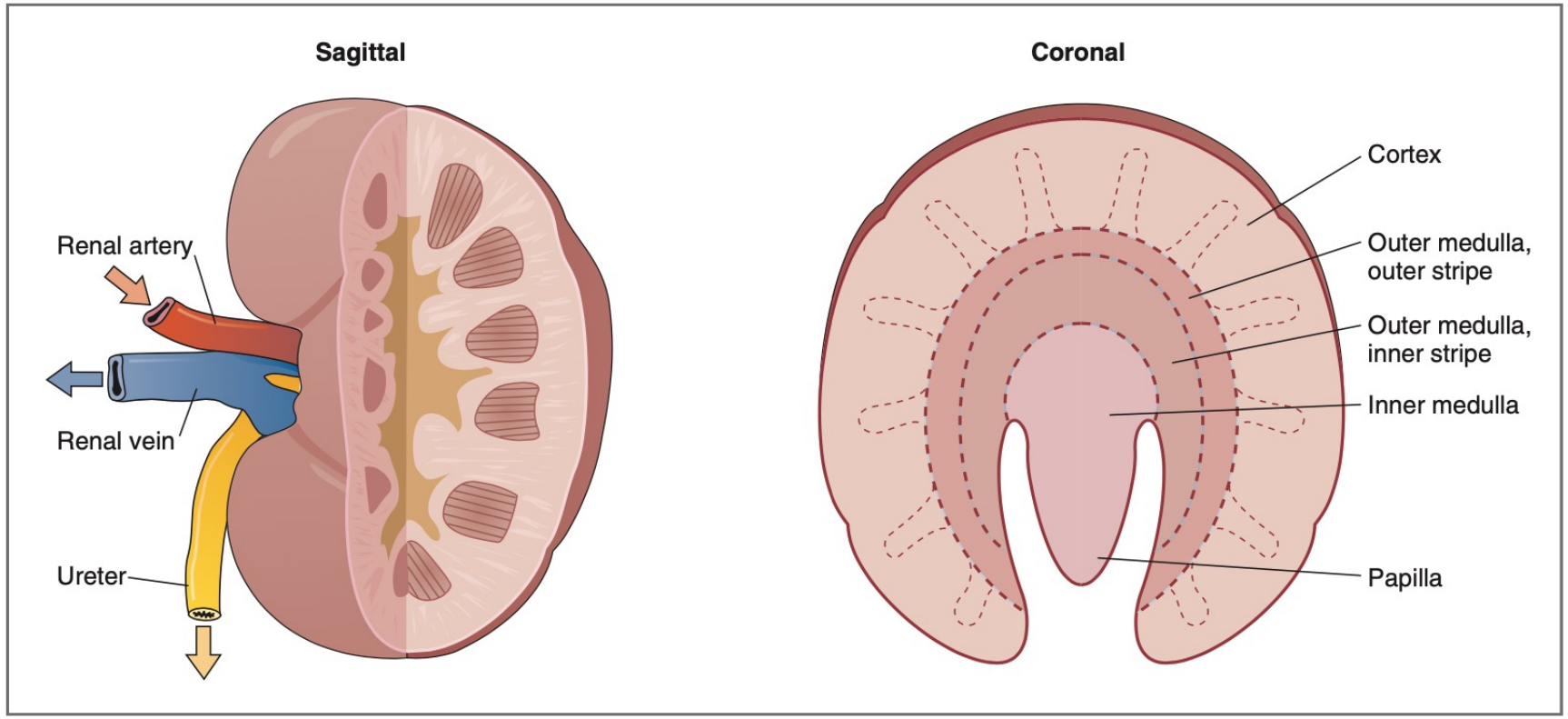


Fig. 6.1 Sagittal and coronal sections of the kidney.

RENAL BLOOD FLOW

- Arterial blood
  - Renal a. → interlobar a. → arcuate a → interlobular (radial) a. → afferent arterioles → **glomerular capillary** → efferent arterioles → **peritubular capillaries** →interlobular v. →arcuate v. → interlobar v. → renal v.

Important to remember that the kidneys have TWO sets of capillaries

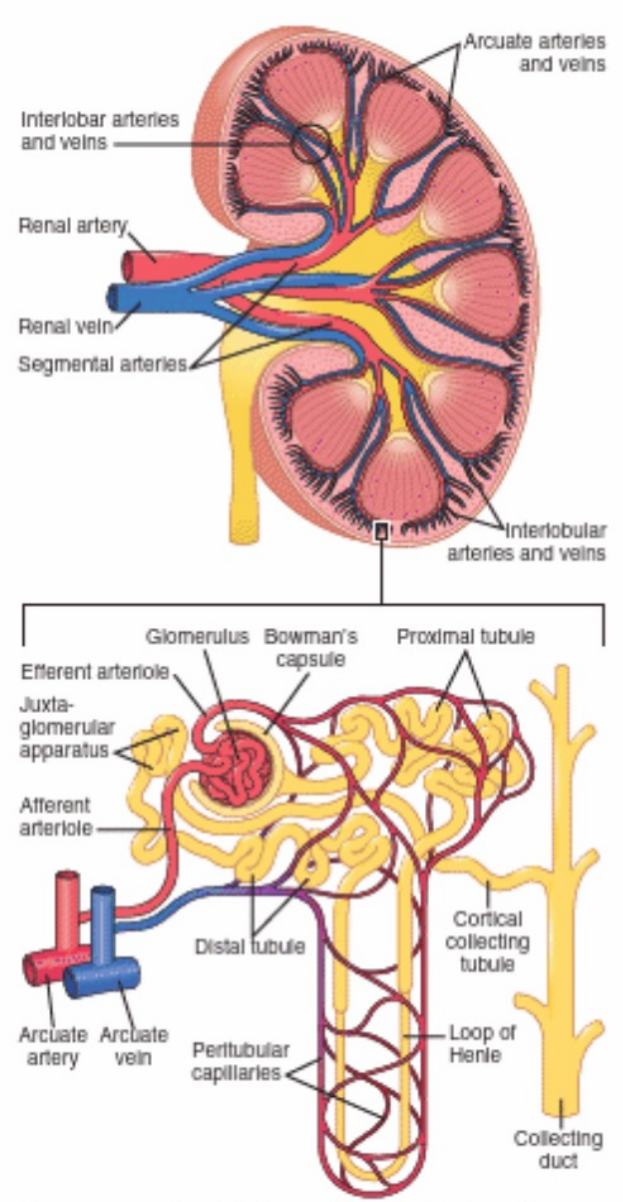


Figure 26-3. Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the micro-circulation of each nephron.

THE NEPHRON:
THE FUNCTIONAL UNIT OF THE KIDNEY

Cortical nephrons

- Glomerulus located in the OUTTER COREX
- Tubules extend into superficial medulla
- Tubular system surrounded by peritubular capillaries

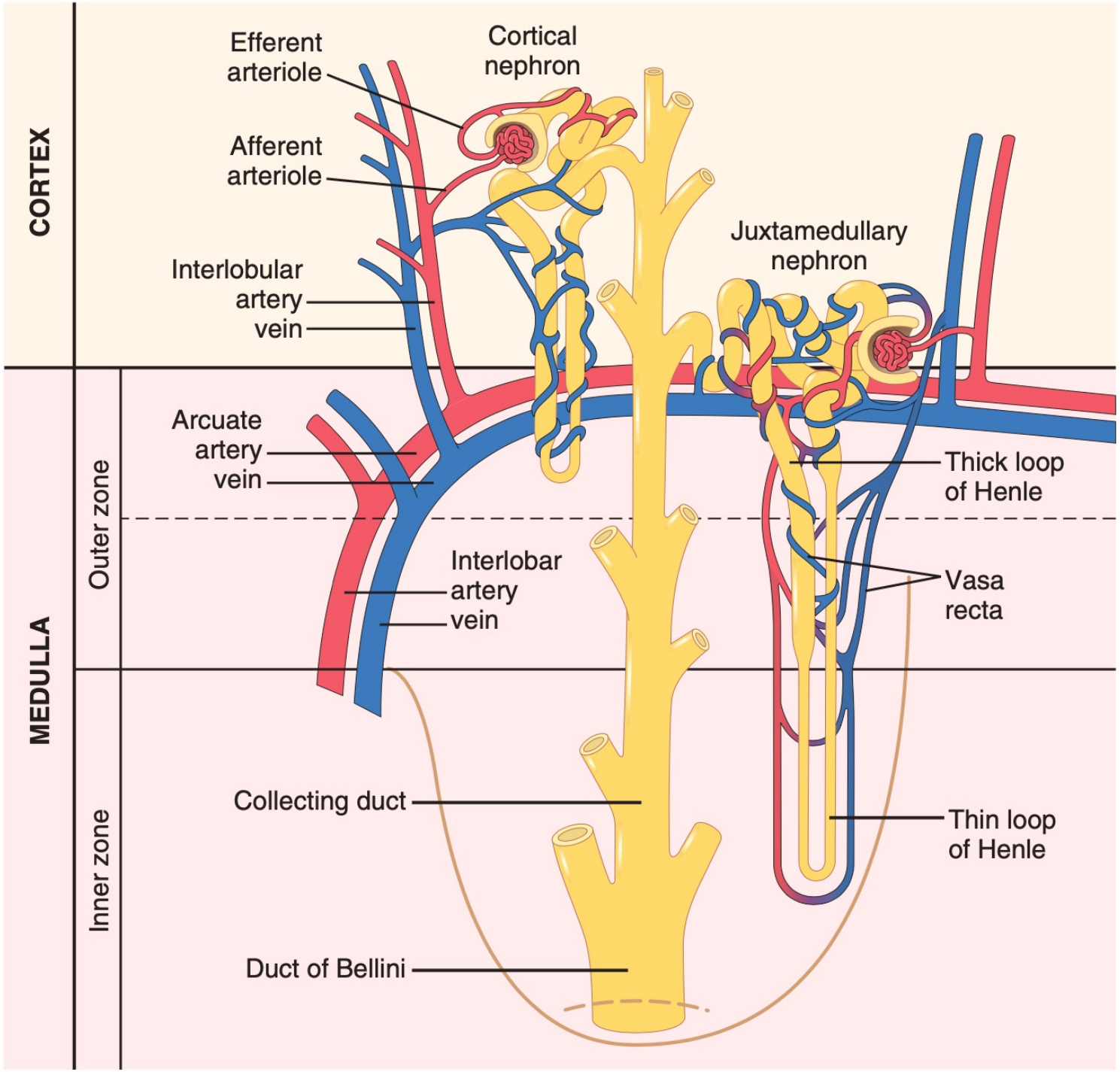
Juxtaglomerular nephrons

- Glomerulus at the INNER CORTEX
- Tubules extend into deep medulla
  - Increased concentrating ability
- Tubular system surrounded by specialized peritubular capillaries called the **vasa recta**

THE N

Cortical ne

- Glomerulu
  COREX
- Tubules e
  medulla
- Tubular sy
  peritubula



CORTEX

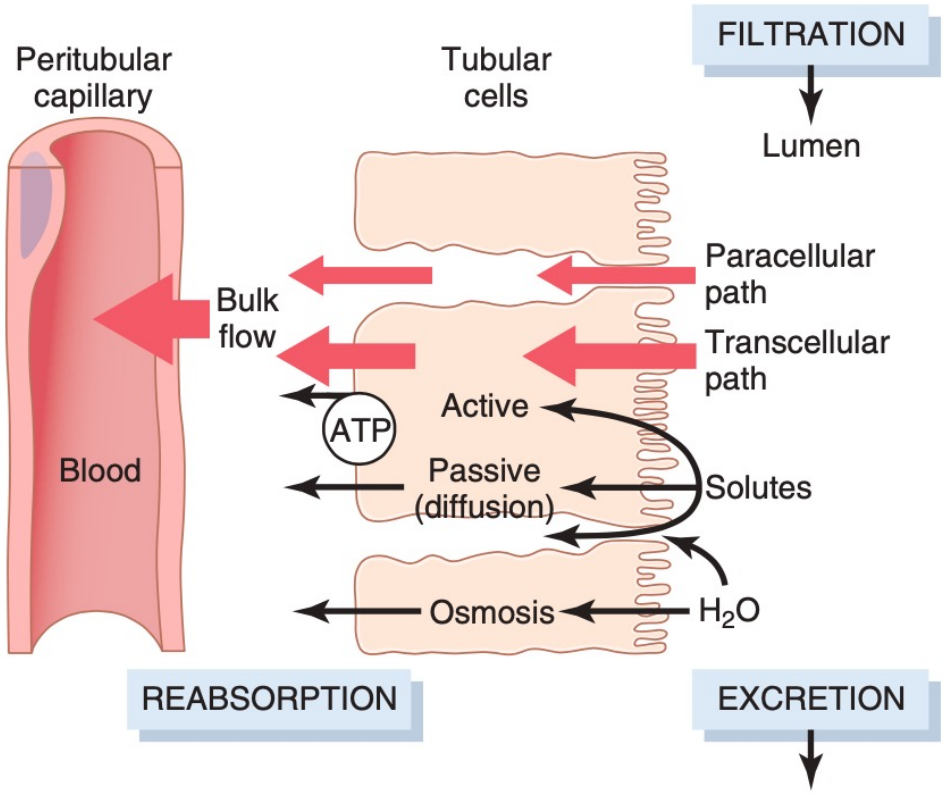
medulla

bility

d by

pillaries

MECHANISMS OF REABSORPTION

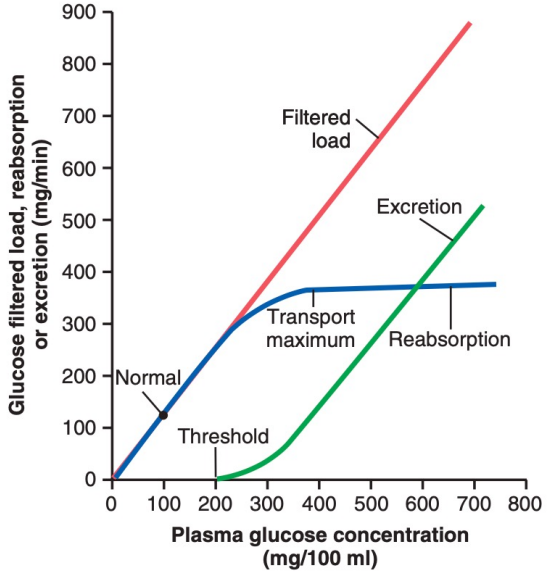


- Solutes
  - Can be absorbed passively or actively
    - Passive transport: WITH electrochemical gradient
    - Active transport: AGAINST electrochemical gradient
      - Primary: Uses ATP as energy source
      - Secondary: Uses energy generated from another substance moving via passive transport
- Water
  - Always absorbed passively (osmosis)

TRANSPORT THRESHOLDS

Threshold maximum

- Limited active transport of a substance due to saturation of transport systems
  - Ex: Glucose, creatinine, phosphate, urates, lactate



Gradient-time transport

- Amount of substance transported depends on its concentration gradient and amount of time in the tubule
  - Ex: Sodium

THE GLOMERULUS

THE GLOMERULUS

- Glomerular capillaries more leaky than most other capillaries (higher K_f)
- Glomerular capillary has THREE (3) layers: thicker than most other capillaries
  - Fenestrated endothelium
  - Basement membrane (negative charge)
  - Epithelium (podocytes)

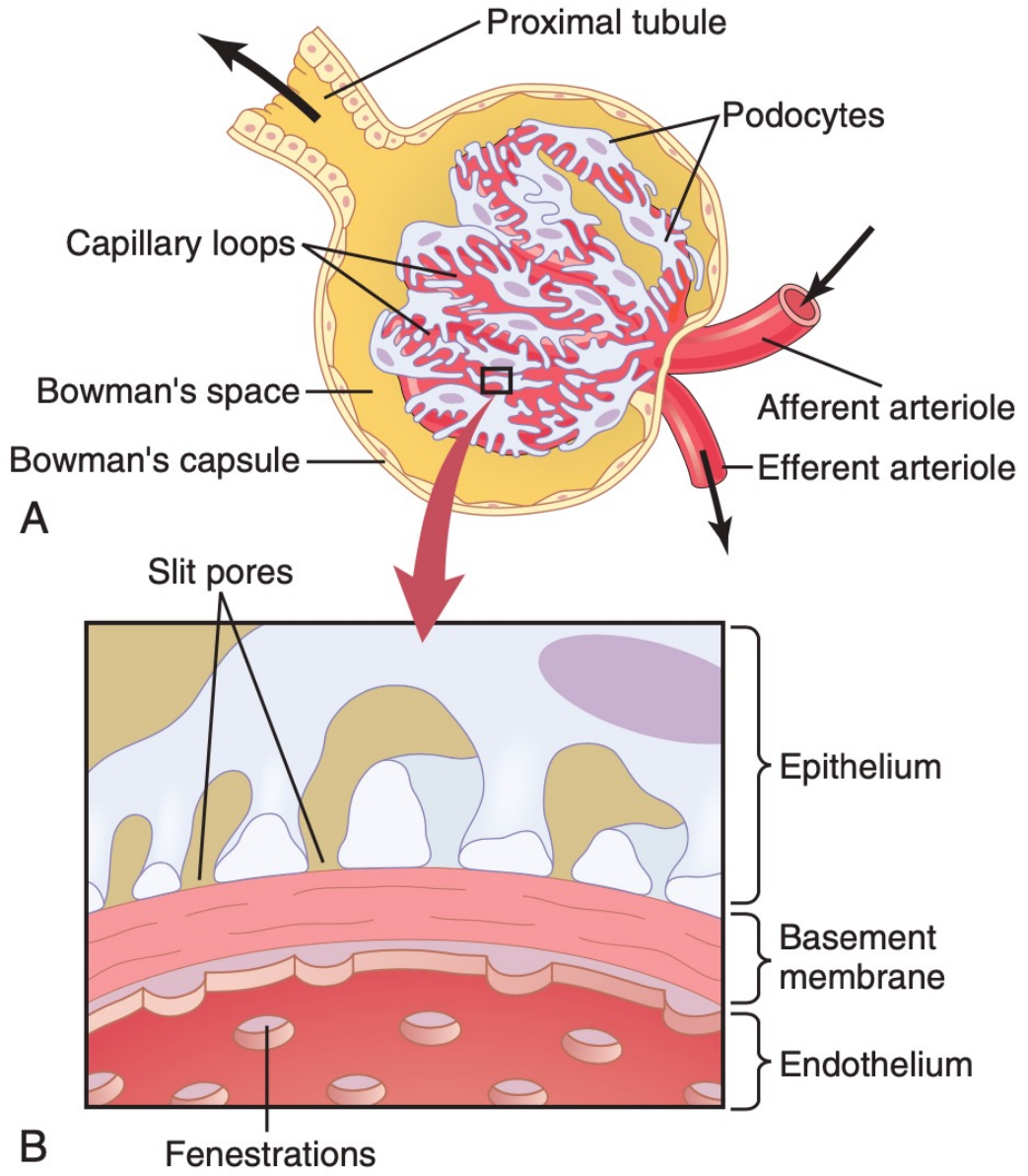


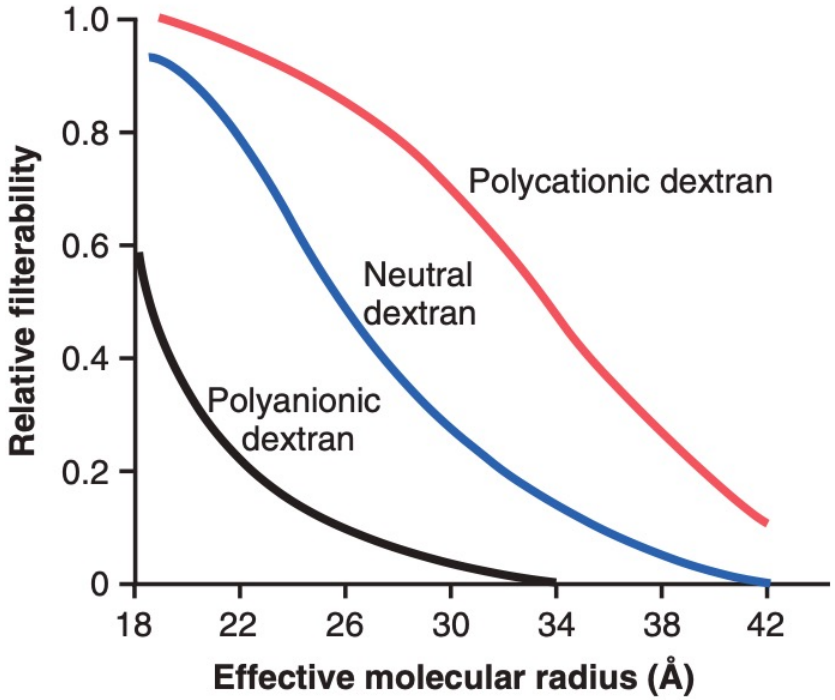
Figure 27-2. A, Basic ultrastructure of the glomerular capillaries. **B,** Cross section of the glomerular capillary membrane and its major components: capillary endothelium, basement membrane, and epithelium (podocytes).

Which of the following subsances will be most easily filtered at the level of the glomerulus?

- Large, positively charged
- Small, positively charged
- Large, negatively charged
- Small, negatively charged
- Small, neutrally charged
- None of the above

THE GLOMERULUS

- Selective permeability based on size and charge
  - Excludes LARGE, NEGATIVELY CHARGED substances
    - Substances </=7,000 Da move freely
      - (ex: albumin=66,000 Da)
    - Negative charge of basement membrane repels negatively-charged substances

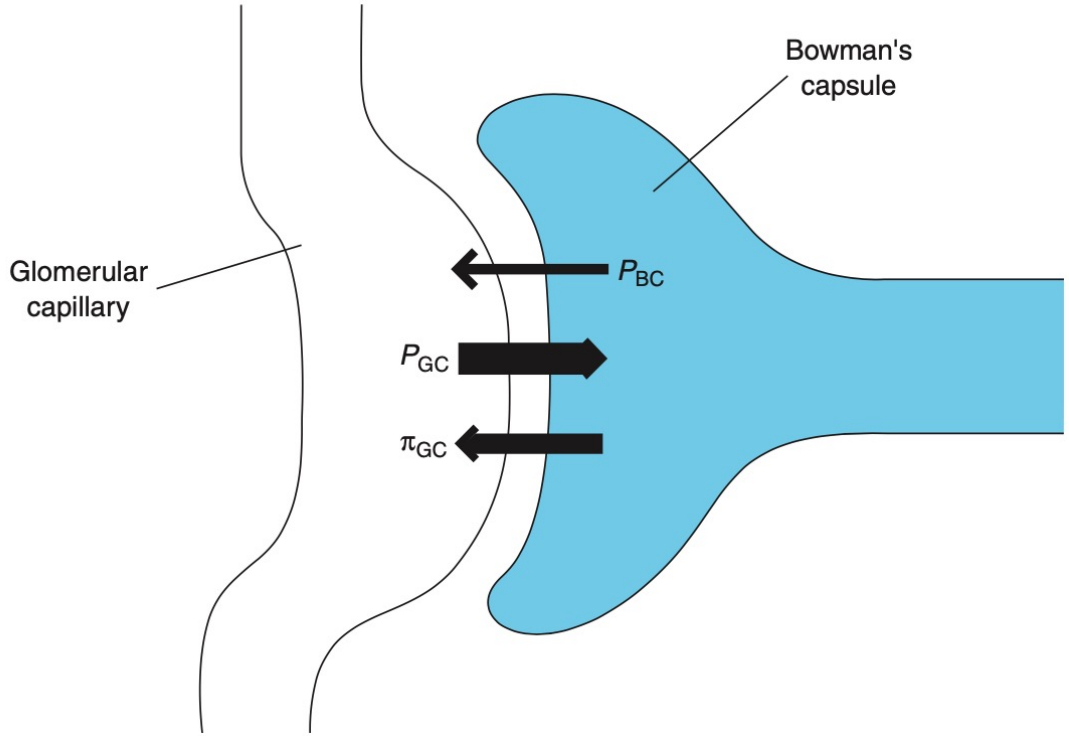


GLOMERULAR FILTRATION RATE (GFR)

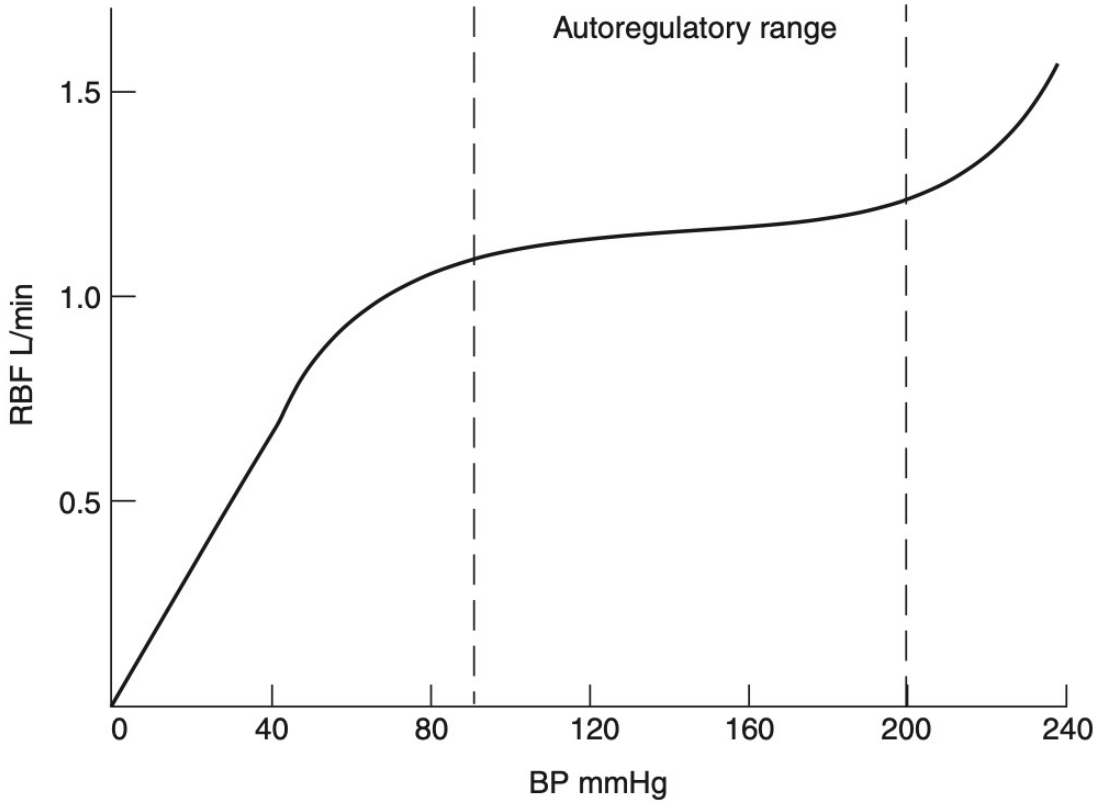
- Net filtration pressure (NFP)
  - NFP= $(P_{GC} - \pi_{GC}) - (P_{BC} - \cancel{\pi_{BC}})$
- Glomerular Filtration Rate (GFR)
  - GFR = $K_f (P_{GC} - \pi_{GC} - P_{BC})$

P_{GC} under physiologic control

- Remainder of variables primarily influenced by disease states



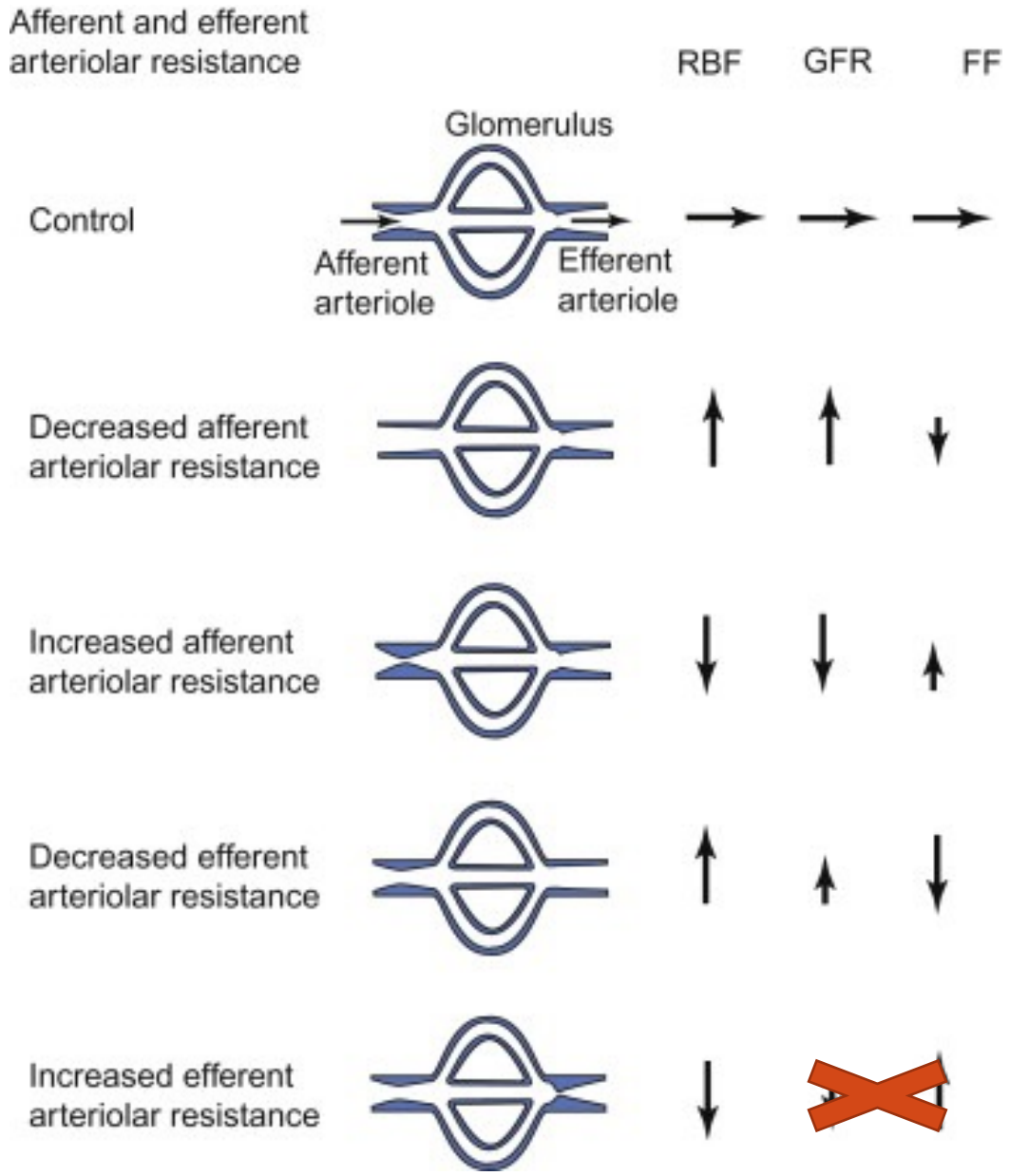
AUTOREGULATION: CONTROL OF P_{GC}



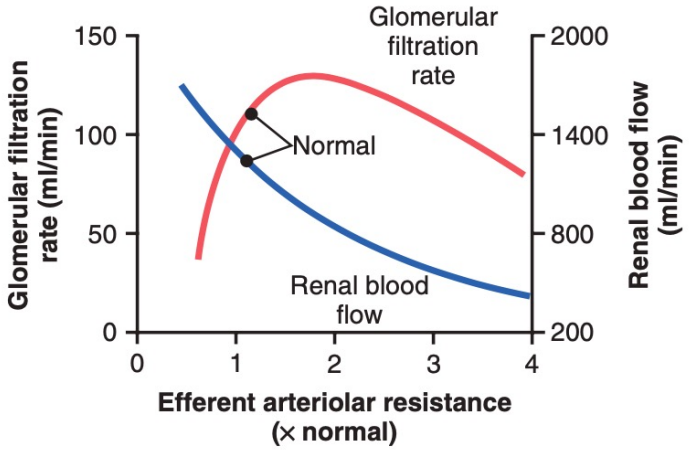
- Changes in MAP cause only small changes in GFR within physiologic range
  - Caused by two different mechanisms
    - 1. **<u>Myogenic response:</u>** Fast response by stretch of smooth muscle at the level of the arteriole (P_{GC})
    - 2. **<u>Tubuloglomerular feedback:</u>** Slower response by Δ[Na] at the level of the macula densa (RBF)

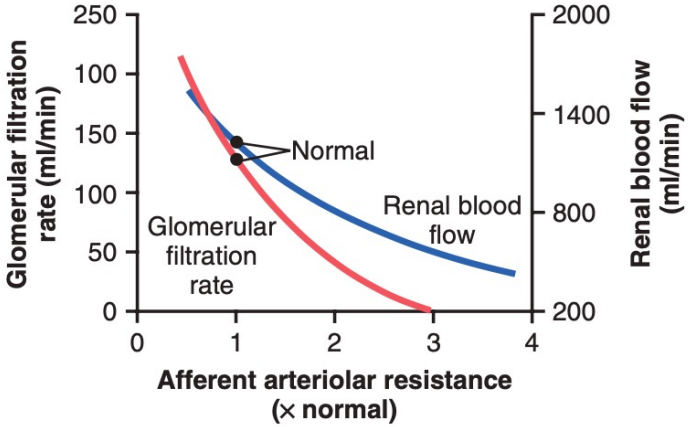
REGULATION OF P_{GC}

- Myogentic regulation of P_{gc} determined by three (3) variables
  - Renal arterial pressure
  - Afferent arteriolar resistance
  - Efferent arteriolar resistance

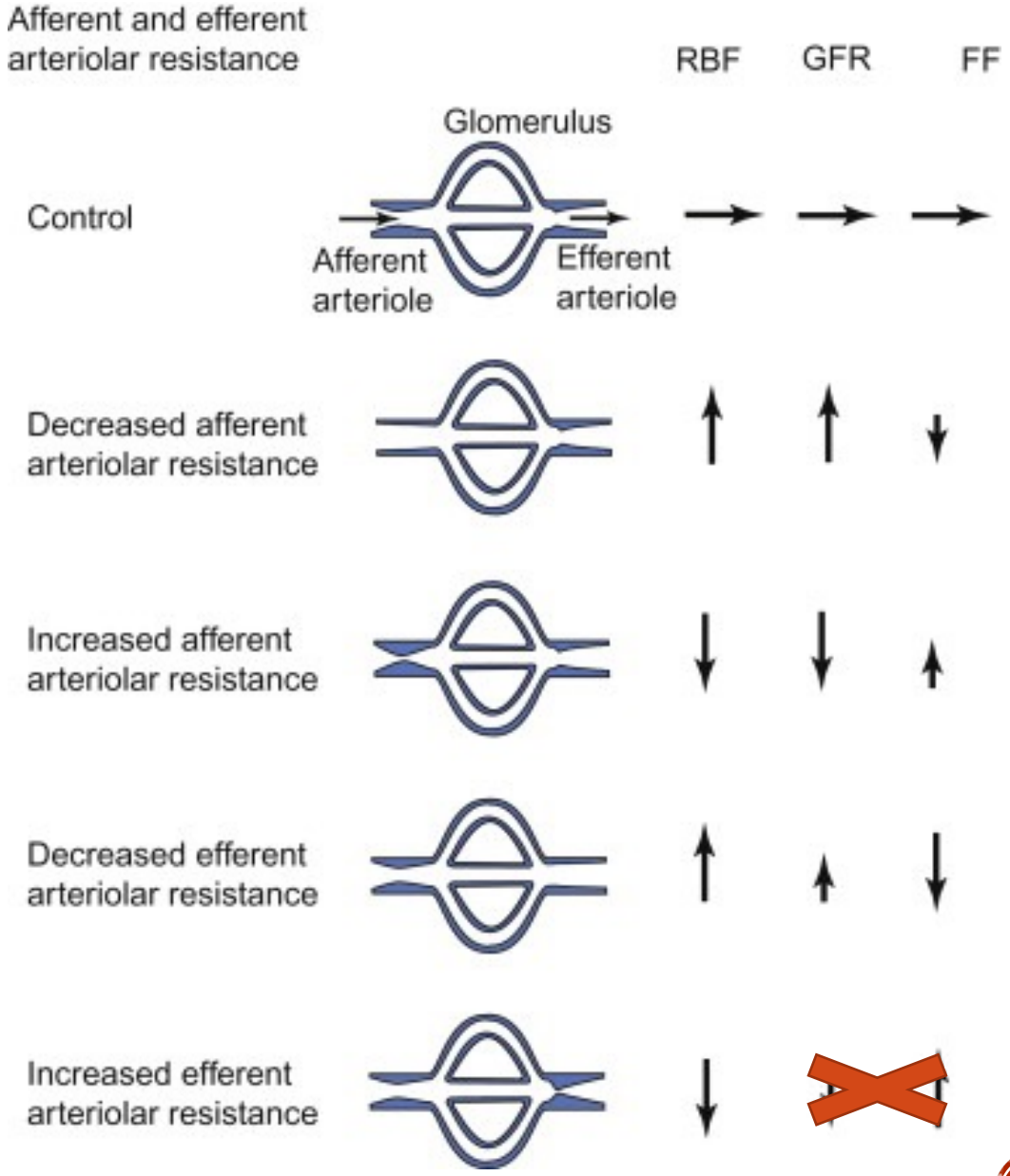


REGULATION OF P_{GC}





Donnan effect

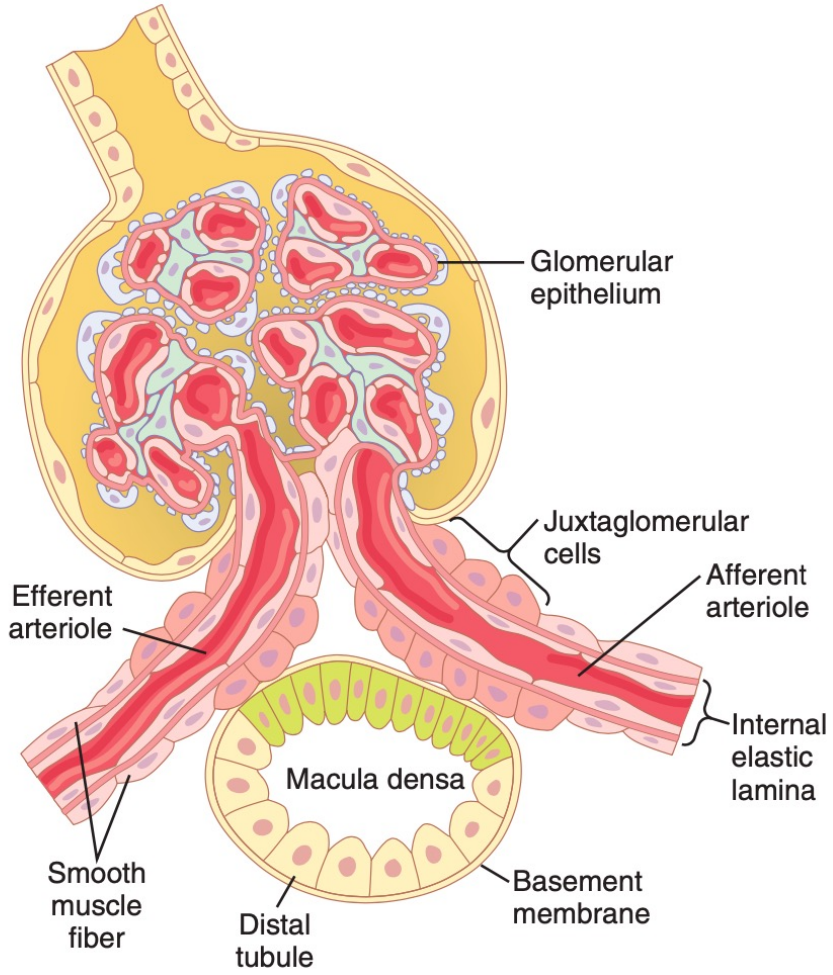


Which of the following substances preferentially constricts the efferent arteriole?

- Epinephrine/Norephinephrine
- Nitric Oxide
- Angiotensin II
- Prostaglandins
- Endothelin
- None of the above

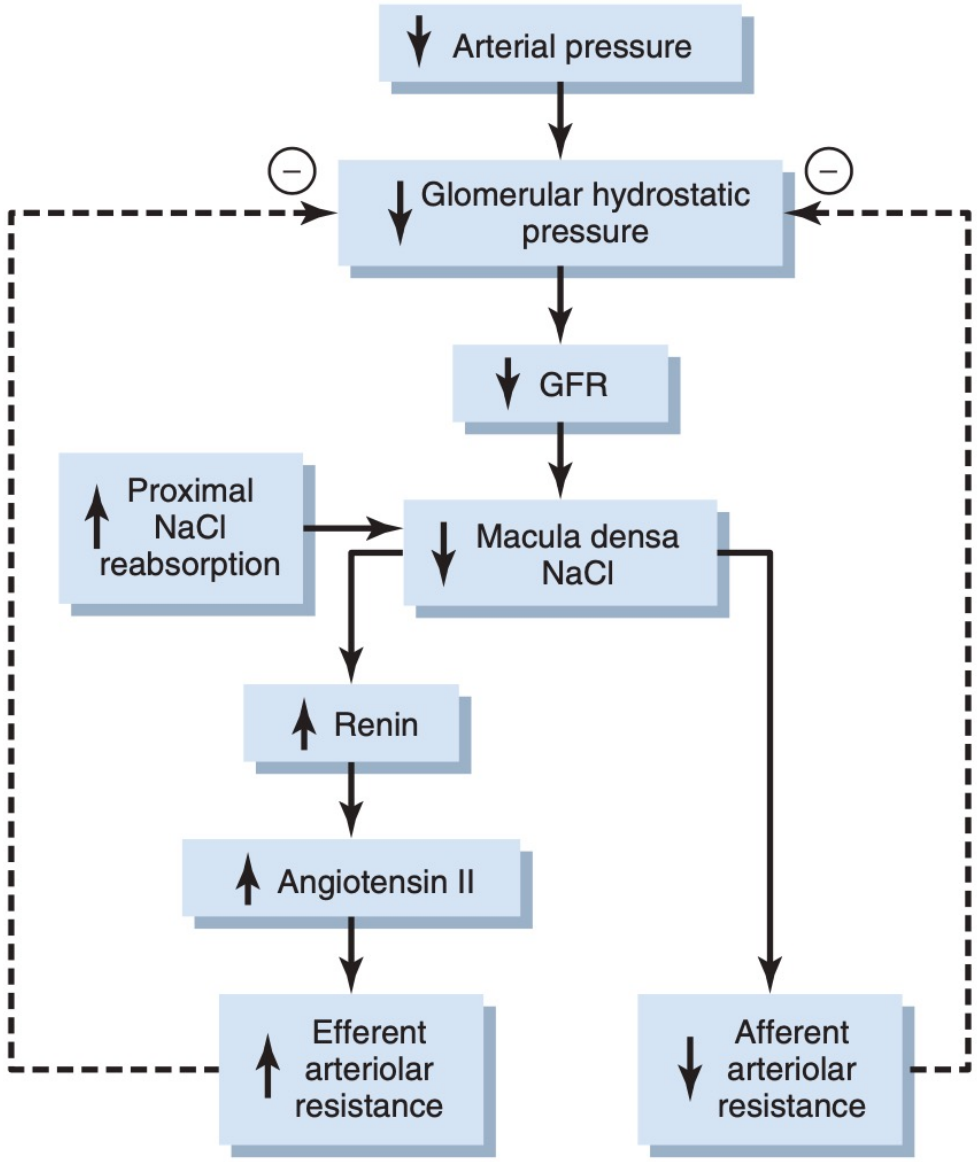
REGULATION OF P_{GC}

- Tubuloglomerular feedback occurs at the level of the juxtaglomerular apparatus
  - Point of contact of the distal tubule and afferent/efferent arterioles
  - Macula densa detects [Na]



REGULATION OF P_{GC}

- Tubuloglomerular feedback occurs at the level of the juxtaglomerular apparatus
  - Point of contact of the distal tubule and afferent/efferent arterioles
  - Macula densa detects [Na]
    - Decreased [Na] interpreted as reduced GFR
      - DILATION of the AFFERENT arteriole
        - PG and NO
      - CONSTRICTION of EFFERENT arteriole
        - AgII

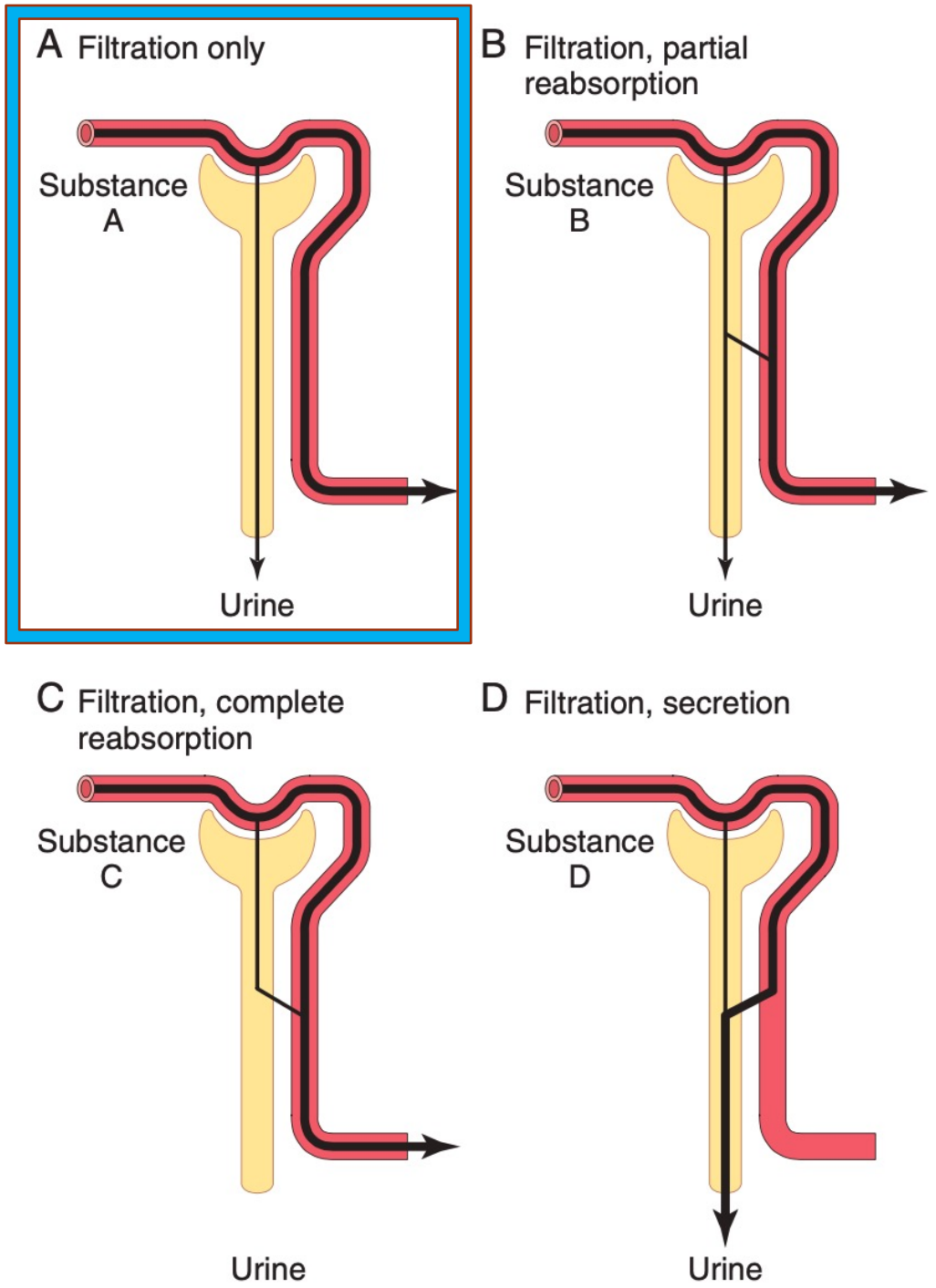


MEASURING GFR

- Urinary excretion rate=

filtration rate – reabsorption rate + secretion rate

- **Ideal substance for measuring GFR is freely filtered but NOT reabsorbed or secreted**
  - Inulin is the gold standard
  - Creatinine used clinically because it is produced at a steady state in the body
    - Small component of secretion → slightly **overestimates** GFR



PROXIMAL TUBULE

BASIC PRINCIPLES OF THE PROXIMAL TUBULE

- Iso-osmotic absorption of solutes/water
- Near-complete reabsorption of organics (glucose, amino acids, etc)
- Glomerulotubular Balance
  - Maintains constant fraction (percentage) of solute reabsorption over a range of GFR
  - Balance can be shifted based on changes in extracellular volume/Starling forces

SODIUM HANDLING

- Active transport of sodium at the basolateral membrane (NaK ATPase) drives movement of other solutes and water
- Solutes and water are absorbed proportionally to each other (iso-osmotic)
  - "High priority" solutes (glucose and aminio acids, bicarb) are absorbed early
    - Causes temporary "negative" lumen due to increased [Cl]
  - Chloride resorption occurs later via paracellular and transcellular routes

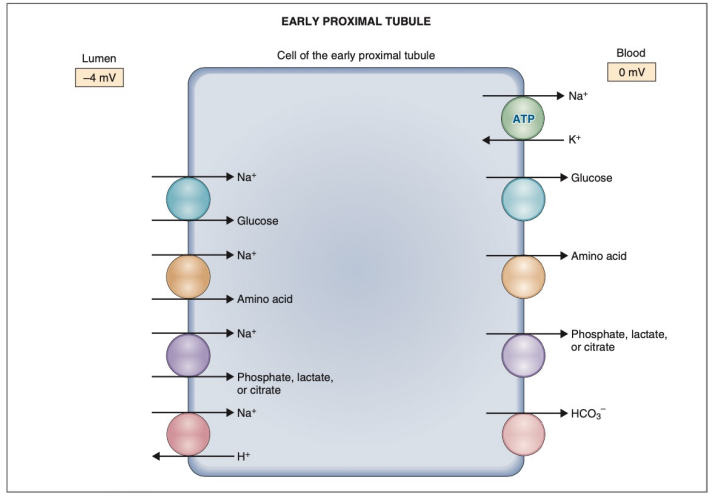


Fig. 6.20 Cellular mechanisms of Na^+ reabsorption in the early proximal tubule. The transepithelial potential difference is the difference between the potential in the lumen and the potential in blood, −4 mV. *ATP,* Adenosine triphosphate.

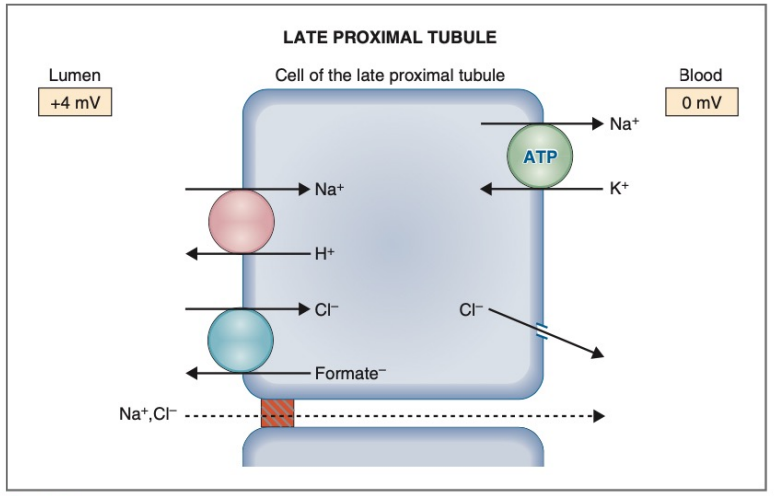
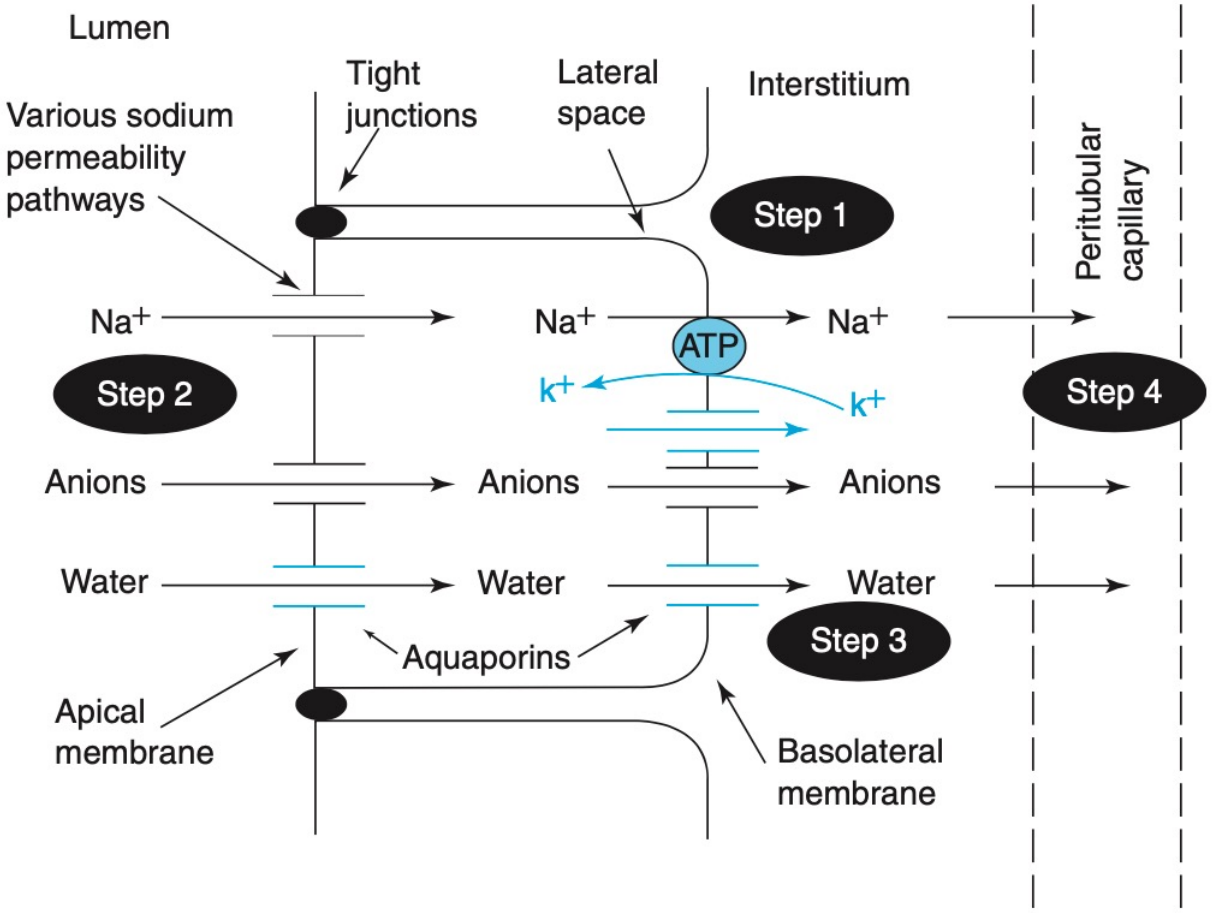


Fig. 6.21 Cellular mechanisms of Na^+ reabsorption in the late proximal tubule. The transepithelial potential difference is +4 mV. *ATP,* Adenosine triphosphate.

PROXIMAL TUBULE



GLUCOSE TRANSPORT

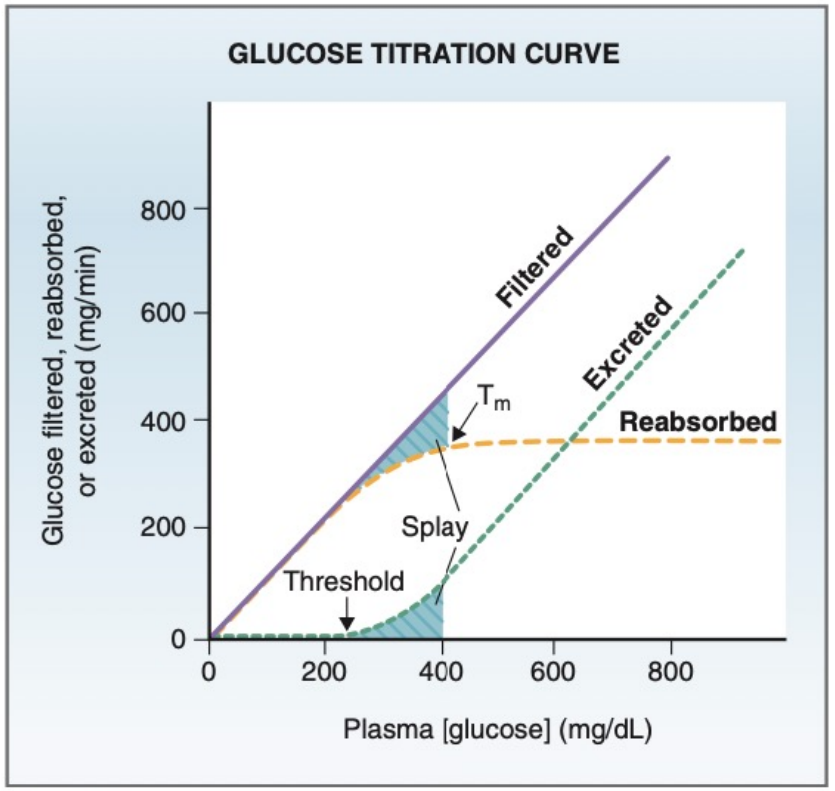


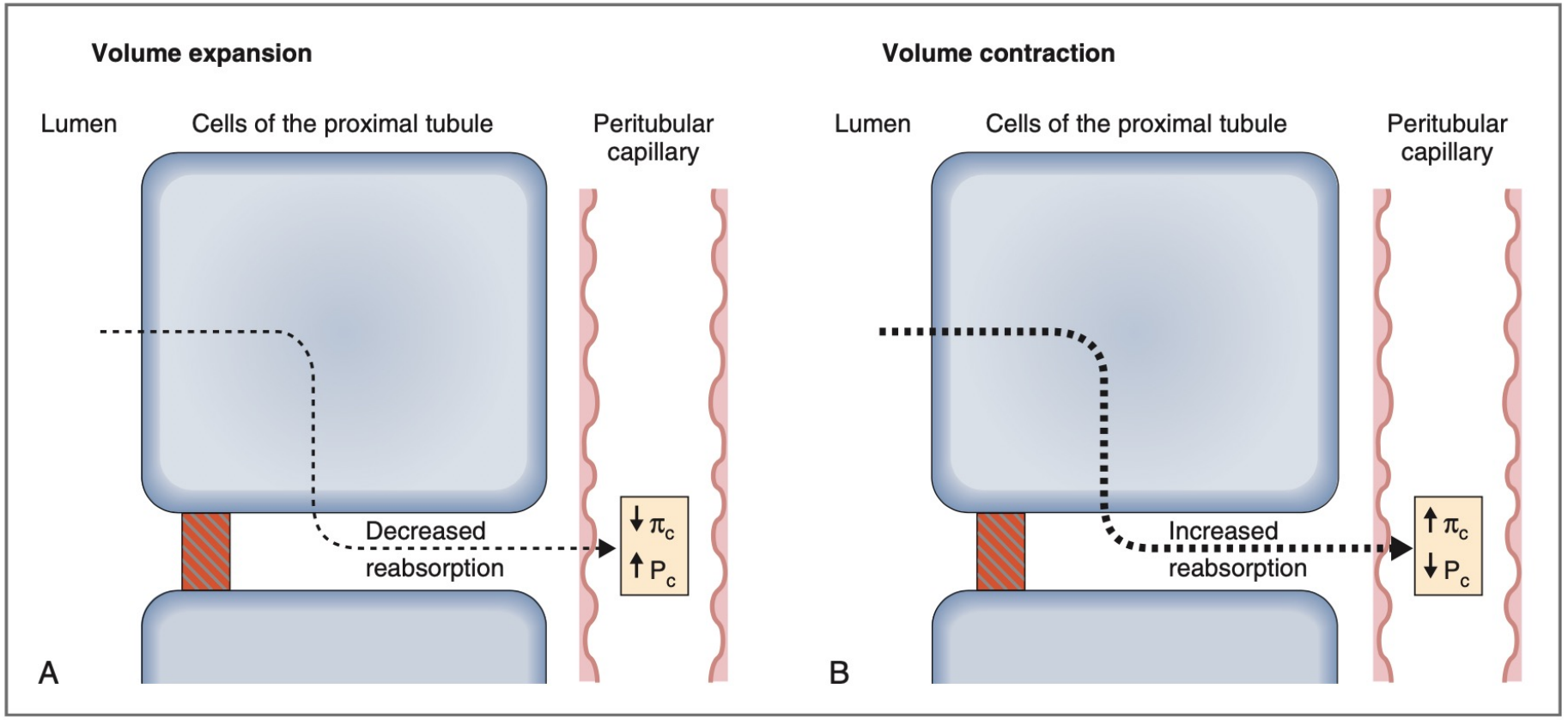
Fig. 6.15 Glucose titration curve. Glucose filtration, reabsorption, and excretion are shown as a function of plasma glucose concentration. *Hatched areas* are the splay. T_m, Tubular transport maximum.

- Transported into the cell via sodium-glucose co-transporters
  - 90% in early tubule by SGLT2
  - 10% in late tubule by SGLT1
- Transport maximum substance
  - Dogs: 180-200mg/dL
  - Cats: 270-290mg/dL
- Glucose in excess of threshold can induce osmotic diuresis due to change in filtrate osmolarity
  - Causes relative increase in Na absorption at the proximal tubule

POTASSIUM HANDLING

- Reabsorption of 65% of filtered K as part of iso-osmotic reabsorption described previously
  - Primarily paracellular

GLOMERULOTUBULAR FEEDBACK



PROXIMAL TUBULE

Substance	% Reabsorbed	Apical Mech	Basolateral Mech
Sodium	65%	Na-cotransport	NaK ATPase
Potassium	65%	Na-cotransport, paracellular	Diffusion
Glucose	100% (if below T_m)	Na-cotransport	Diffusion

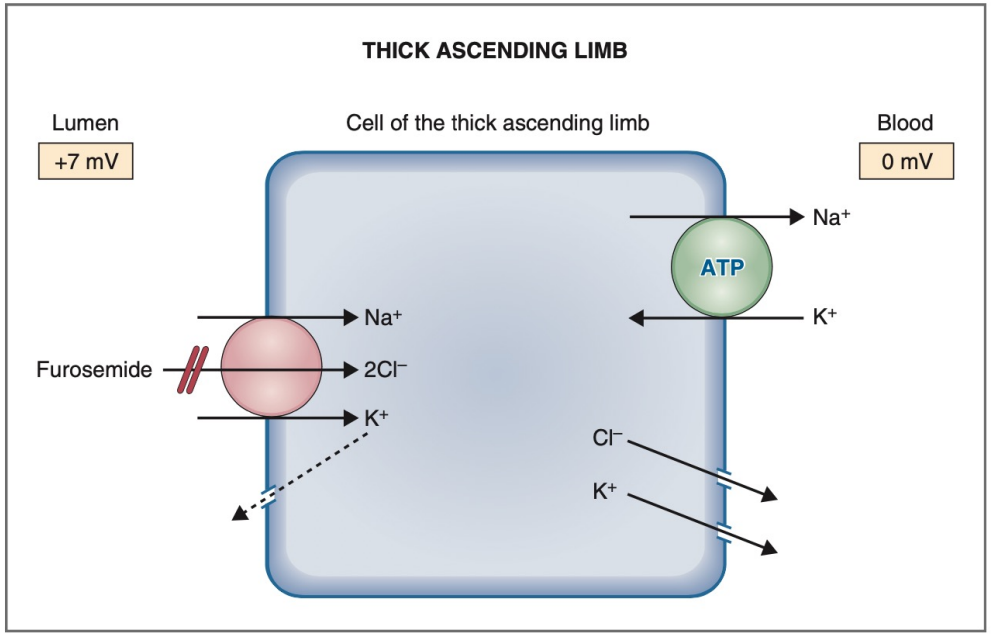
LOOP OF HENLE

BASIC PRINCIPLES OF THE LOOP OF HENLE

- Ascending limbs (thin and thick) impermeable to H_2O → referred to as a diluting segment
- Thick ascending loop **actively** reabsorbes 25% of Na (load dependent) via the NaK2Cl cotransporter
  - Small amount of transported K leaks back into lumen (electrogenic; and drives movement of P and Mg)
  - Thick ascending limb of juxtaglomerular nephrons sets up the countercurrent multiplication mechanism
-

SODIUM HANDLING

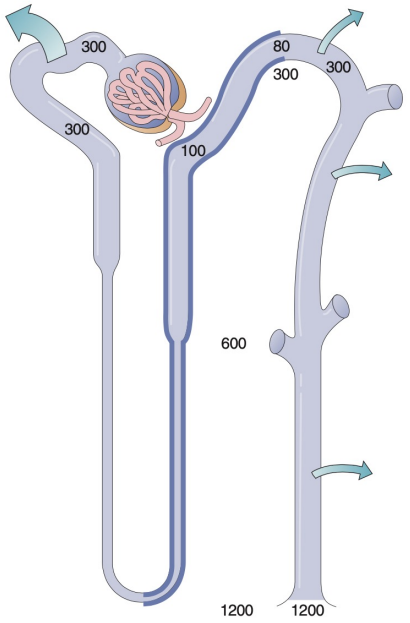
- Active sodium reabsorption occurs at the thick ascending limb via NaK2Cl pump
  - Water is NOT absorbed with NaCl in this segment
  - Activity of transporter upregulated by ADH
- Furosemide blocks the Cl site of receptor resulting in decreased solute resorption



LOOP OF HENLE

Descending Limb

- Thin limb
  - Permeable to water and NaCl



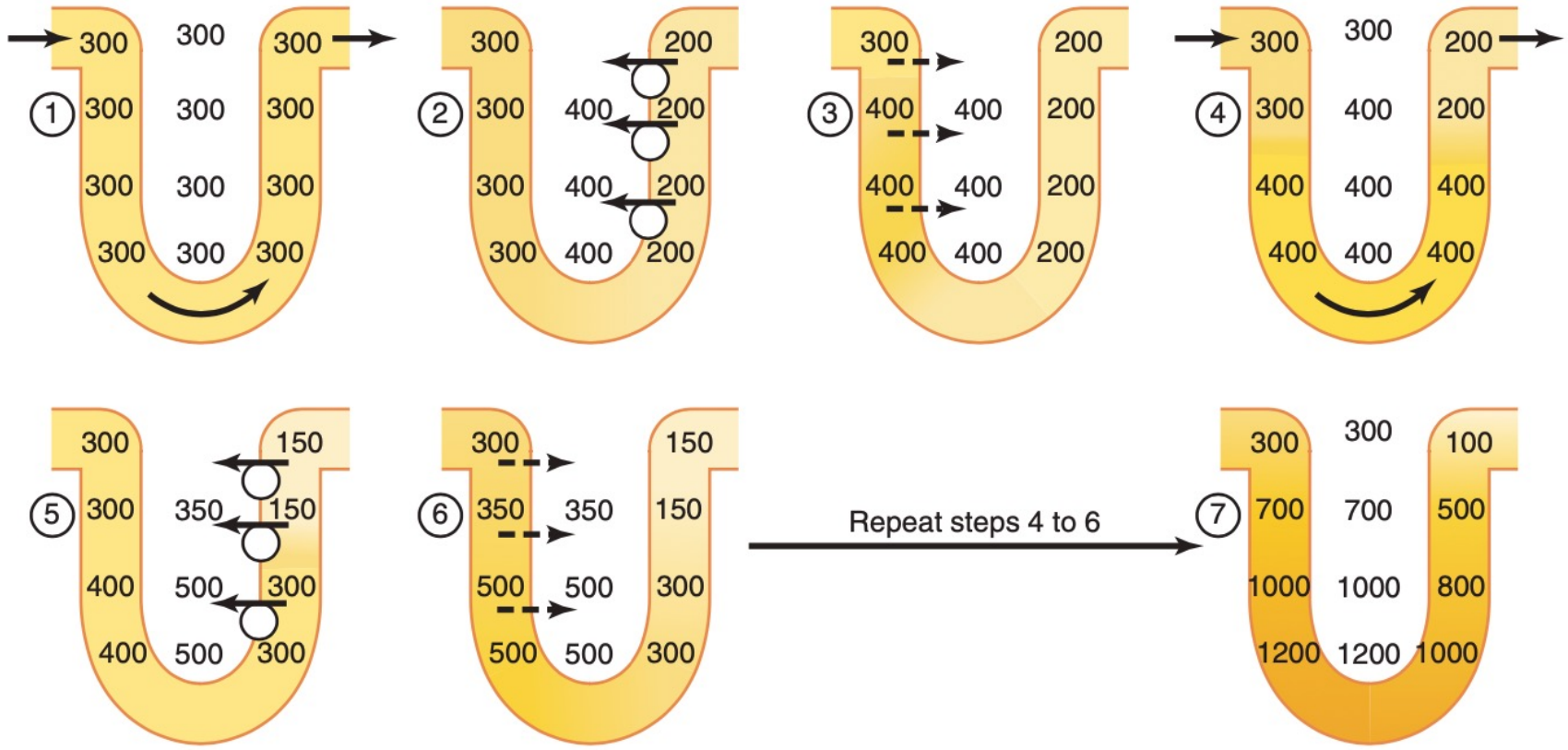
Ascending Limb

- Thin limb
  - Passive resorption of NaCl
  - Impermeable to H_2O
- Thick limb
  - Active reabsorption of NaCl
  - Impermeable to H_2O
- **Lack of water reabsorption makes these segments DILUTING SEGMENTS**

COUNTERCURRENT MULTIPLICATION

- Occurs via two repeating steps
  1. Active NaCl reabsorption at the level of the thick ascending limb increases [NaCl] in the renal interstitium (increases gradient up to 200mOsm)
     - Fluid in the descending limb equilibrates with the new interstitial osmolarity
  2. Equilibrated fluid from descending limb moves into the ascending limb where further NaCl absorption occurs
- Vasa recta provides blood supply to the medulla (~5% of renal blood flow) without destroying the gradient

COUNTERCURRENT MULTIPLICATION



POTASSIUM HANDLING

- 25% of filtered load reabsorbed at thick ascending limb via NaK2Cl cotransporter.
  - Approximately 5% diffuses back into lumen → net 20% reabsorption
  - Back-diffusion causes a positive lumen potential difference which drives the reabsorption of divalent cations (Ca and Mg)

LOOP OF HENLE (THICK ASCENDING LIMB)

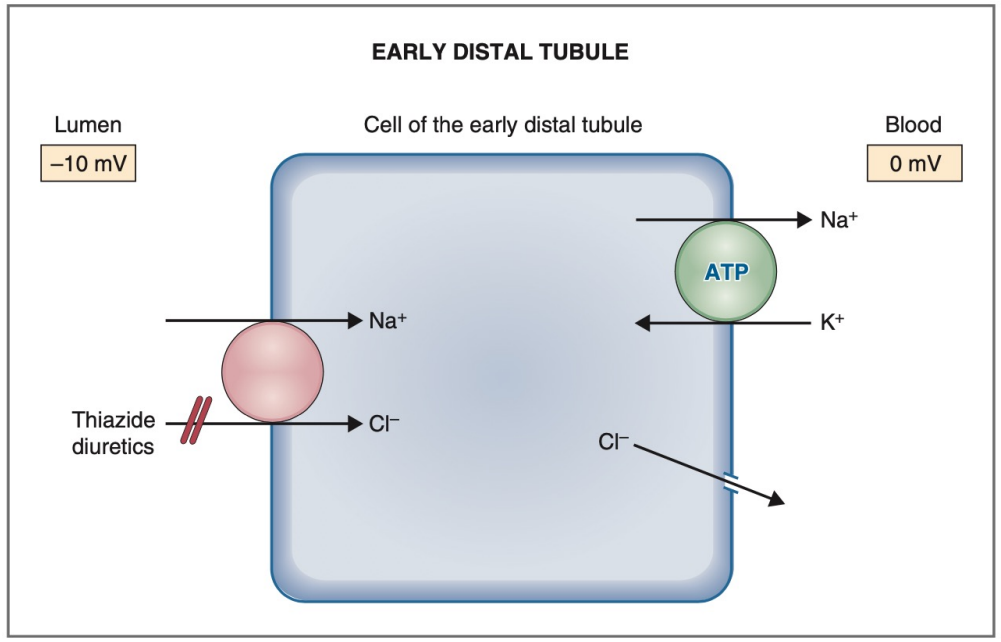
Substance	% Reabsorbed	Apical Mech	Basolateral Mech
Sodium	25%	NaK2Cl	NaK ATPase
Potassium	20%	NaK2Cl Some diffuses back into lumen	Diffusion
Glucose	NA	---	--

DISTAL TUBULE

BASIC PRINCIPLES OF THE DISTAL TUBULE

- Diluting segment due to high absorption of solutes (NaCl) an impermeability to water
  - Called the cortical diluting segment
- Electroneutral ion reabsorption (different than the LoH)

SODIUM HANDLING



- Reabsorption of 5% of filtered Na via NaCl cotransporter
  - Water also not reabsorbed (similar to thick ascending limb)
- Thiazide diuretics block the Cl site of the transporter

DISTAL TUBULE

Substance	% Reabsorbed	Apical Mech	Basolateral Mech
Sodium	5%	NaCl cotrasporter	NaK ATPase
Potassium	--	--	--
Glucose	NA	--	--

COLLECTING DUCT

BASIC PRINCIPLES OF THE COLLECTING DUCT

- Made up of two primary types of cells
  - Principal cells: Na and H_2O reabsorption and K excretion
  - a-intercalated cells: K reabsorption and H excretion
- Amount of Na/K reabsorption is dictated by aldosterone levels
- Amount of H2O reabsorption is dictated by ADH levels
  - Increased ADH levels driven by serum osmolality receptors

SODIUM HANDLING

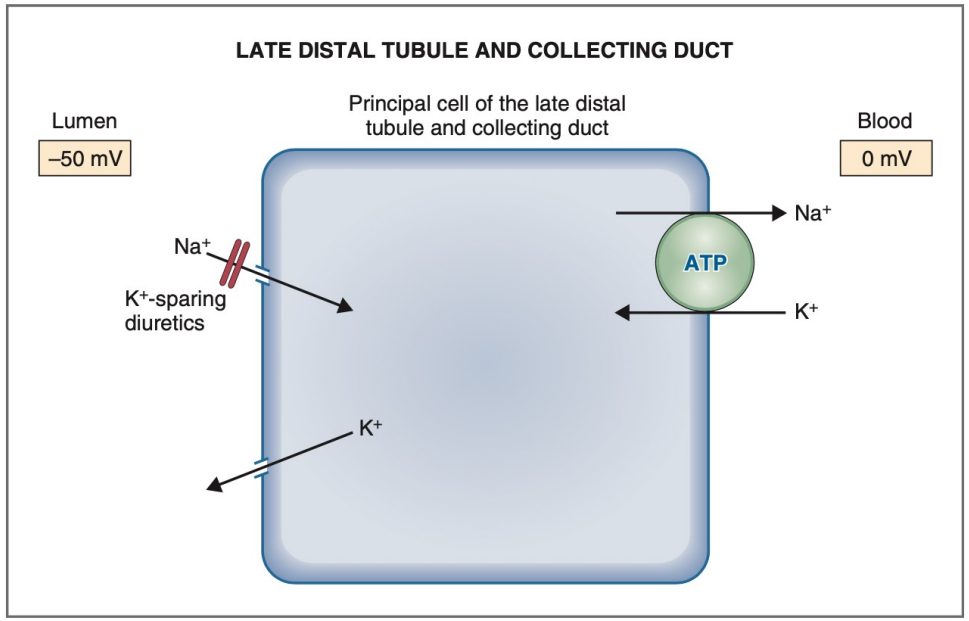
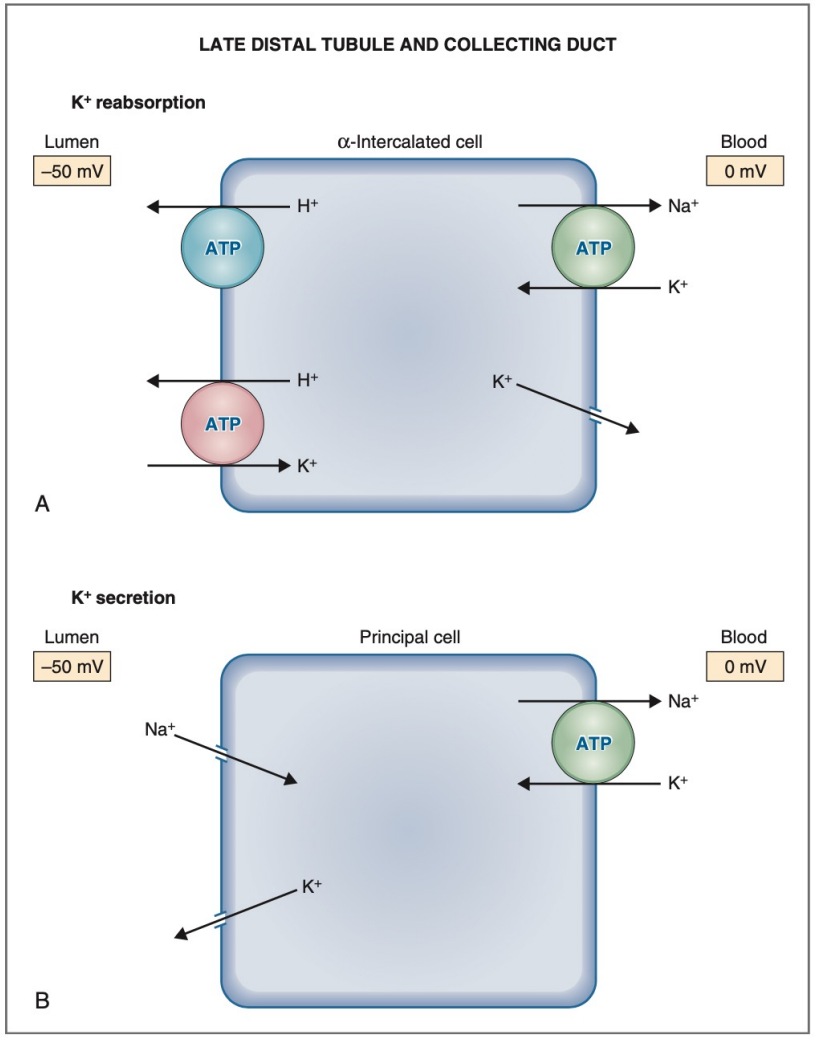


Fig. 6.27 Cellular mechanism of Na^+ reabsorption in the principal cells of the late distal tubule and collecting duct. The transepithelial potential difference is –50 mV. *ATP,* Adenosine triphosphate.

- **Aldosterone** induces insertion of **epithelial Na channels (ENaC)** on the luminal membrane of **principal cells**
  - ENaC is an INDEPENDENT Na transporter (not a cotransporter)
- Aldosterone inhibited by K-sparing diuretics that prevents insertion of ENaC
  - Very small diuretic effect because of small ΔNa at this site

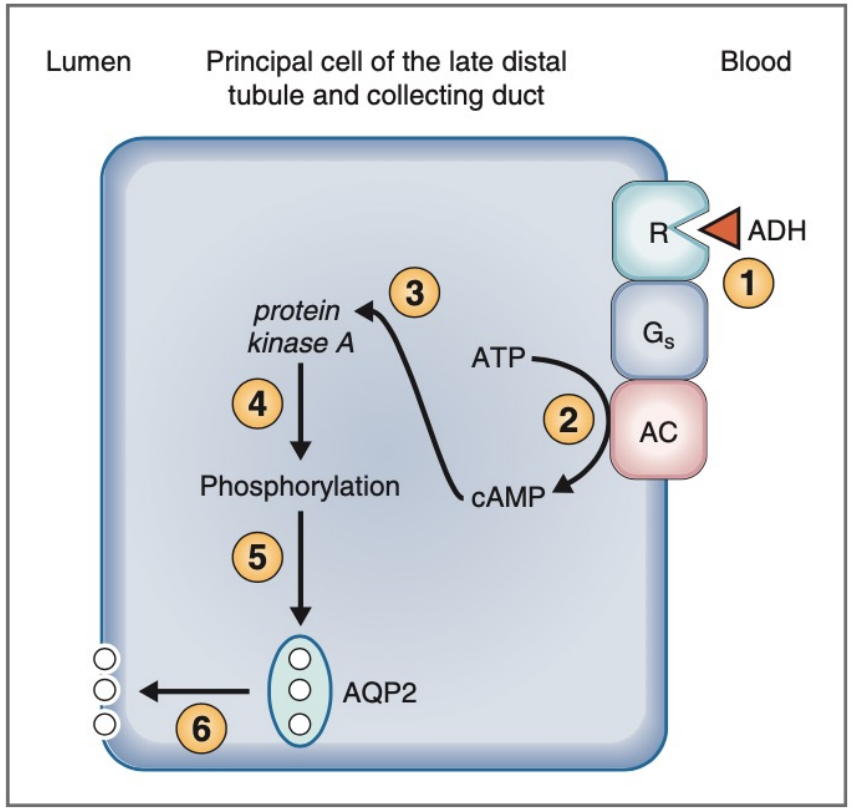
POTASSIUM HANDLING

- Collecting ducts site of varying reabsorption/secretion based on dietary intake
  - a-intercalated cells: most active in setting of low K
    - Cause K reabsorption
  - Principal cells: most active in setting of excess K
    - Cause K secretion
    - Stimulated by aldosterone

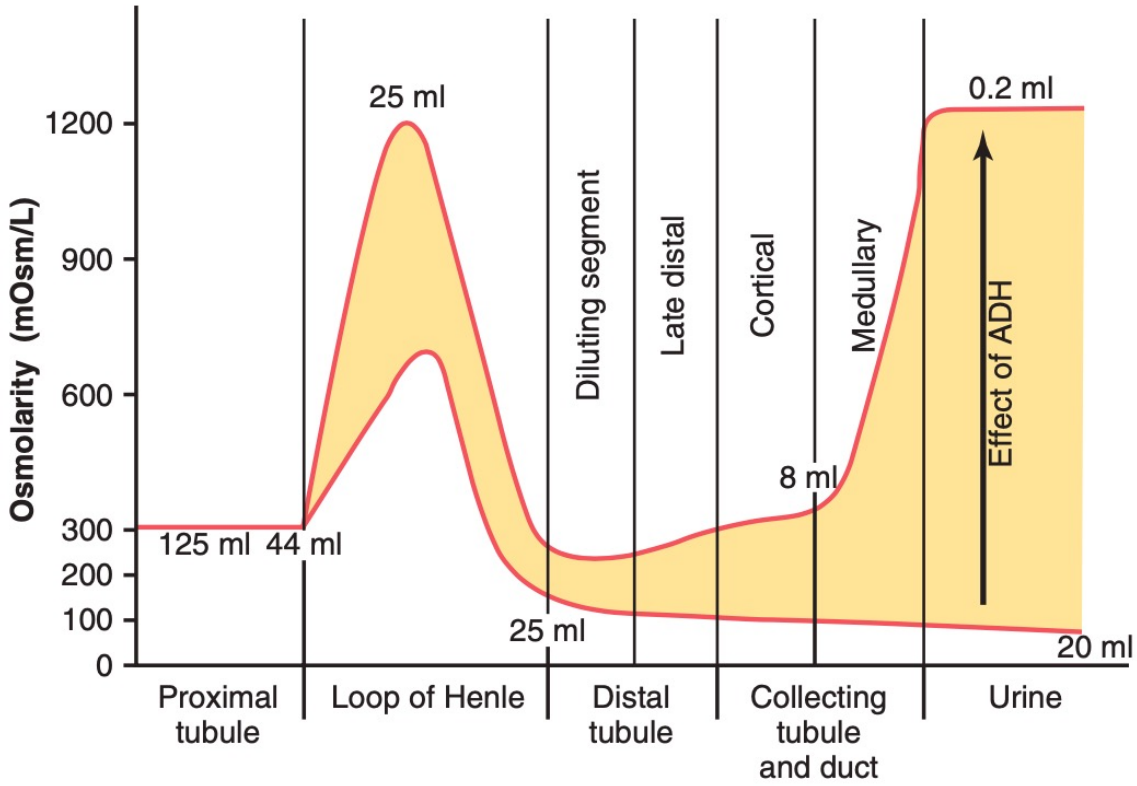


WATER REABSORPTION

- Water reabsorption mediated by anti-diuretic hormone (ADH)
  - ADH interacts with V2 receptors on basolateral side of principal cells
  - G protein coupled reaction leads to expression of aquaporin2 (AQP2) on the luminal membrane
    - Increased absorption of water from the collecting duct



URINE OSMOLARITY



UREA RECYCLING

- ADH causes insertion of UT1 transporters in the **inner medullary collecting ducts**
  - Urea concentrated in filtrate from previous H_2O absorption in proximal (cortical) collecting duct
- Increased urea in medulla increases osmotic gradient/countercurrent multiplication for H_2O reabsorption
- Contributes ~half of medullary osmolarity/concentrating ability

- Decreased levels of ADH and active diuresis can lead to medullary washout and decreased concentrating ability

Table 29-2 Control of ADH Secretion

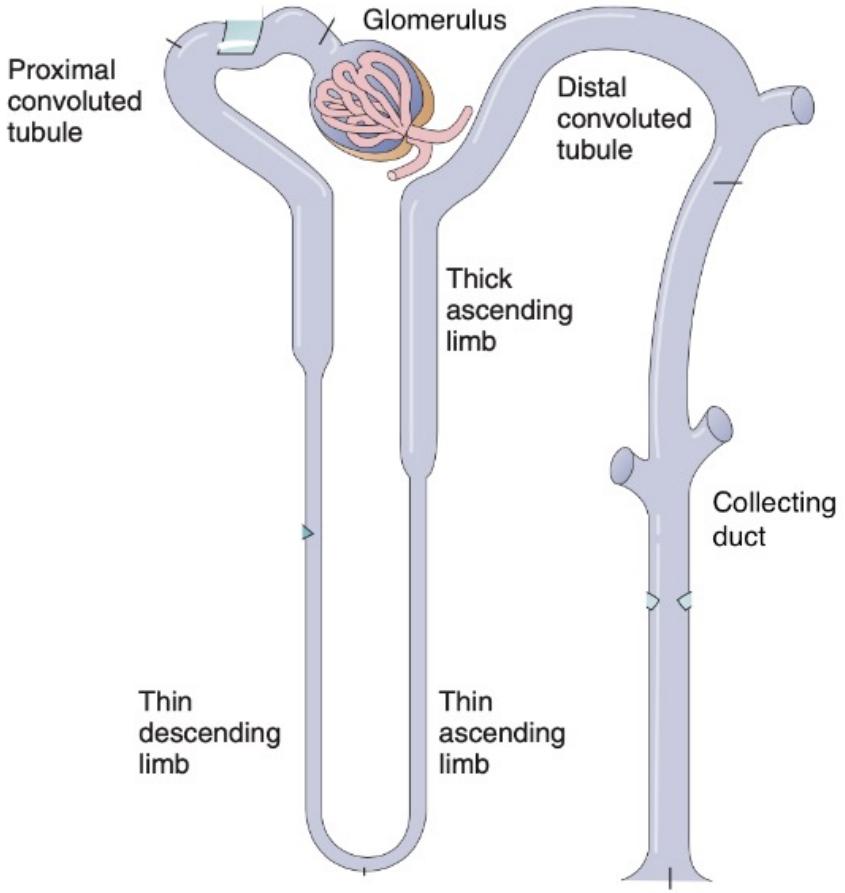
Increase ADH	Decrease ADH
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
Nausea	
Hypoxia	
Drugs:	Drugs:
Morphine	Alcohol
Nicotine	Clonidine (antihypertensive)
Cyclophosphamide	Haloperidol (dopamine blocker)

COLLECTING DUCT

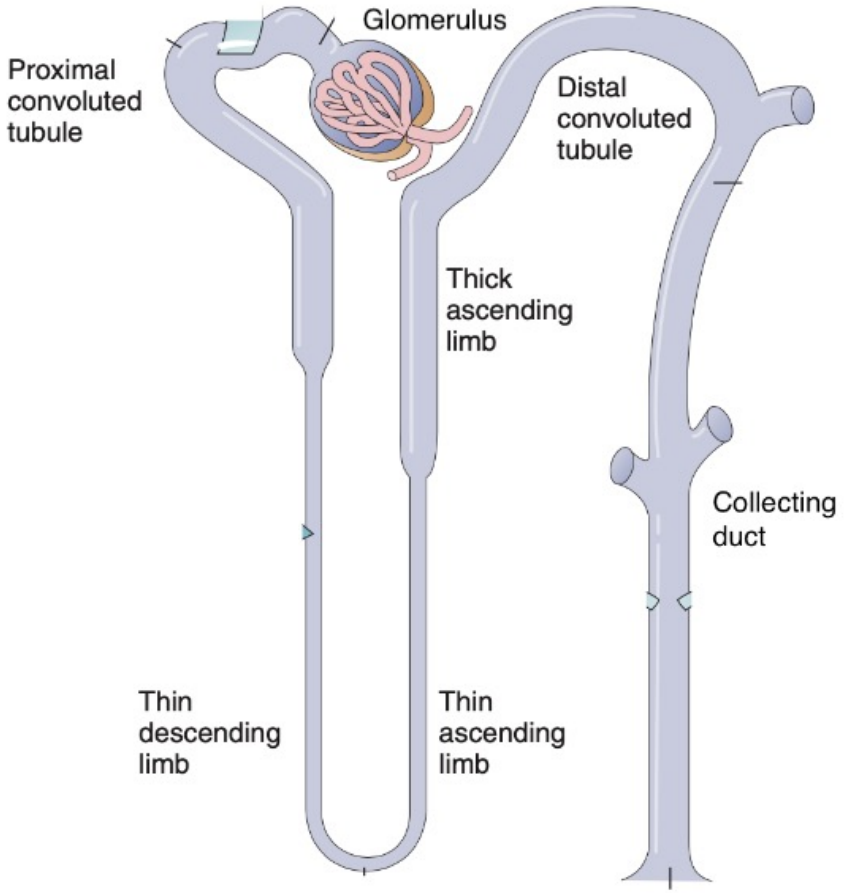
Substance	% Reabsorbed	Apical Mech	Basolateral Mech
Sodium	3%	ENaC Principal cells	NaK ATPase
Potassium	1-110%	HK ATPase on a-intercalated cells	NaK ATPase
		Diffusion	NaK ATPase on Principal cells
Glucose	NA	--	--

DIURETICS

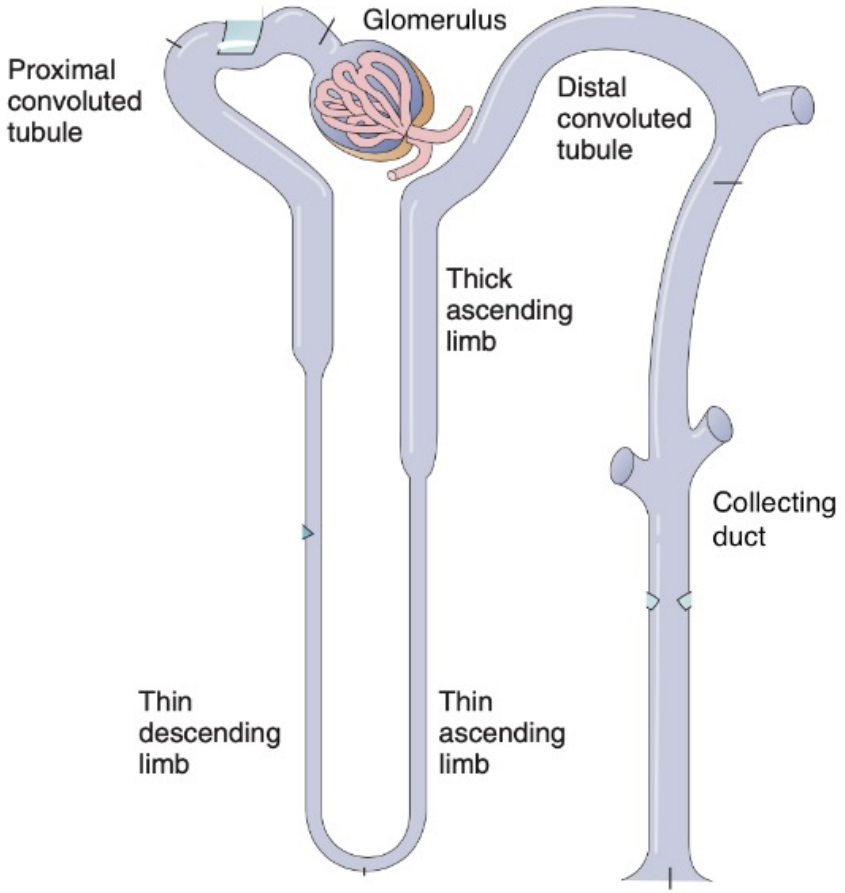
What portion of the nephron do loop diuretics act on?



What portion of the nephron do osmotic diuretics act on?



What portion of the nephron do thiazide diuretics act on?

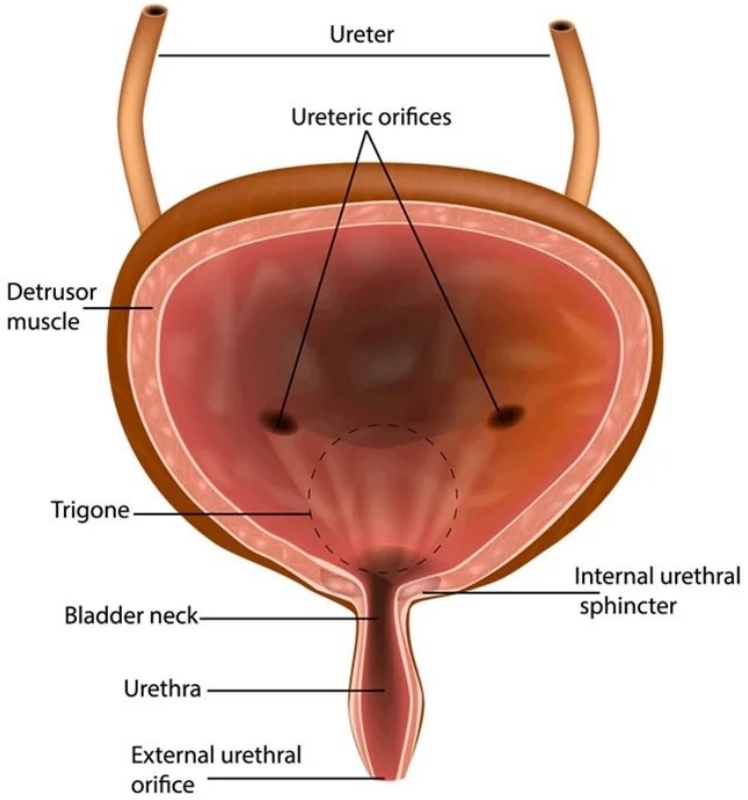


REVIEW OF DIURETICS

Diuretic	Example	Site of action	Mechanism of Action
Osmotic Diuretic	Mannitol	Proximal tubule	Increased osmolarity resulting in increased Na resorption
Loop diuretic	Furosemide	Thick ascending LoH	Blocks Cl site of NaK2Cl transporter
Thiazide diuretic	Hydrochlorothiazide	Distal tubule	Blocks Cl site of NaCl transporter
K-Sparing diuretic	Spirinolactone	Collecting ducts	Prevents aldosterone action on principal cells

MICTURITION

LOWER URINARY TRACT ANATOMY



- **Detrusor muscle**:
  - Smooth muscle that makes up majority of the bladder wall
- **Internal Sphincter**:
  - Extension of smooth muscle from detrusor at the proximal urethra
- **External Sphincter**:
  - Striated muscle at the distal urethra

BLADDER INNERVATION

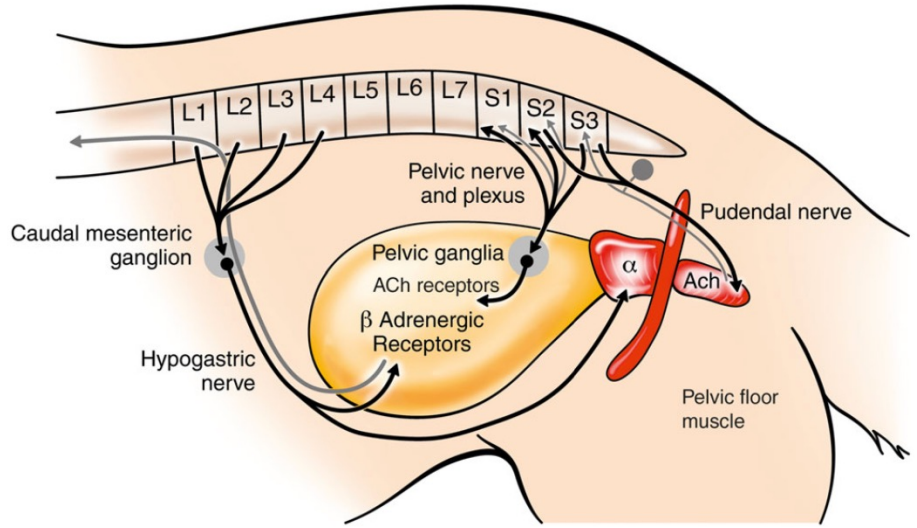


Figure 1: Anatomic organization of the local innervations of the bladder and urethra. Motor innervations are represented by the darker lines; sensory innervations are represented by the lighter lines. Image from Lorenz[5] (with permission).

- Hypogastric nerve (autonomic)
  - Sympathetic function
    - Stimulation of B receptors on detrusor: cause bladder relaxation/filling
    - Stimulation of a receptors on internal sphincter: cases constriction/closure
- Pelvic Nerve (autonomic)
  - Sensory and parasympathetic function
    - Detection of detrusor muscle stretch
    - Parasympathetic stimulation causes bladder contraction and opening of INTERNAL urethral sphincter
- Pudendal Nerve (somatic)
  - Stimulation causes contraction of the external sphincter

Bladder rupture from attempted manual expression is most commonly associated with which type of neurogenic micturin disorder ?

Upper motor neuron (UMN)

Lower motor neuron (LMN)

NEUROGENIC MICTURITION DISORDERS

Upper motor neuron (UMN)

- Lesion between the pons and L7
- Large, turgid, difficult to express
  - Incomplete detrusor contraction
  - Spasm of urethral sphincter

Lower motor neuron (LMN)

- Lesion caudal to L7
- Distended, soft, easy to express/overflow incontinent
  - Detrusor and sphincter areflexia

TABLE 333-1 Peripheral Nervous System Components of Micturition

TYPE	LOCATION	NERVE	FUNCTION WHEN STIMULATED	FUNCTION WHEN BLOCKED	FUNCTION WHEN INAPPROPRIATELY STIMULATED	FUNCTION WHEN INAPPROPRIATELY BLOCKED
Parasympathetic (M3 muscarinic)	Bladder body (detrusor)	Pelvic nerve (S1-S3)	Contraction and bladder emptying	Detrusor relaxation and bladder filling	Overactive bladder	Bladder atony, urine retention
Sympathetic (beta-3 adrenergic)	Bladder body (detrusor)	Hypogastric nerve (L1-L4)	Detrusor relaxation and filling	Detrusor relaxation and urination	Urine retention	Decreased bladder compliance and increased filling pressure
Sympathetic (alpha-1 adrenergic)	Bladder neck/urethra	Hypogastric nerve (L1-L4)	Contraction and continence	Urination	Urine retention	Open urethra, incontinence
Somatic (nicotinic)	Distal urethra/pelvic floor	Pudendal nerve (S1-S2)	Conscious/reflex contraction and continence	Urination	Urine retention	Open urethra, incontinence

TREATING NEUROGENIC MICTURITION DISORDERS

Upper motor neuron (UMN)

- Urinary catheterization
- Alpha sympatholytics
  - Prazosin, ace, phenoxybenzamine, tamsulosin
- Parasympathomimetics
  - Bethanechol

Lower motor neuron (LMN)

- Urinary catheterization
- Parasympathomimetics
  - Bethanechol

QUESTIONS