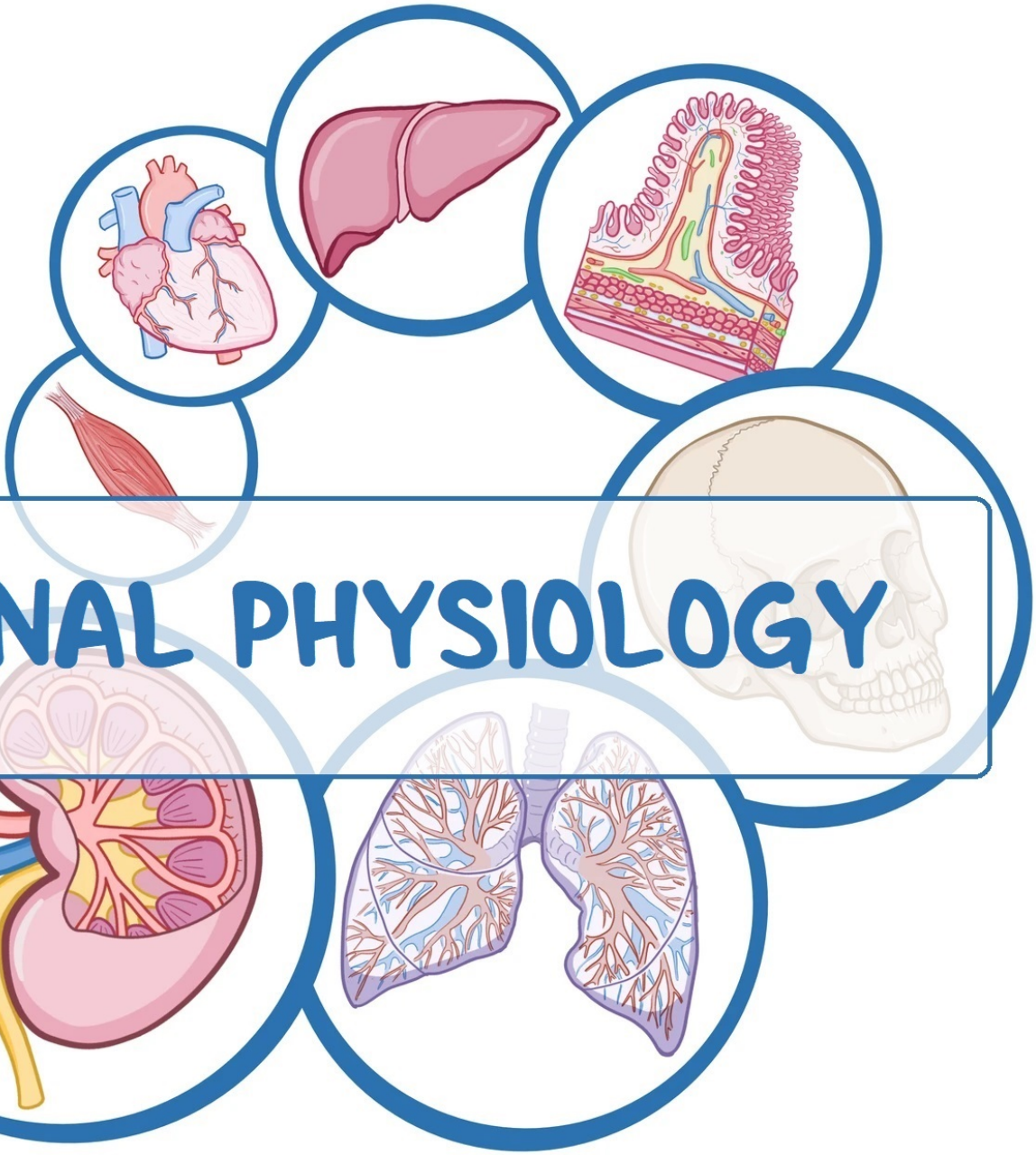
PHYSIOLOGY



RENAL PHYSIOLOGY

HIGH-YIELD NOTES

AfraTafreeh.com

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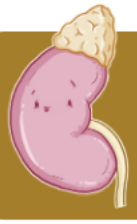


NOTES
ANATOMY & PHYSIOLOGY

RENAL ANATOMY & PHYSIOLOGY

osms.it/renal-anat-phys

RENAL SYSTEM

- Two kidneys
  - Filter the blood from harmful substances
  - Regulate blood pH, volume, pressure, osmolality
  - Produce hormones
- Located between T12, L3 vertebrae; partially protected by ribs 11, 12; behind peritoneal membrane (retroperitoneal)
- Right kidney slightly lower due to larger portion of the liver on right side
- Filter 150 liters of blood everyday; receive ¼ of cardiac output from renal arteries (from aorta)
  - Renal arteries divide → segmental arteries → interlobar arteries (between renal columns) → arcuate arteries (cover bases of renal pyramids) → cortical radiate arteries (supply the cortex) → afferent arterioles (supply nephrons)

MORPHOLOGY

Renal hilum

- Indentation in the middle of each kidney
- Entry/exit point for ureter, arteries, veins, lymphatics, nerves

Surrounding tissue (three layers)

- Renal fascia (outer)
  - Dense connective tissue
  - Anchors kidney
- Adipose capsule (middle)
  - Fatty tissue
  - Protects kidney from trauma
- Renal capsule (inner)
  - Dense connective tissue
  - Gives kidney shape

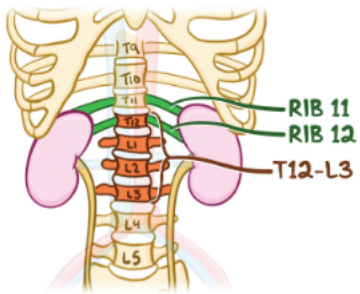


Figure 57.1 Kidney placement in relation to ribs and vertebrae.

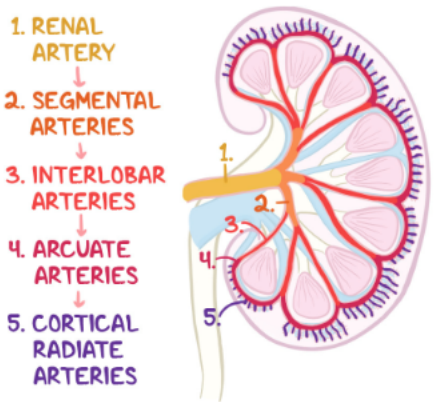


Figure 57.2 Arterial bloodflow in the kidney.

Renal cortex (outer portion)

- Outer cortical zone
- Inner juxtamedullary zone
- Renal columns project into the kidney, separating medulla

Renal medulla (inner portion)

- 10-18 renal pyramids with pointy ends (renal papilla/nipples) towards center of kidney
- *Renal lobes:* renal pyramids including cortex above them
- Renal papilla → minor calyces → major calyces → renal pelvis → ureter

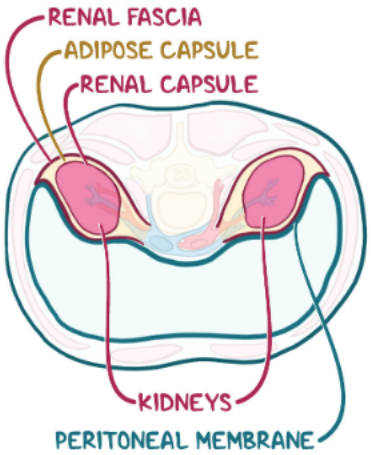


Figure 57.3 Transverse cross-section showing retroperitoneal position of kidneys, surrounding tissue layers.

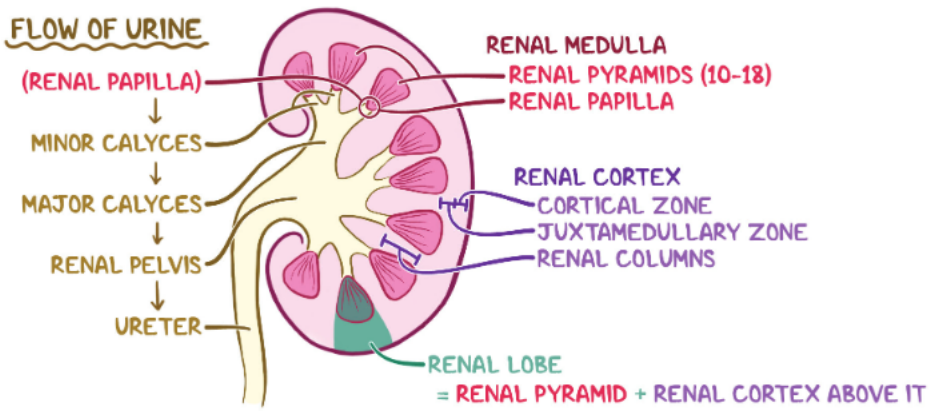


Figure 57.4 Cross-section through kidney showing renal medulla, renal cortex, and urine flow through kidney.

Nephron

- Functional unit of kidney (about one million in each kidney)
- Composed of renal corpuscle, renal tubule
- Blood filtration starts in renal corpuscle
  - Includes glomerulus, a tuft of capillaries supplied by afferent arteriole, and Bowman's capsule
  - Blood flows into glomerulus → water, solutes (e.g. sodium) pass through capillary endothelium → through basement membrane → through epithelium → into Bowman's space (becoming filtrate)
  - Epithelium comprises podocytes wrapped around basement membrane; gaps called filtration slits allow small solutes through but block large proteins, red blood cells
  - Blood leaving glomerulus enters efferent arteriole → divides into peritubular capillaries → these reunite into cortical radiate veins → arcuate veins → interlobar veins → renal veins → inferior vena cava

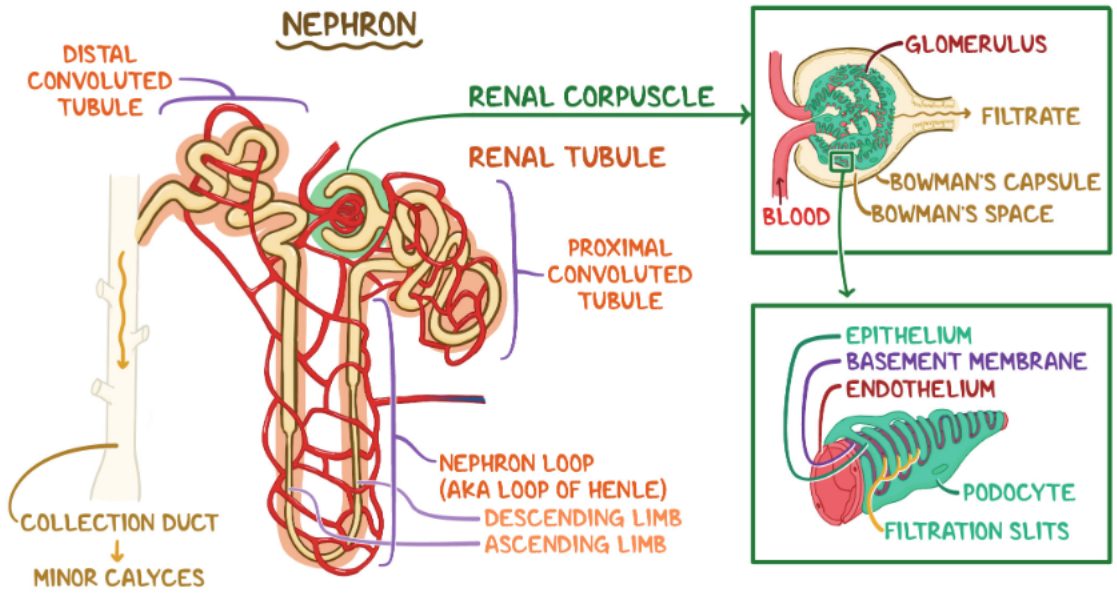


Figure 57.5 Nephron anatomy.

- Filtrate from Bowman's capsule enters renal tubule
  - Made up of proximal convoluted tubule, descending/ascending limbs of nephron loop (loop of Henle), distal convoluted tubule, collection ducts (which send urine to minor calyces)
  - Filtrate is further filtered by passing water, solutes between filtrate, blood in peritubular capillaries
- Blood pressure, glomerular filtration rate regulated by juxtaglomerular complex
  - Located between distal convoluted tubule and afferent arteriole
  - *Contains three types of cells:* macula densa, extraglomerular mesangial, juxtaglomerular (granular) cells

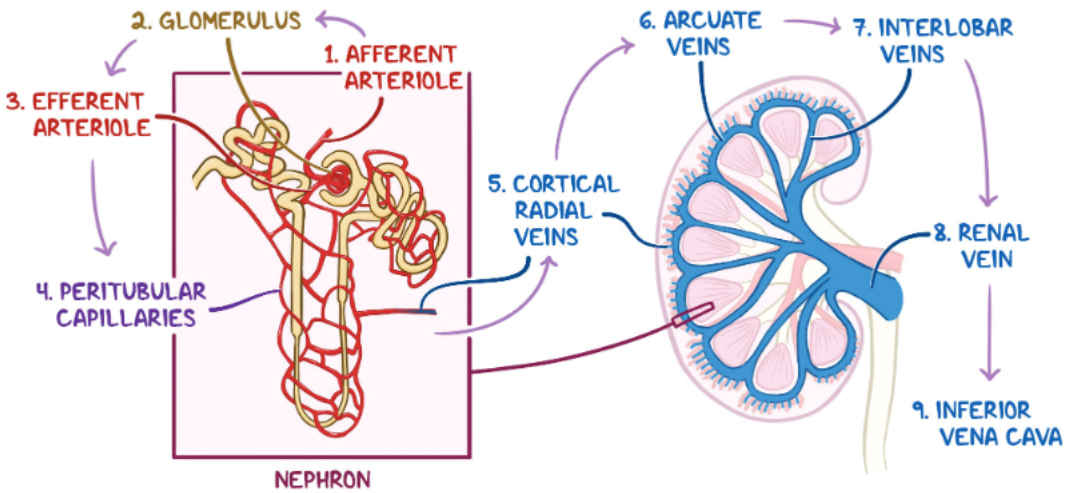


Figure 57.6 Blood flow through nephron and venial bloodflow in kidney.

- Macula densa cells in distal convoluted tubule sense ↓ sodium/blood pressure → juxtaglomerular cells secrete renin → ↑ sodium reabsorption, constricting blood vessels → ↑ blood pressure via the renin–angiotensin–aldosterone system (RAAS)
- Urine from renal tubules enters minor calyces → major calyces → renal pelvis → ureter

Bladder

- Bladder receives urine from ureter
  - Urine enters at ureterovesical junctions
  - Muscular walls fold into rugae as bladder empties
- Bladder wall contains multiple layers
  - *Transitional epithelium:* allows bladder to distend while maintaining a barrier
  - *Detrusor muscle:* helps with bladder contraction
  - *Fibrous adventitia:* holds bladder loosely in place
- Located in front of rectum in biologically-male individuals; in front of vagina, uterus, and rectum in biologically-female individuals
- Holds 750mL of urine
  - *Biologically-female individuals:* slightly less due to crowding from uterus
- Contains smooth triangular region (trigone region) on bladder floor
  - Bounded by two ureterovesical junctions and internal urethral orifice
  - Highly sensitive to expansion → signals brain as bladder fills

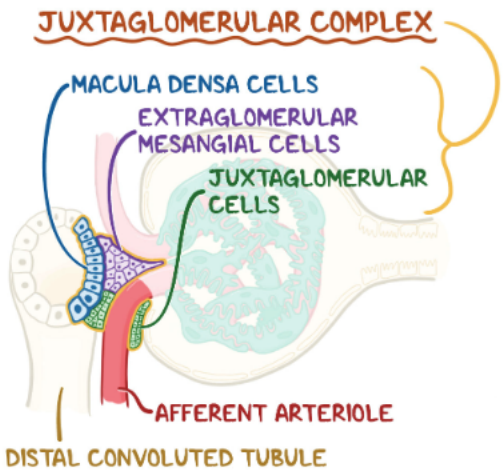


Figure 57.7 Cross-section through renal capsule showing juxtaglomerular complex.

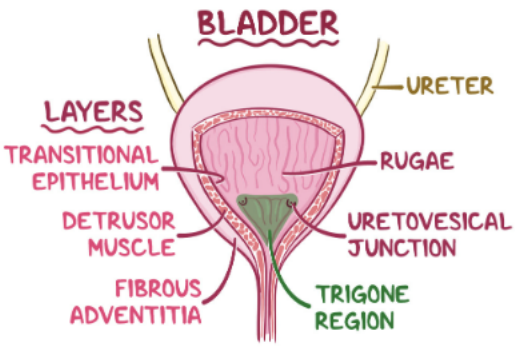


Figure 57.8 Bladder anatomy.

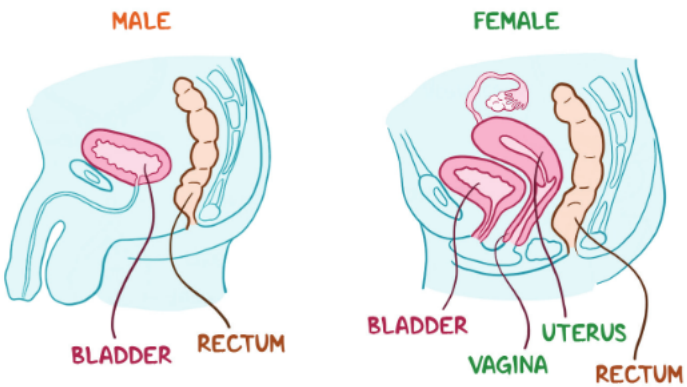


Figure 57.9 Sagittal cross-section showing placement of bladder in relation to other organs.

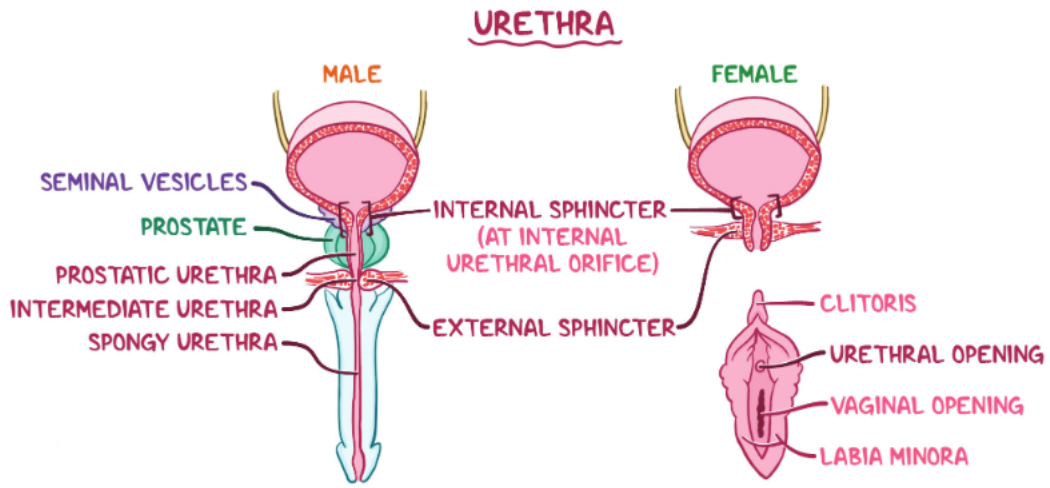


Figure 57.10 Coronal cross-section through bladder showing urethra anatomy.

Urethra

- Drains urine from bladder
- Structured differently in biologically male and female people
  - Starts at internal urethral orifice
  - *Male:* passes through prostate (prostatic urethra), deep peritoneum (intermediate urethra), penis (spongy urethra); also used during ejaculation (semen enters via seminal vesicles)
  - *Female:* passes through perineal floor of pelvis, exits between labia minora (above vaginal opening but below clitoris)
  - Detrusor muscle thickens at internal urethral orifice forming internal sphincter (involuntary control; controlled by autonomic nervous system; keeps urethra closed when bladder isn't full)
  - External sphincter is located at level of urogenital diaphragm in floor of pelvis (voluntary control; can be used to stop urination with kegel exercises)

Urination

- Involves close coordination between nervous system and bladder muscles
- Bladder volume of > 300–400mL, sends signals to micturition center in spinal cord (located at S2 and S3) → micturition reflex causes contraction of bladder and relaxation of both sphincters
  - Pontine storage center in pons of brain can be activated to stop micturition reflex
  - Pontine micturition center can be activated to allow micturition reflex

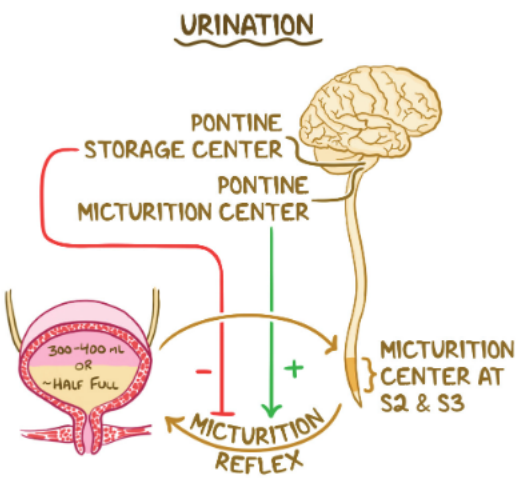
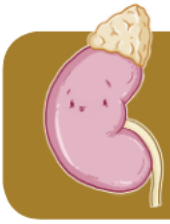


Figure 57.11 Signal pathways of micturition reflex.



NOTES
ACID-BASE PHYSIOLOGY

ACID-BASE MAP & COMPENSATORY MECHANISMS

osms.it/acid-base_map_and_ compensatory_mechanisms

ACID-BASE MAP

- Main physiologic pH factors
  - HCO_3^-, CO_2
- Acid-base map
  - HCO_3^- concentration (x-axis)/CO_2 partial pressure (y-axis) diagram
- Henderson–Hasselbalch equation
  - $pH = 6.1+\log([HCO_3^-]/0.03PCO_2)$
  - P_{CO2} is partial pressure of CO_2
- Diagonal lines
  - Drawn where each point on graph has same pH (isohydric lines)
- Drawing lines for pH = 7.35, pH = 7.45
  - Comprises area where all HCO_3^-, CO_2 combinations correspond to "normal" pH

pH out of normal range

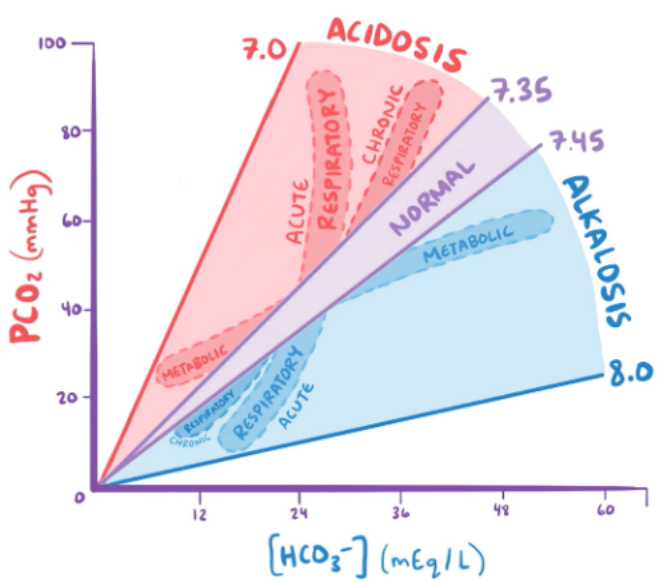
- One of two ways
  - *Acidosis*: pH ↓ 7.35, enters top-left portion of map
  - *Alkalosis*: pH ↑ 7.45, enters bottom-right portion of map
- One of two reasons
  - *Respiratory*: P_{CO2} too ↑/↓
  - *Metabolic*: $[HCO_3^-]$ too ↑/↓

COMPENSATORY MECHANISMS

- Simple acid-base disorder
  - Single problem changing pH
- Mixed acid-base disorder
  - Multiple problems compounding/ cancelling out

Multiple compensatory mechanisms

- Respiratory acidosis
  - Kidneys retain more HCO_3^-
- Respiratory alkalosis
  - Kidneys excrete more HCO_3^-
- Metabolic acidosis
  - Lungs blow off CO_2 (deeper, more frequent breaths)
- Metabolic alkalosis
  - Lungs retain CO_2 (shallower, less frequent breaths)



RESPIRATORY

	PCO_2	$[HCO_3^-]$	pH
ACIDOSIS (ACUTE)	↑	–	↓↓
ACIDOSIS (CHRONIC)	↑	↑	↓
ALKALOSIS (ACUTE)	↓	–	↑↑
ALKALOSIS (CHRONIC)	↓	↓	↑

METABOLIC

	PCO_2	$[HCO_3^-]$	pH
ACIDOSIS	↓	↓	↓
ALKALOSIS	↑	↑	↑

Figure 8.1 An acid-base map shows the relationship between pH, bicarbonate concentration, and partial pressure of carbon dioxide in respiratory and metabolic acidosis or alkalosis, and how these values are adjusted when there is renal or respiratory compensation. The accompanying tables depict the changes in PCO_2, $[HCO_3^-]$, and pH associated with respiratory/metabolic acidosis/alkalosis.

BUFFERING & HENDERSON-HASSELBALCH EQUATION

osms.it/buffering_&_henderson-hasselbalch_equation

BUFFERING

- *Buffers*: pH change-resisting solutions
- Can comprise
  - *Acidic buffer*: weak acid, conjugate base
  - *Basic buffer*: weak base, conjugate acid
- Weak acids, bases do not dissociate fully → equilibrium formation (e.g. $HA \rightleftarrows H^+ + A$ or $B + H_2O \rightleftarrows BH^+ + OH^-$)
  - *Le Chatelier's principle*: equilibriums move forward/backward, balance products/reactants' gain/loss

Resisting pH change

- Acidic, basic buffers resist all pH changes
- Strong base added to acidic buffer
  - OH^- ions react with H^+ ions → ↑ pH
  - H^+ ion loss shifts acid's equilibrium → more H^+ ions created, resists pH change
- Strong acid added to acidic buffer
  - H^+ ions would ↓ pH
  - Shifts acid equilibrium in opposite direction → conjugate base reacts with H^+ ions → resists pH change
- Strong acid added to basic buffer
  - H^+ ions would ↓ pH, also reacts with excess OH^- ions
  - OH^- loss ions shifts base's equilibrium → ↑ OH ion creation → resists pH change
- Strong base added to basic buffer
  - OH^- ions would react with H^+ ions to ↑ pH
  - Shifts base's equilibrium in opposite direction → conjugate acid reacting with OH^- ions → resists pH change

HENDERSON-HASSELBALCH EQUATION

- Henderson–Hasselbalch equation determines buffer's pH
  - $pH = pK + \log([A^-]/[HA])$
- This is derived
  - *Weak acid equilibrium*: equilibrium constant K → $K = [H^+][A^-]/[HA]$
  - Solving for H^+ → $[H^+] = K([HA]/[A^-])$
  - Negative log of both sides → $pH = pK + \log([A^-]/[HA])$
- Note
  - If $[A^-] = [HA]$, then $pH = pK$

PHYSIOLOGIC pH & BUFFERS

osms.it/physiologic-pH-and-buffers

PHYSIOLOGIC pH

- Measures balance between acids, bases in body
- *pH*: $-\log[H^+]$
  - *[H⁺]*: hydrogen ion concentration
- *Ideal*: $[H^+] = 40 \times 10^{-9}$ Eq/L = 40 nEq/L → pH = 7.4 (slightly alkaline)
  - *Acidemia*: pH < 7.4
  - *Alkalemia*: pH > 7.4
- ↑ $[H^+]$ → ↓ pH (negative sign in equation)
- pH, $[H^+]$ has logarithmic (not linear) relationship

PHYSIOLOGIC BUFFERS

- Physiologic buffers occur naturally in body
  - Maintains stable pH between 7.35–7.45

Bicarbonate buffer system

- Extracellular, most important
- *Acidic buffer*: carbonic acid (H_2CO_3)
- *Conjugate base*: bicarbonate ion (HCO_3^-)
- Carbonic acid can be formed from H_2O, CO_2 (carbonic anhydrase catalyzes reaction)
- Equilibrium reaction
  - $H2O + CO_2 \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$
- Excess
  - CO_2 blown off by lungs
  - HCO_3^- eliminated by kidneys

Phosphate buffer system (extracellular)

- *Acidic buffer*: dihydrogen phosphate ($H_2PO_4^-$)
- *Conjugate base*: monohydrogen phosphate (HPO_4^{2-})
- Equilibrium reaction
  - $H_2PO_4^- \rightleftarrows H^+ + HPO_4^{2-}$

Protein buffer system (extracellular)

- Protein amino acids may have exposed carboxyl (-COOH), amine (NH_2) groups
- Results in separate acidic ($-COOH \rightleftarrows -COO^- + H^+$), basic ($-NH_2 + H^+ \rightleftarrows -NH_3^+$) buffers

Intracellular buffer systems

- *Hemoglobin*: buffer in red blood cells (selectively binds H^+ ions)
- Organic phosphates (e.g. ATP) can buffer similarly

PLASMA ANION GAP

osms.it/plasma-anion-gap

PLASMA ANION GAP

- Cations, anions coexist within plasma
  - To keep plasma electrically neutral sum of cation charges must equal sum of anion charges
- Not all cation, anion concentrations can be measured
  - Often gap ("plasma anion gap") between measured cation charges (mainly Na^+), smaller measured anion charges sum (mainly Cl^-, HCO_3^-)
- *Plasma anion gap range*: 3–11 mEq/L
  - High gap → high unmeasured anion number
  - Low gap → low unmeasured anion number
- Unmeasured anions include anion component of several organic acids, negatively charged plasma proteins (e.g. albumin)

DIAGNOSTIC TOOL

- Plasma anion gap serves as useful diagnostic tool

Metabolic acidosis

- Organic acids' H^+ ions convert HCO_3^- into H_2CO_3
  - Organic anions aren't measured → plasma anion gap ↑
  - Organic acids include lactic acid, ketoacids, oxalic acid, formic acid, hippuric acid
- Some cases (e.g. diarrhea/renal tubular acidosis)
  - Kidneys reabsorb more Cl– ions → plasma anion gap remains normal (hyperchloremic metabolic acidosis)

High gap may suggest

- Unmeasured anion buildup (e.g. hyperphosphatemia, hyperalbuminemia)
- Metabolic alkalosis (high pH triggers albumin to release H^+ ions → negative charge ↑ on unmeasured albumin molecules)

Low gap may suggest

- Unmeasured anion ↓ (e.g. hypoalbuminemia)
- Unmeasured cation ↑ (rarely)
  - E.g. hyperkalemia, hypercalcemia, hypermagnesemia

THE ROLE OF THE KIDNEY IN ACID-BASE BALANCE

osms.it/kidney_and_acid-base_balance

KIDNEYS' FUNCTION

- Kidneys maintain acid-base balance in two ways
  - *HCO_3^- reabsorption*: urine into blood
  - *H^+ secretion*: blood into urine
- Kidneys consist of nephrons
  - Each has glomerulus (capillaries clump)
- During filtration, plasma leaves glomerulus entering renal tubule (consists of proximal convoluted tubule, loop of Henle, distal convoluted tubule)

- Tubules lined with brush border cells (apical surface facing tubular lumen, basolateral surface facing peritubular capillaries)

HCO_3^- reabsorption

- Primarily in proximal convoluted tubule
  - Na+ ions exchanged for H^+ ions through apical surface → bind with HCO_3^- → form H_2CO_3
  - Carbonic anhydrase type 4 splits H_2CO_3 into H_2O, CO_2
  - H_2O, CO_2 diffuse across membrane
  - Carbonic anhydrase type 2 recombines them into H_2CO_3
  - H_2CO_3 dissolve into H^+,HCO_3^-
  - Sodium/chloride bicarbonate cotransporters on basolateral surface snatch up HCO_3^-, nearby sodium/chloride ion, moving both into blood

H^+ secretion

- Primarily in proximal convoluted tubule
  - *Sodium-hydrogen countertransport*: H^+ ions exchanged for Na^+ ions through apical surface
  - Another mechanism in distal convoluted tubule, collecting ducts involving alpha-intercalated cells
  - Chemical buffers (ammonia, phosphate) prevent urine pH from dropping too low in tubules (< 4.5)

METABOLIC ACIDOSIS

osms.it/metabolic-acidosis

METABOLIC ACIDOSIS

- HCO_3^- ion reduction → blood pH ↓ to < 7.35

TYPES

- Distinguished by high/normal anion gap
  - Measured cation concentration
  - E.g. Na^+ ions, minus measured anion concentration (e.g. Cl^-, HCO_3^- ions)

High anion gap

- H^+ ions from organic acids convert HCO_3^- to H_2CO_3
  - ↓ HCO_3^- ion concentration (measured in anion gap), ↑ organic anion concentration (not measured)
  - *Naturally-occurring organic acids*: e.g. lactic acid production (lactic acidosis), ketoacid production (diabetic ketoacidosis), excessive uric, sulfur-containing acid retention (chronic renal failure)
  - *Ingestible organic acids*: e.g. oxalic acid (antifreeze), formic acid (methanol), hippuric acid (toluene)

Normal anion gap

- HCO_3^- lost in various ways, Cl^- ↑ prevents anion gap change (hyperchloremic metabolic acidosis)
- Possible causes
  - Diarrhea, renal tubular acidosis

REGULATORY MECHANISMS

- Body has several regulatory mechanisms to reverse ↓ pH
  - H^+ ions moved from blood into cells, exchanged for K^+ ions (may cause hyperkalemia); if organic anions present, can enter cells with H^+ ions → K^+ ions are not released
  - Chemoreceptors fire more in low pH → ↑ respiratory rate, breath depth → ↑ ventilation, CO_2 movement out of body
  - H^+ ions excreted by kidneys → HCO_3^- reabsorbed (with normal renal function)

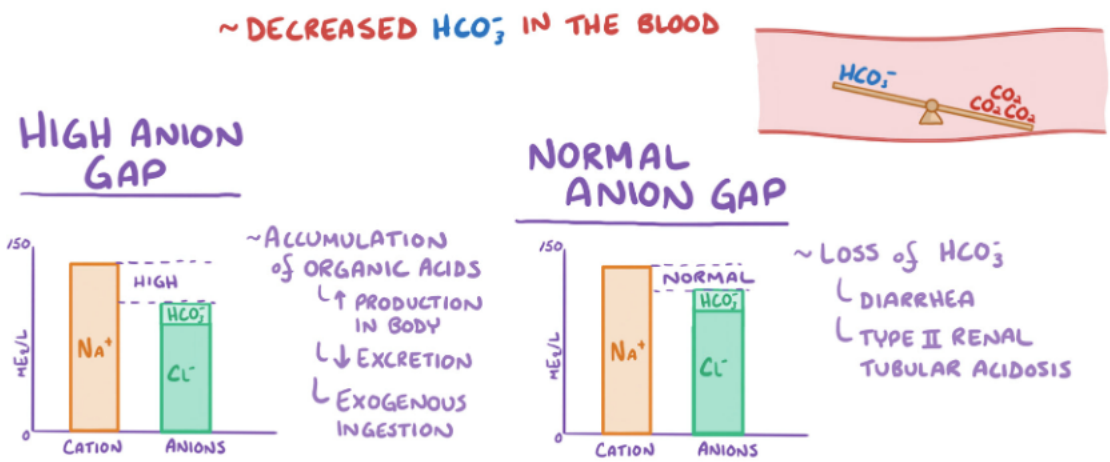


Figure 8.2 Illustration depicting the two kinds of metabolic acidosis: high anion gap (where H^+ from organic acids converts HCO_3^- to H_2CO_3), and normal anion gap (where a Cl^- increase maintains the normal anion gap).

METABOLIC ALKALOSIS

osms.it/metabolic-alkalosis

METABOLIC ALKALOSIS

- HCO_3^- ion gain → blood pH ↑ > 7.45

CAUSES

- Associated with direct HCO_3^- ion gain/ loss of H^+ ion loss (thus → HCO_3^- ion gain), usually both
- Hypokalemia
  - Metabolic alkalosis cause
  - May also be result of other root causes

Excessive H^+ ion loss causes

- Vomiting (gastric secretions acidic)
  - Also causes HCO_3^- ion buildup in pancreas (would normally neutralize gastric secretions)
- Abnormal renal function
  - E.g. adrenal tumors secrete aldosterone → distal convoluted tubule dumps H^+ ions, reabsorbs HCO_3^- ions

Excessive HCO_3^- ion gain causes

- ↑ kidney reabsorption
  - Volume contraction with loop/thiazide diuretics/severe dehydration cases (contraction alkalosis)
- Hypokalemia
  - Diarrhea/diuretic use, triggering renin-angiotensin-aldosterone mechanism → distal convoluted tubule dumps H^+ ions, reabsorbs HCO_3^- ions
- HCO_3^- ion ingestion
  - E.g. excessive antacid use ($NaHCO_3$)

REGULATORY MECHANISMS

- Body has regulatory mechanisms to reverse ↑ pH
  - K^+ ions move from blood into cells → exchanged for H^+ ions (may contribute to hypokalemia)
  - Chemoreceptors fire less in high pH → ↓ respiratory rate, breathing depth → ↓ ventilation, CO_2 retention
  - HCO_3^- ions excreted by kidneys → H^+ reabsorbed (normal renal function)

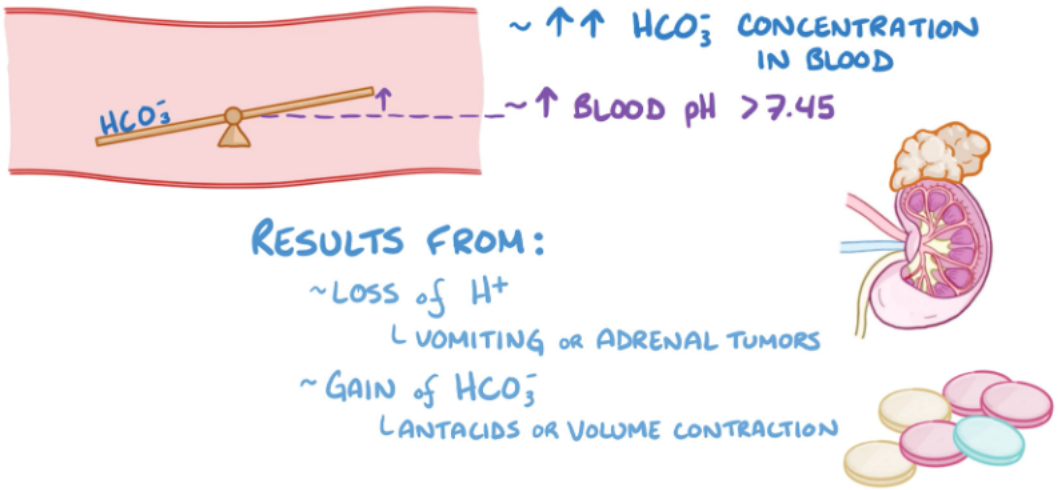


Figure 8.3 Illustration summarizing the definition and causes of metabolic alkalosis.

RESPIRATORY ACIDOSIS

osms.it/respiratory-acidosis

RESPIRATORY ACIDOSIS

- CO_2 gain → blood pH ↓ < 7.35

CAUSES

- Ventilation ↓ (frequency, breath depth) for variety of reasons → lungs blow off too little CO_2
  - Stroke/medication overdose/etc. → respiratory-center abnormality in brainstem
  - Obesity, trauma, neuromuscular disorders (myasthenia gravis), etc. → respiratory muscle-contraction failure
  - Airway obstruction
  - Alveoli damage (chronic obstructive pulmonary disease); alveoli fluid buildup (pneumonia); fluid buildup between alveoli, capillary walls (pulmonary edema) → impaired gas exchange between alveoli, capillary

REGULATORY MECHANISMS

- Body has several regulatory mechanisms to reverse pH ↓
  - Low pH → chemoreceptors fire more → attempted ↑ in respiratory rate, breathing depth → ↑ ventilation
  - H^+ ions bind to basic protein molecules (mainly exposed hemoglobin -NH_2 groups), although in small amounts
  - H^+ ions excreted by kidneys, HCO_3^- reabsorbed

RESPIRATORY ALKALOSIS

osms.it/respiratory-alkalosis

RESPIRATORY ALKALOSIS

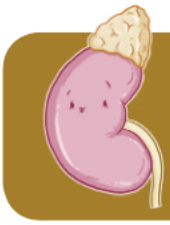
- CO_2 loss ⟶ blood pH ↑ > 7.45

CAUSES

- Ventilation ↑ (frequency, breath depth) for variety of reasons ⟶ lungs blowing off too much CO_2
  - Respiratory-center abnormality in brainstem
  - Pneumonia, pulmonary embolism, etc. ⟶ low oxygen levels (hypoxia)
  - Anxiety, panic attacks, sepsis, salicylates overdose
  - Incorrectly-set ventilator ⟶ medical intervention

REGULATORY MECHANISMS

- Body has several regulatory mechanisms to reverse pH ↑
  - High pH ⟶ chemoreceptors fire less ⟶ attempted ↓ in respiratory rate, breathing depth ⟶ ↓ ventilation
  - H^+ ions released from acidic protein molecules (mainly exposed hemoglobin -COOH groups), although in small amounts
  - HCO_3^- ions excreted by kidneys, H^+ are reabsorbed



NOTES
FLUIDS IN THE BODY

BODY FLUID COMPARTMENTS

osms.it/body-fluid-compartments

GENERAL CHARACTERISTICS

- Fluid divisions in body
  - Includes intracellular fluid, extracellular fluid
- "60-40-20 rule"
  - Total body water is 60% of body weight, of which two thirds is intracellular → total intracellular fluid is 40% of body weight, total extracellular fluid is 20% of body weight
- Due to macroscopic electroneutrality principle, fluid compartments have same concentration of positive charges as negative charges

INTRACELLULAR & EXTRACELLULAR FLUID

- Large difference between intracellular fluid and extracellular fluid (e.g. Na^+K^+ ATPases establish high concentration of K^+ inside cell and high concentration of Na^+ outside cell)

Intracellular fluid

- Dissolves cations (esp. K^+ and Mg^{2+}) and anions (esp. proteins and organic phosphates e.g. ATP)

Extracellular fluid

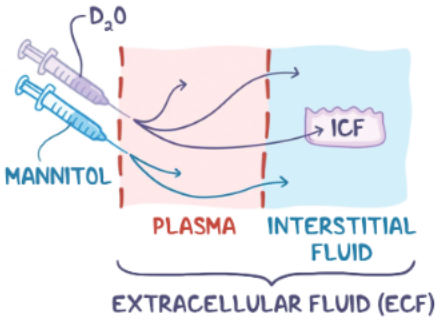
- Includes interstitial fluid (around cells) and plasma (aqueous part of blood, containing about 10% proteins e.g. albumin)
  - Both dissolve cations (esp. Na^+) and anions (esp. Cl^- and HCO_3^-)
  - Solutes and water travel between the interstitial fluid and plasma through pores in endothelial cells of capillaries
  - Negative plasma proteins are too big to travel through pores; electroneutrality is maintained by repelling small anions into interstitial fluid and attracting small cations into plasma (Gibbs–Donnan effect) → interstitial fluid has ↑ small anion concentration (e.g. Cl-) and ↓ small cation concentration (e.g. Na^+)

VOLUMES OF BODY FLUID COMPARTMENTS

- Determined by administering and measuring concentration of substances that are known to settle in specific compartments (dilution method)
  - Radiolabeled albumin for plasma (cannot pass into interstitial fluid)
  - Smaller molecules like mannitol and inulin for interstitial fluid (cannot pass through cell membranes)
  - Heavy water (D_2O) for total body water (knowing this and above, intracellular fluid can be calculated too)
  - Measuring concentration of these substances in their respective body fluid compartments allows us to calculate volume $\left(= \frac{Amount Given}{Concentration}\right)$
  - To account for loss of these substances in urine, subtract amount lost from amount given and use this value in formula

DILUTION METHOD SAMPLE PROBLEM

A 70 kg man is injected with 150mCi of D_2O and 650mg of mannitol. During a two hour equilibration period, he excretes 10% of the D_2O and 10% of the mannitol in his urine. After that, the concentration of D_2O in the plasma is 0.32mCi/100 mL, and the concentration of mannitol is 4.6 mg/100mL. Calculate the total body water (TBW), extracellular fluid (ECF), and intracellular fluid (ICF) volumes.



	INJECTED	EXCRETED	CONCENTRATION
D_2O	150 mCi	10%	0.32 mCi/100 mL
MANNITOL	650 mg	10%	4.6 mg/100 mL

STEP 1: CALCULATE $VOLUME_{TBW}$ (D_2O) & $VOLUME_{ECF}$ (MANNITOL)

STEP 1a: Determine amount remaining in body after excretion

Amount remaining = amount injected - amount excreted

$Amount_{D_2O}$ = 150mCi - (10% x 150mCi)
= 150mCi - 15mCi
= 135mCi

$Amount_{mannitol}$ = 650mg - (10% x 650mg)
= 650mg - 65mg
= 585mg

STEP 1b: Divide remaining amount by concentration

$Volume_{TBW} = Volume_{D2O}$

$$= 135\text{mCi} \times \frac{100\text{mL}}{0.32\text{mCi}}$$

= 42.2L

$Volume_{ECF} = Volume_{mannitol}$

$$= 585\text{mg} \times \frac{100\text{mL}}{4.6\text{mg}}$$

= 12.7L

STEP 2: CALCULATE $VOLUME_{ICF}$

$Volume_{ICF} = Volume_{TBW} - Volume_{ECF}$

= 42.2 L - 12.7 L
= 29.5 L

Figure 59.1 A sample problem demonstrating how to solve for total body water, extracellular fluid, and intracellular fluid volumes using information gained from D_2O and mannitol.

WATER SHIFTS BETWEEN BODY FLUID COMPARTMENTS

osms.it/water-shifts-between-body-fluid-compartments

Key features

- Movement of water between body fluid compartments to maintain constant osmolarity
- Shifts are characterized by change in volume and concentration of extracellular fluid
  - *ECF volume:* ↑ = expansion; ↓ = contraction
  - *ECF osmolarity:* ↑ = hyperosmotic; ↓ = hyposmotic; no change = isosmotic
- Six possible combinations

VOLUME CONTRACTION

Isosmotic volume contraction

- Loss of isosmotic fluid from ECF
- Volume ↓ but osmolarity is constant → no water shift
- ↓ plasma volume and arterial pressure; ↑ plasma protein concentration and hematocrit
- E.g. diarrhea

Hyperosmotic volume contraction

- Loss of hyposmotic fluid from ECF
- Volume ↓ and osmolarity ↑ → water shifts from ICF (net effect is still volume contraction)
- ↓ plasma volume and arterial pressure; ↑ plasma protein concentration but hematocrit is unchanged (since red blood cells lose volume too)
- E.g. heavy sweating (sweat is hyposmotic relative to ECF)

Hyposmotic volume contraction

- Loss of solutes/hyperosmotic fluid from ECF
- Volume ↓ and osmolarity ↓ → water shifts to ICF
- ↓ plasma volume and arterial pressure; ↑ plasma protein concentration and hematocrit
- E.g. adrenal insufficiency (deficiency in several hormones, including aldosterone). Aldosterone important for sodium reabsorption from kidneys; ↓ aldosterone = ↑ sodium loss in urine

VOLUME EXPANSION

Isosmotic volume expansion

- Gain of isosmotic fluid in ECF
- Volume ↑ but osmolarity is constant → no water shift
- ↑ plasma volume and arterial pressure; ↓ plasma protein concentration and hematocrit
- E.g. receiving an infusion of isotonic NaCl solution

Hyperosmotic volume expansion

- Gain of solutes or hyperosmotic fluid in ECF
- Volume ↑ and osmolarity ↑ → water shifts from ICF
- ↑ plasma volume and arterial pressure; ↓ plasma protein concentration and hematocrit
- E.g. eating salty chips

Hyposmotic volume expansion

- Gain of hyposmotic fluid in ECF
- Volume ↑ and osmolarity ↓ → water shifts to ICF (net effect is still volume expansion)
- ↑ plasma volume and arterial pressure; ↓ plasma protein concentration but hematocrit is unchanged
- E.g. too much antidiuretic hormone causing excessive water reabsorption

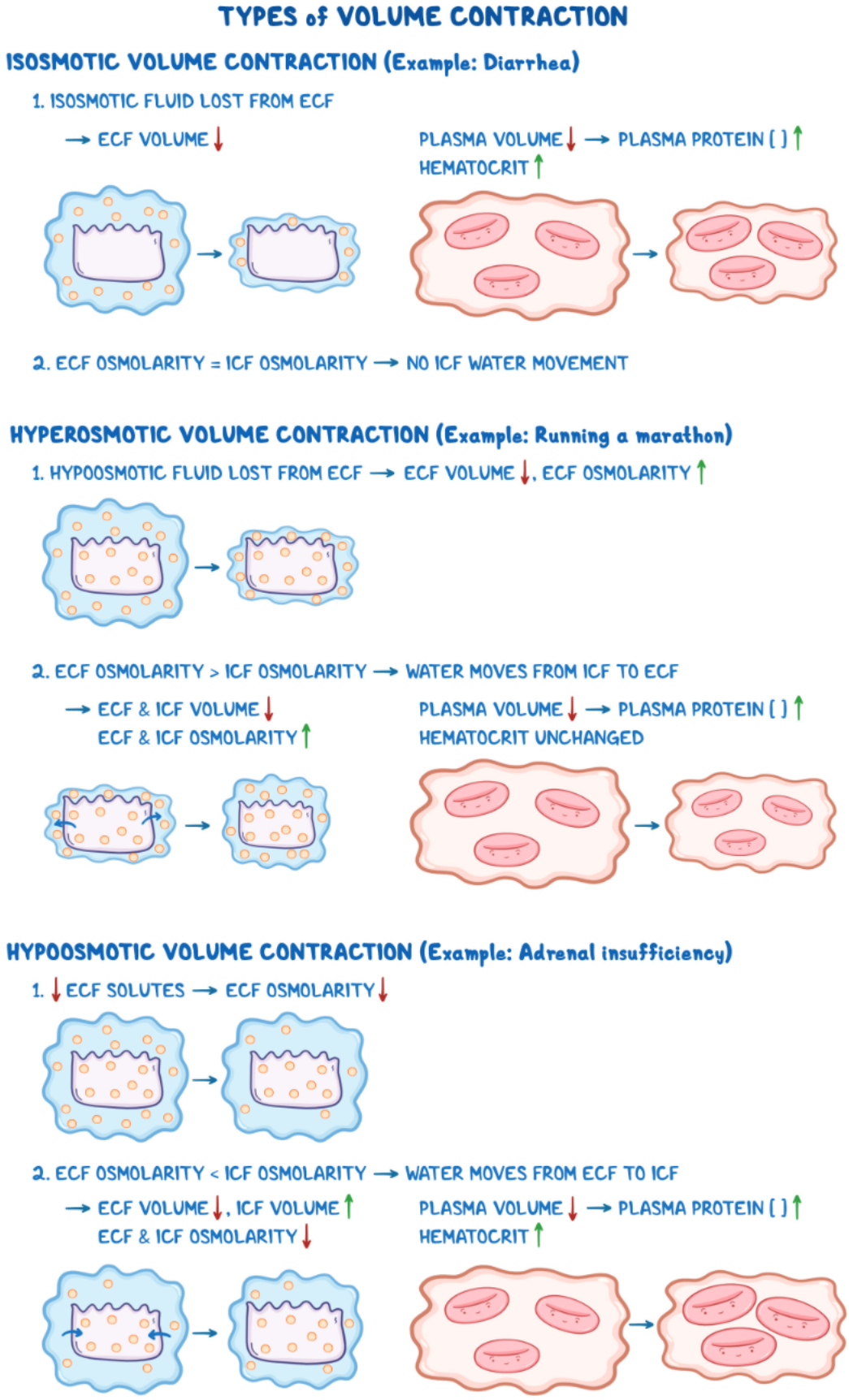


Figure 59.2 Visualization of the types of volume contraction.

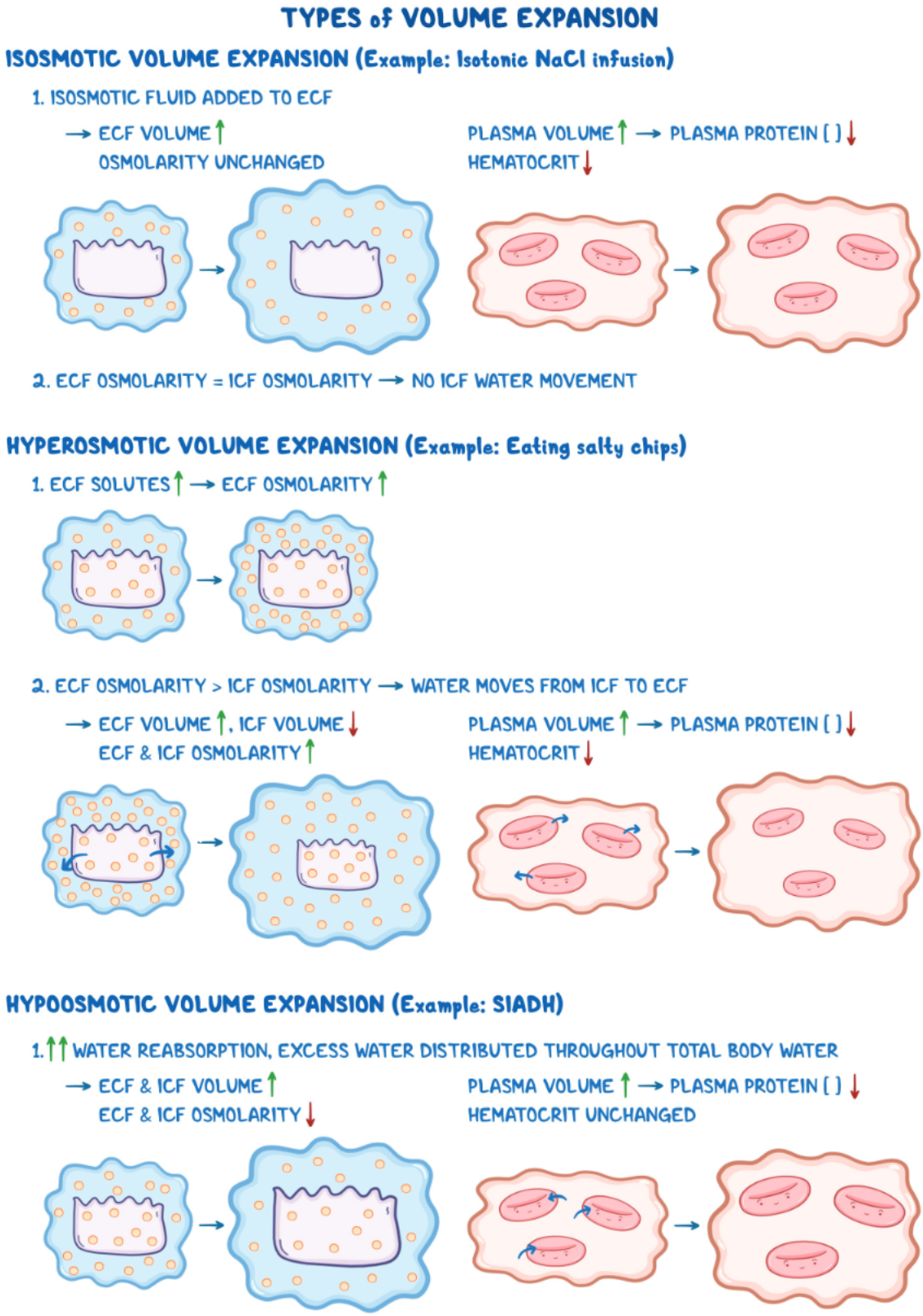


Figure 59.3 Visualization of the types of volume expansion.

RENAL CLEARANCE

osms.it/renal-clearance

- Rate at which kidneys clear blood plasma of substance
- For substance "x", renal clearance

$$C = \frac{[U]_x \times V}{[P]_x}$$

  - [U]x: urine concentration of x
  - [P]x: plasma concentration of x
  - V: urine flow rate
- To measure reabsorption/secretion of substance in kidneys, inulin can be used as reference point
  - Inulin is freely filtered
  - Inulin is not reabsorbed/secreted
- Clearance ratio for substance x is

$$\frac{C_x}{C_{inulin}}$$

  - = 1 → x is freely filtered, not secreted
  - > 1 → x is freely filtered, secreted
  - < 1 → x is not freely filtered/is reabsorbed

- Free water clearance is renal clearance of pure water

$$C_{H_2O} = V - \frac{U_{osm}}{P_{osm}} V$$

  - U_{osm}: urine osmolarity
  - P_{osm}: plasma osmolarity

RENAL CLEARANCE SAMPLE PROBLEM

PART 1

In a 24 hour period, a man has 2 liters of urine. His plasma Na^+ concentration is 145mEq/L, whereas his urine Na^+ concentration is 190mEq/L. What is the man's renal clearance for sodium?

$$C = \frac{[U]_x \times \dot{V}}{[P]_x}$$

STEP 1: CALCULATE $\dot{V}$

$$\dot{V} = \frac{\text{URINE VOLUME}}{\text{TIME}} = \frac{2000\text{mL}}{1440\text{min}} = 1.39\text{mL/min}$$

STEP 2: CALCULATE C_{Na^+}

$$C_{Na^+} = \frac{[U]x \times \dot{V}}{[P]x} = \frac{190\text{mEq/L} \times 1.39\text{ mL/min}}{145\text{mEq/L}} = 1.43\text{mL/min}$$

→ 1.43mL of plasma is cleared of Na^+ per minute.

PART 2

Returning to the scenario in Part 1, let's assume we gave that man an infusion of inulin over 2 hours. The urine concentration of inulin is 140mg/mL, and the plasma concentration of inulin is 1mg/mL. The urine flow rate is 1.39mL/min (the value calculated in Part 1). What is the man's clearance of inulin? What is the clearance ratio for Na^+?

$$C = \frac{[U]_x \times \dot{V}}{[P]_x}$$

STEP 1: CALCULATE C_{INULIN}

$$C_{INULIN} = \frac{[U]x \times \dot{V}}{[P]x} = \frac{140\text{mg/mL} \times 1.39\text{ mL/min}}{1\text{mg/mL}} = 194.6\text{mL/min}$$

→ 194.6mL of plasma is cleared of inulin per minute.

STEP 2: CALCULATE CLEARANCE RATIO FOR Na^+

$$C_{Na^+} = \frac{C_{Na^+}}{C_{INULIN}} = \frac{1.43\text{mL/min}}{194.6\text{mL/min}} = 0.007$$

→ 0.007 << 1, so very little Na^+ is excreted in the urine. Since it is freely filtered, it must be extensively reabsorbed by the nephron to have such a low clearance ratio.

FREE WATER CLEARANCE SAMPLE PROBLEM

A woman has a urine flow rate of 1.5mL/min, a urine osmolarity of 130mOsm/L, and a plasma osmolarity of 280mOsm/L. What is her free water clearance?

$$CH_2O = \dot{V} - C_{OSM}$$

$$CH_2O = \dot{V} - \frac{[U]_{OSM} \times \dot{V}}{[P]_{OSM}}$$

$$= 1.5\text{mL/min} - \frac{130\text{mOsm/L} \times 1.5\text{mL/min}}{180\text{mOsm/L}}$$

$$= 1.5\text{mL/min} - 0.7\text{mL/min}$$

$$= 0.8\text{mL/min}$$

→ 0.8mL of plasma is cleared of solute-free water every minute by the kidneys.

Figure 59.4 Sample questions solving for renal clearance of a solute and free water clearance.

NOTES
RENAL BLOOD FLOW REGULATION

RENAL BLOOD FLOW REGULATION

osms.it/renal-blood-flow-regulation

- Blood enters kidney via renal artery, leaves via renal vein
  - Blood enters glomerulus via afferent arteriole, leaves via efferent arteriole
- *Renal blood flow:* volume of blood that reaches kidneys in unit time; determined by pressure gradient (pressure in renal artery - pressure in renal vein) divided by arteriolar resistance
  - ↑ blood pressure → ↑ pressure in renal artery → ↑ renal blood flow
  - ↓ arteriolar resistance → ↑ renal blood flow
- Renal blood flow determines glomerular filtration rate (GFR)
  - ↑ renal blood flow → ↑ GFR
- *Regulation of renal blood flow:* increasing/ decreasing arteriolar resistance

Key hormones: increasing arteriolar resistance (decreasing renal blood flow)

- Adrenaline (epinephrine)
  - Secreted by adrenal gland in response to sympathetic stimulation
  - Binds to alpha-1 adrenergic receptors along afferent, efferent arterioles → smooth muscle cells contract
- Angiotensin II
  - Renin produced by juxtaglomerular cells in afferent arteriole → released into blood, becomes angiotensin I in response to low blood pressure → converted into angiotensin II by angiotensin-converting enzyme (ACE), synthesized in endothelial cells (esp. in lungs)
  - Binds to angiotensin receptors along afferent, efferent arterioles → smooth muscle cells contract
  - Efferent arterioles more sensitive to angiotensin II → constrict more → blood builds up in glomerulus → GFR constant
  - High levels of angiotensin II → afferent arterioles constrict equally → ↓ GFR

Key hormones: decreasing arteriolar resistance (increasing renal blood flow)

- Atrial natriuretic peptide
  - Secreted by atria of heart in response to increased cardiac workload
  - Binds to natriuretic peptide receptors along afferent, efferent arterioles → smooth muscle cells relax
- Brain natriuretic peptide
  - Secreted by ventricles of heart in response to increased cardiac workload
  - Binds to natriuretic peptide receptors along afferent, efferent arterioles → smooth muscle cells relax
- Prostaglandins (e.g. prostaglandin E2, I2)
  - Produced by kidneys in response to sympathetic stimulation
  - Binds to prostaglandin receptors along afferent, efferent arterioles → smooth muscle cells relax
  - Prevents kidney damage during sympathetic stimulation
- Dopamine
  - Synthesized in brain, kidneys
  - Binds to dopaminergic along afferent, efferent arterioles → smooth muscle cells relax

AUTOREGULATION OF RENAL BLOOD FLOW

- Keeps renal blood flow, GFR constant over range of systemic blood pressures (80–200mmHg)
  - *80mmHg:* smooth blood cells in arterioles completely relaxed, renal blood flow optimal
  - Systemic blood pressure increases → smooth blood cells contract to maintain optimal renal blood flow

Mechanisms for autoregulation

- *Myogenic mechanism:* smooth muscle cells in arterioles automatically contract when stretched by high blood pressure (related to increased renal blood flow)
- *Tubuloglomerular mechanism:* macula densa cells release adenosine → increases resistance in afferent arteriole when more sodium, chloride ions detected in distal convoluted tubule (related to increased GFR, renal blood flow)

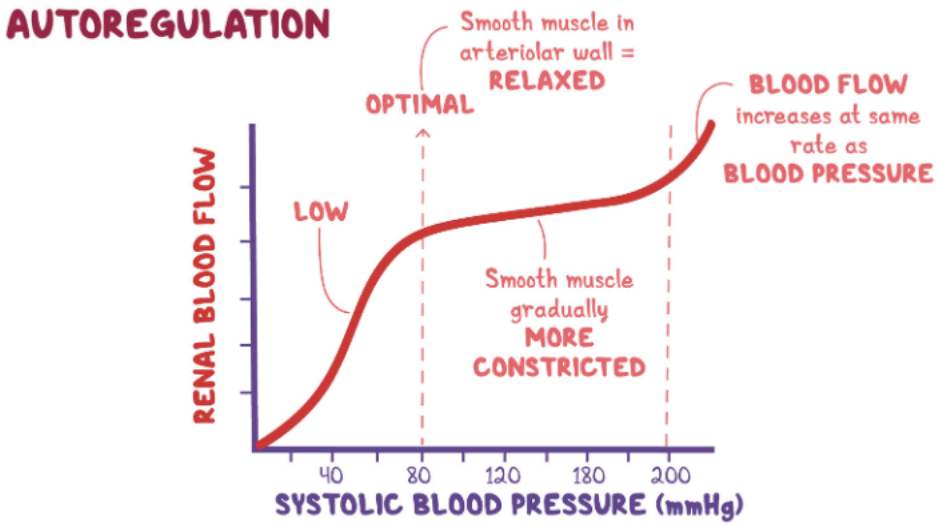


Figure 60.1 Graph displaying the relationship between systolic blood pressure and renal blood flow. The kidneys achieve consistency between 80–200mmHg by adjusting their own arteriole resistance.

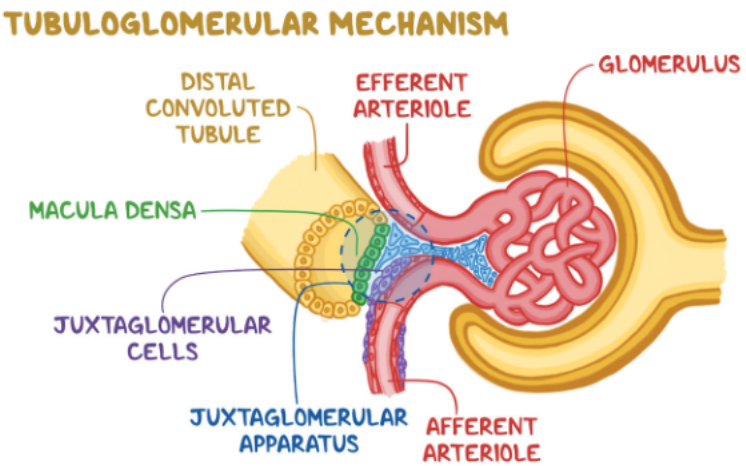


Figure 60.2 The region where the distal convoluted tubule and the afferent arteriole are close to one another is called the juxtaglomerular apparatus. This proximity allows adenosine from the macula densa cells to diffuse over to the juxtaglomerular cells of the afferent arteriole, alerting them to ↑ GFR. This increases arteriolar resistance → ↓ GFR.

MEASURING RENAL PLASMA FLOW & RENAL BLOOD FLOW

osms.it/measuring-renal-plasma-blood-flow

- *Fick principle:* amount of substance in blood that flows into organ = amount that flows out (if organ doesn't produce/degrade that substance)

True renal plasma flow

- Add para-aminohippuric acid (PAH) to body (isn't made in body, doesn't affect renal function)
- *Fick principle:* amount of PAH that flows into kidneys through renal artery = amount of PAH that flows out (through urine, renal veins)
  - Inwards flow of PAH = outwards flow of PAH
  - $[PAH]_{artery}$ x renal plasma flow = ($[PAH_{vein}$ x renal plasma flow) + ($[PAH_{urine}$ x urine flow)
  - Renal plasma flow x ($[PAH]_{artery}$ - $[PAH]_{vein}$) = $[PAH]_{urine}$ x urine flow
  - $$Renal\ plasma\ flow = \frac{[PAH]_{urine} \times Urine\ flow}{[PAH]_{artery} - [PAH]_{vein}}$$
- Measure concentration of PAH in renal artery/vein, urine; measure urine flow

Effective renal plasma flow

- Two assumptions
  - 90% of PAH leaves kidneys in urine → 10% leaves in renal vein negligible
  - Concentration of PAH in renal artery = concentration of PAH in any peripheral vein
- $$Effective\ renal\ plasma\ flow = \frac{[PAH]_{urine} \times Urine\ flow}{[PAH]}$$
- Effective renal plasma flow = 90% of true renal plasma flow

Renal blood flow

- $$Renal\ blood\ flow = \frac{Renal\ plasma\ flow}{(1 - hematocrit)}$$
  - Hematocrit: blood volume fraction occupied by red blood cells (i.e. fraction of blood volume not plasma)

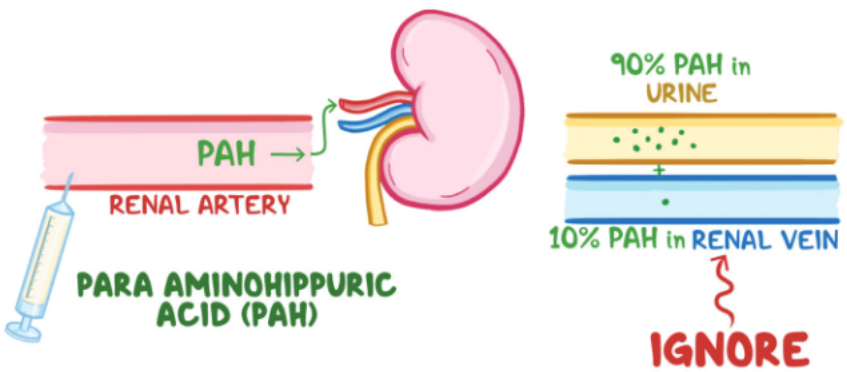


Figure 60.3 Para-aminohippuric acid (PAH) is used to measure effective renal plasma flow. It is assumed that about 90% of PAH that enters kidneys through renal artery is excreted in urine, and only 10% enters the renal vein → ignore this, assume that effective renal plasma flow = 90% of true renal plasma flow.

NOTES
RENAL ELECTROLYTE REGULATION

GLOMERULAR FILTRATION

osms.it/glomerular-filtration

- Fluid passage through glomerular filtration barrier; approx. 125mL/min
- *Glomerular filtrate:* fluid that passes through all glomerular filtration barriers
  - Blood minus red blood cells, plasma proteins
- Anything remaining in glomerulus carried away by efferent arteriole
- Starling forces → glomerular filtration
  - Different pressures of fluids, proteins in glomerular capillaries, Bowman's space
- Most filtration occurs at beginning of glomerulus, nearer afferent arteriole

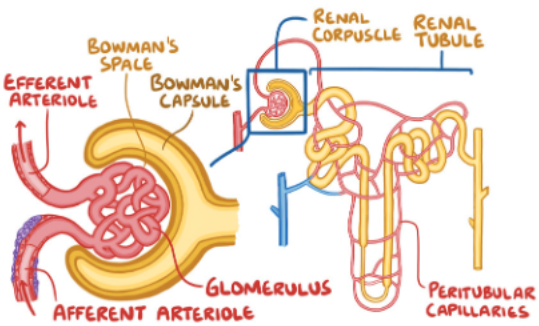


Figure 61.1 An illustration depicting the glomerulus and its relationship to the rest of the nephron.

GLOMERULAR FILTRATION BARRIER

- Capillary walls of glomerulus
  - *Glomerulus:* tuft of capillaries in nephron's renal corpuscle
  - Blood enters glomerulus through afferent arteriole → leaves through efferent arteriole → divides into peritubular capillaries
- Separates blood in capillaries from Bowman's space, Bowman's capsule
- Allows only water, some solutes to pass into Bowman's space
- *Three layers:* endothelium, basement membrane, epithelium
- *Juxtaglomerular apparatus:* secretes renin

Endothelium

- Comprised of glomerular capillary endothelial cells featuring pores (AKA fenestrations)
- Allows passage of solutes, proteins
- Blocks red blood cell passage

Basement membrane

- Gel-like layer with tiny pores
- Blocks plasma protein passage
  - Due to pore size, negative membrane charge

Epithelium

- Comprised of podocytes (wrap around basement membrane)
- Also blocks plasma protein passage

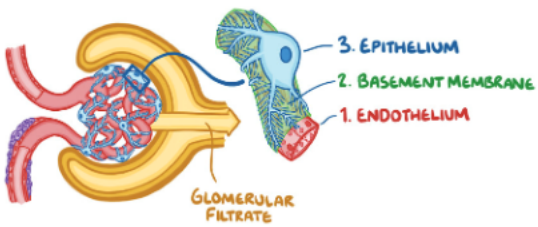


Figure 61.2 The three layers of the glomerular filtration barrier.

STARLING FORCES

- Determine fluid movement through capillary wall
- Includes hydrostatic/fluid pressures, oncotic/protein pressures
- Three Starling forces at play in glomerular filtration barrier
  - Hydrostatic pressure of blood in capillary (P_{gc})
  - Hydrostatic pressure of filtrate in Bowman's space (P_{bs})
  - Oncotic pressure of proteins in capillary (π_{gc})
- Determines net ultrafiltration pressure of glomerulus: $P_{uf} = P_{gc} - (P_{bs} + \pi_{gc})$
  - Net ultrafiltration pressure ↓ along each glomerular capillary—as fluid removed, proteins remain (↑ π_{gc})
  - At filtration equilibrium, net ultrafiltration pressure equals 0 (no fluid filtered)

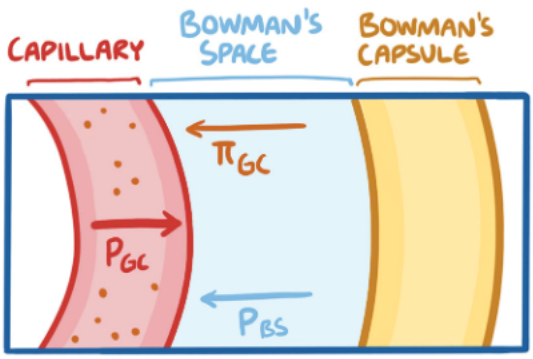


Figure 61.3 Illustration depicting the three Starling forces at play in the glomerular filtration barrier.

GLOMERULAR FILTRATION RATE (GFR)

- Filtrate volume produced by all of body's glomeruli in one minute
- $GFR = P_{uf} \times K_f$ where K_f is filtration coefficient
  - *Kf:* indicates capillary's fluid permeability
  - Fenestrations, large surface area → high K_f for glomerular capillaries
- Depends on all three Starling forces

Hydrostatic blood pressure in capillary

- Positive relationship
- Afferent arteriole vasoconstriction → ↓ renal blood flow
  - ↓ hydrostatic blood pressure in capillary (↓ GFR)
- Afferent arteriole vasodilation → ↑ renal blood flow
  - ↑ hydrostatic blood pressure in capillary (↑ GFR)
- Efferent arteriole vasoconstriction → ↑ fluid in glomerular capillary
  - ↑ hydrostatic blood pressure in capillary (↑ GFR)
- Efferent arteriole vasodilation → ↓ fluid in glomerular capillary
  - ↓ hydrostatic blood pressure in capillary (↓ GFR)

Hydrostatic filtrate pressure in Bowman's space

- Negative relationship
- Doesn't normally occur
- Urine flow blockage → urine backup (e.g. stone lodged in ureter)
  - ↑ hydrostatic filtrate pressure in Bowman's space (↓ GFR)

Oncotic protein pressure in capillary

- Negative relationship
- ↑ plasma protein concentration can ↑ oncotic protein pressure in capillary (↓ GFR)
- ↓ plasma protein concentration can ↓ oncotic protein pressure in capillary (↑ GFR)

FILTRATION FRACTION (FF)

- Ratio of glomerular filtration rate to renal plasma flow
  - *FF = GFR / RPF*
- Indicates how much fluid reaching kidneys is filtered into renal tubules

PROXIMAL CONVOLUTED TUBULE

osms.it/proximal-convoluted-tubule

- First renal tubule segment
- Receives filtrate from renal corpuscle
- Passes filtrate to loop of Henle
- Lined by brush border cells
  - Apical surface faces lumen; lined with microvilli
  - Basolateral surface faces interstitium
- Surrounded by peritubular capillaries → reabsorption, secretion of solutes to/from blood via interstitium
- Reabsorbs Na^+, K^+, Ca^{2+}, Cl^-, Mg^{2+} into bloodstream

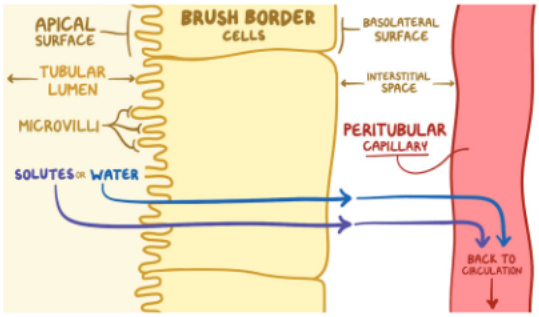


Figure 61.4 The relationship between the proximal convoluted tubule's brush border cells and a peritubular capillary.

NA^+ MOVEMENT

Natural concentration gradient from lumen into cells

- *Cotransporters:* use this energy to move other solutes (e.g. Na^+-glucose cotransporter)
- *Na^+/K^+ ATPase:* pumps $3Na^+$ from cell into interstitium, $2K^+$ from interstitium into cell
  - Movement against two concentration gradients → ATP required
- *Na^+/H^+ exchanger:* pumps Na^+ from cell into cell, H^+ from cell into lumen
  - Assists HCO_3^- reabsorption by creating $H_2CO_3 \rightarrow H_2O + CO_2$

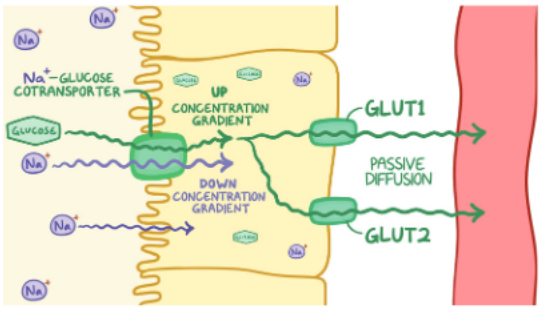


Figure 61.5 The Na^+-glucose cotransporter uses the concentration gradient of Na^+ to transport glucose against its concentration gradient.

Paracellular route

- Leaky tight junctions → some Na^+ movement between cells
  - ↓ claudin proteins → ↑ permeability
- Urea, water diffuse straight across cells → interstitium
- Glutamine breakdown inside cell → NH_4^+ (cell → lumen) + HCO_3^- (cell → interstitium)
- Organic acids, some medications diffuse directly from capillaries into lumen (e.g. penicillin)

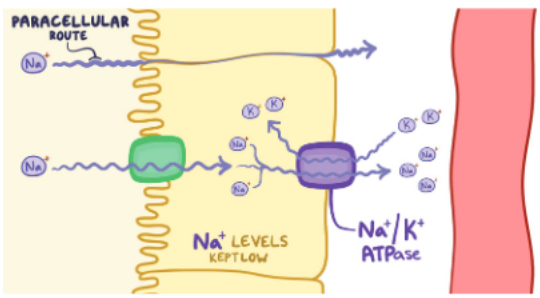


Figure 61.6 Na^+/K^+ ATPase and the paracellular route of Na^+ movement.

LOOP OF HENLE

osms.it/loop-of-henle

- Receives filtrate from proximal convoluted tubule
- Passes filtrate to distal convoluted tubule
- Composed of descending, thin ascending, thick ascending limbs
- Establishes osmotic gradient; allows varying urine concentration
- Lined by epithelial cells
  - Apical surface faces lumen
  - Basolateral surface faces interstitium
- Surrounded by peritubular capillaries
  - AKA vasa recta
  - Reabsorption, secretion of solutes to/from blood via interstitium

Descending limb

- Filtrate that enters has osmolarity of ~300mOsm/L (interstitial osmolarity)
- Squamous epithelial cells have aquaporins on both surfaces
  - Water moves across cells into interstitium
- Osmolarity ↑ to ~1200mOsm/L at bottom of loop

Thin ascending limb

- No aquaporins on thin ascending limb; Na^+, Cl^- channels instead
  - Move from lumen into interstitium along concentration gradient
- Osmolarity ↓ to ~600mOsm/L at top of thin loop

Thick ascending limb

- Cuboidal epithelium in thick ascending limb has Na-K-2Cl cotransporters
  - Na^+, K^+, $2Cl^-$ moved from lumen into cells using Na^+ concentration gradient
- Na^+/K^+ ATPase works as previously
- K^+, Cl^- channels → move from cell into interstitium along concentration gradient
- Osmolarity ↓ to ~325mOsm/L at top of thick loop
- *Countercurrent multiplication*: process of creating concentration gradient along loop

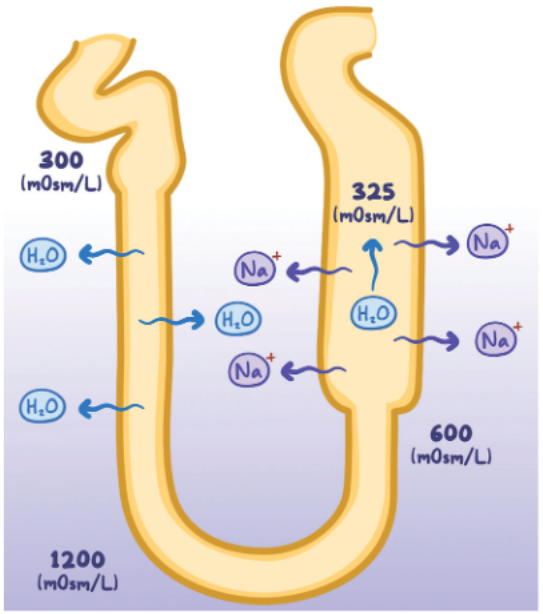


Figure 61.7 Countercurrent multiplication is the process of creating the concentration gradient along the loop of Henle. It uses ATP.

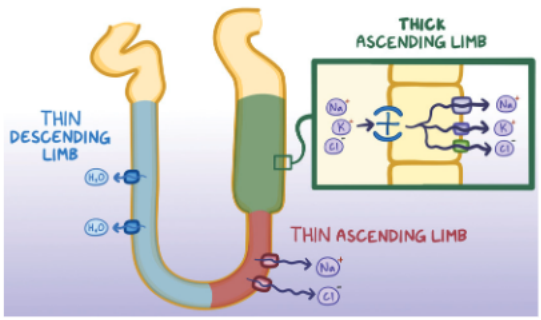


Figure 61.8 Aquaporins transport H_2O out of the thin descending limb; channel proteins transport Na^+ and Cl^- out of the thin ascending limb; Na-K-2Cl cotransporters and channels transport Na^+, K^+, and Cl^- out of the thick ascending limb.

DISTAL CONVOLUTED TUBULE

osms.it/distal-convoluted-tubule

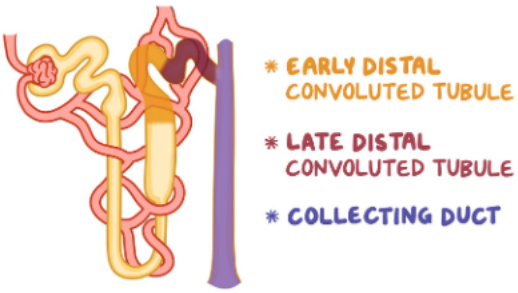


Figure 61.9 Filtrate passes through the early and late portions of the distal convoluted tubule, then reaches the collecting duct.

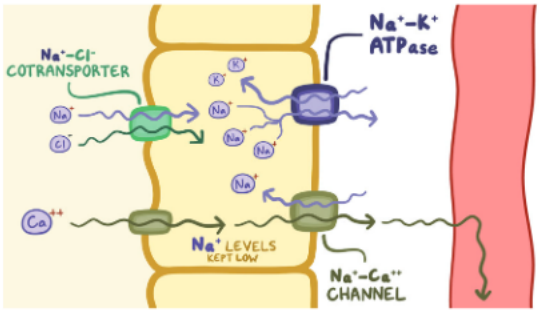


Figure 61.10 Illustration of transporters present in the early distal convoluted tubule.

- Receives filtrate from loop of Henle
- Passes filtrate to collecting ducts
- Composed of early, late distal convoluted tubules
- Lined by brush border cells
  - Apical surface faces lumen; not lined with microvilli
  - Basolateral surface faces interstitium
- Surrounded by peritubular capillaries → reabsorption, secretion of solutes to/from blood via interstitium

Early distal convoluted tubule

- Impermeable to water
- Na^+: natural concentration gradient from lumen → cells
- Cotransporters use this energy to move other solutes (e.g. Na^+-Cl^- cotransporter)
- Cl^- moves from cells → interstitium through direct channels
- Ca^{2+} moves across cells → interstitium through direct channels
  - On basolateral surface: Na^+-Ca^{2+} channel pumps Na^+ from interstitium → cell, Ca^{2+} from cell → interstitium
- Ca^{2+} reabsorption regulated by parathyroid hormone
  - Creates more Na^+-Ca^{2+} channels
- Na^+/K^+ ATPase works as previously

Late distal convoluted tubule

- → collecting ducts
- Principal cells, α-intercalated cells dispersed among brush border cells
- Aldosterone upregulates pump synthesis
- Principal cells have
  - K+ pumps (cell → lumen; uses ATP)
  - Na+ pumps ("ENaC"; lumen → cell)
  - Na+/K+ ATPases
- Aquaporin 2 in principal cells allows for water reabsorption in response to antidiuretic hormone
- α-intercalated cells have
  - H^+ ATPases, H^+-K^+ ATPases (movement against concentration gradients → ATP required)
  - Na^+/K^+ ATPases

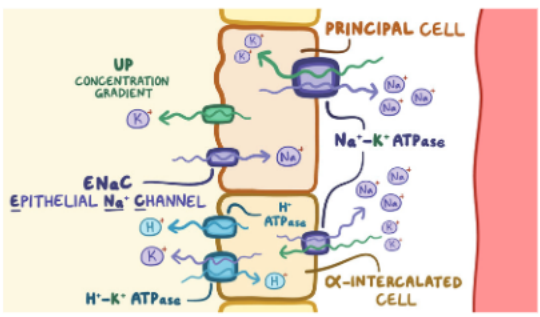


Figure 61.11 Illustration of transporters present in the late distal convoluted tubule.

TF/P_x RATIO & TF/P_{INULIN}

osms.it/TF_Px-ratio-TF_Pinulin

$[TF/P]_x$ RATIO

- Refers to concentration of substance (X) in tubular fluid (TF) and plasma (P) at given point in nephron

Helps determine substance net secretion/ absorption

- [TF/P]x = 1
  - X: not reabsorbed/secreted (e.g. freely filtered)
  - X: reabsorbed in proportion to water
  - E.g. $[TF/P]_{glucose}$ = 1 when glucose, water reabsorbed equally in Bowman's space
- [TF/P]x < 1
  - X: reabsorbed more than water
  - E.g. $[TF/P]_{glucose}$ < 1 when glucose reabsorbed more than water along proximal tubule
- [TF/P]x > 1
  - X: reabsorbed less than water/X secreted into tubular fluid
  - E.g. $[TF/P]_{urea}$ > 1 in presence of antidiuretic hormone (ADH) at collecting ducts (water reabsorbed, not urea)

$[TF/P]_{INULIN}$

- Inulin (inert substance—neither reabsorbed nor secreted) concentration throughout nephron helps determine how much is reabsorbed
- Inulin concentration will ↑ as water is reabsorbed
- Determined using this formula:

$$Fraction\ of\ filtered\ water\ reabsorbed = 1 - \frac{1}{[TF/P]_{inulin}}$$

  - Fraction of filtered water reabsorbed = 1 - 1/2 = 0.5 (50%)
  - $[TF/P]_{inulin}$ = 2 when 50% of water is reabsorbed (inulin concentration doubles)
- Double ratio formula determines fraction of filtered load of substance in nephron at any point

$$\frac{[TF/P]x}{[TF/P]_{inulin}}$$

- If $[TF/P]_{Na+}$ divided by [TF/P]inulin = 0.3, then 30% sodium remains in tubule, 70% reabsorbed

CALCIUM HOMEOSTASIS

osms.it/calcium-homeostasis

- 1% Ca^{2+} found in intracellular fluid (ICF), extracellular fluid (ECF); 99% in bones, teeth
- *Functions:* cell membrane permeability, blood clotting, muscle contraction
- 40% plasma Ca^{2+} bound to protein
  - Unbound is physiologically active
  - Regulated by parathyroid hormone (PTH)

Ca^{2+} HANDLING

Filtration

- Only unbound Ca^{2+} (60%) is filtered
- Calculation of Ca^{2+} filtered load if total plasma Ca^{2+} = 5mEq/L and GFR = 180L/day
  - 180 X 5 X 0.6 = 540mEq/day

Filtered load reabsorption

- Coupled with Na^+ reabsorption in proximal tubule, loop of Henle (passively reabsorbed via electrochemical gradient created by Na^+, water)
  - 67% reabsorbed by proximal tubule
  - 25% reabsorbed in thick ascending limb of loop of Henle (paracellular route); loop diuretics ↓ reabsorption/↑ secretion
- 8% reabsorbed in distal tubule
  - Reabsorptive Ca^{2+} regulation site: only nephron segment not coupled with Na^+ reabsorption; PTH, thiazide diuretics → ↑ Ca^{2+} reabsorption (hypocalciuric action)

Excretion

- < 1%

MAGNESIUM HOMEOSTASIS

osms.it/magnesium-homeostasis

- < 1% Mg^{2+} found in ECF; 60% in bones, 20% in skeletal muscle, 19% in soft tissues, remainder found in ICF
- *Functions:* neuromuscular activity; enzymatic reactions within cells; ATP production; Na^+, Ca^{2+} transport across cell membranes
- 20% plasma Mg^{2+} bound to protein
  - Unbound is physiologically active

Mg^{2+} HANDLING

Filtration

- Only unbound Mg^{2+} (80%) is filtered

Filtered load reabsorption

- 30% reabsorbed by proximal tubule
- 60% reabsorbed by thick ascending limb of loop of Henle
  - Loop diuretics ↓ Mg^{2+} reabsorption (↑ excretion)
- 5% reabsorbed by distal tubule

Excretion

- 5%

PHOSPHATE HOMEOSTASIS

osms.it/phosphate-homeostasis

- ICF phosphate (15%) used for DNA, ATP synthesis, other metabolic processes
  - ECF phosphate (<0.5%) serves as buffer for H^+
  - 85% in bones

PHOSPHATE HANDLING

Filtration

- Freely filtered across glomerular capillaries

Filtered load reabsorption

- 70% reabsorbed by proximal tubule; 15% by proximal straight tubule via Na^+-phosphate cotransporter in luminal membrane
- Excess phosphate excreted when T_m (transport maximum) is reached
- PTH inhibits Na^+-phosphate cotransporter → ↓ phosphate T_m → phosphaturia

Excretion

- 15%

POTASSIUM HOMEOSTASIS

osms.it/potassium-homeostasis

- *Potassium (K^+)*: primary intracellular cation
  - Regulates intracellular osmolarity
  - Concentration gradient across cell membrane establishes resting membrane potential, essential for excitable cell function (e.g. myocardium)

INTERNAL K^+ BALANCE

- Difference between intracellular K^+ concentration (98% of total K^+), extracellular K^+ concentration (2% of total K^+) maintained by Na^+-K^+ ATPase
- K^+ shifts in/out of cells
  - Potentially causes hypo-/hyperkalemia

Outward K^+ shifts

- ↓ insulin
  - ↓ Na^+-K^+ ATPase activity → ↓ cellular K^+ uptake
- Cell lysis
  - K^+ released from ICF
- H^+-K^+ exchange in acidosis
  - ↑ blood H^+ → H^+ enters cell → K^+ moves from ICF to ECF
- ↑ ECF osmolarity
  - Osmotic gradient causes H_2O movement out of cells → ↑ intracellular K^+ → diffusion of K^+ from ICF to ECF (H_2O brings K^+ with it)
- Exercise
  - Cellular ATP stores depleted → K^+ channels open in muscle cell membrane → K^+ moves down concentration gradient to ECF
- **α**-adrenergic receptor activation
  - Hepatic Ca^{2+}-dependent-K^+-channel activation → K^+ moves from ICF to ECF

Inward K^+ shifts

- Insulin
  - ↑ Na^+-K^+ ATPase activity → ↑ cellular K^+ uptake
- H^+-K^+ exchange in alkalosis
  - ↓ blood H^+ → H^+ leaves cell → K^+ enters cell
- ↓ ECF osmolality
  - Osmotic gradient causes H_2O movement into cells → ↓ ICF K^+ concentration → diffusion of K^+ from

ECF to ICF
- β_2-adrenergic receptor activation
  - ↑ Na^+-K^+ ATPase activity → K^+ enters cell

EXTERNAL K^+ BALANCE

- Dietary K^+ intake = renal excretion of K^+ via renal mechanisms

K^+ HANDLING

Filtration

- Freely filtered across glomerular capillaries

Filtered load reabsorption

- 67% reabsorbed by proximal tubule (isosmotic fluid reabsorption along with water, Na^+)
- 20% reabsorbed by thick ascending limb
  - K^+ reabsorbed without water (impermeable to water) via Na^+-K^+-$2Cl^-$ cotransporter
  - K^+ diffuses through K^+ channels across basolateral membrane (reabsorption)/K^+ diffuses into lumen (no reabsorption)
- Fine-tuning of K^+ balance at distal tubule, collecting duct depending on current physiological requirements
- Reabsorbed by **α**-intercalated cells/ secreted by principal cells
  - *Dietary K^+:* high K^+ diet—K^+ enters cells (via insulin) → ↑ intracellular K^+ → ↑ K^+ in principal cells → ↑ K^+ secretion across luminal membrane → ↑ K^+ excretion; low K^+ diet—↓ K^+ secretion by principal cell, ↑ K^+ reabsorption by **α**-intercalated cells
  - *Aldosterone effects on principal cells:* presence of aldosterone/ hyperaldosteronism (↑ K^+ secretion); hypoaldosteronism (↓ K^+ secretion)
- *Acid-base imbalance effects on principal cells:* alkalosis (↑ K^+ secretion); acidosis (↓ K^+ secretion)
- *Diuretic effects on principal cells:* loop, thiazide (↑ K^+ secretion); K^+ sparing (inhibit aldosterone effects → ↓ K^+ secretion)
- Luminal anions (e.g. sulfate, HCO_3^-) in distal tubule, collecting duct (↑ lumen electronegativity by non-reabsorbable anions → ↑ K^+ secretion)

Excretion

- Varies from 1–110% of filtered load

SODIUM HOMEOSTASIS

osms.it/sodium-homeostasis

- *Sodium (Na^+):* primary cation in ECF
  - Determines ECF osmolarity

Na^+ BALANCE REGULATION

- Na^+ balance (Na^+ excretion = Na^+ intake) determines ECF volume, blood volume, blood pressure (BP)
  - *Positive Na^+ balance:* ↑ Na^+ retained → ↑ Na^+ in ECF → ECF expansion → ↑ blood volume, ↑ blood pressure
  - *Negative Na^+ balance:* ↑ excreted, lost in urine → ↓ Na^+ in ECF → ECF contraction → ↓ blood volume, ↓ blood pressure

Effective arterial blood volume (EABV)

- ECF volume with arterial system perfuses tissue
- Normal ECF changes → parallel EABV changes (e.g. ↑ ECF = ↑ EABF)
- *Edema:* fluid filtered into interstitial space → ↑ ECF → ↓ EABV (↓ BP) → Na^+ excretion altered by kidneys (attempts to restore normal EABF, BP)

Na+ excretion regulation (↑/↓) mechanisms

- Sympathetic nervous system activity
  - Baroreceptors detect ↓ BP → sympathetic nervous system activation → afferent arteriole vasoconstriction, ↑

Na^+ reabsorption by proximal tubule

- *Natriuretic hormones:* respond to ↑ ECF volume → ↑ GFR, natriuresis (renal Na^+, water excretion) → ↓ ECF
  - *Atrial natriuretic peptide (ANP):* volume receptors detect atrial wall stretching → ANP secreted by cells in atria
  - *Brain natriuretic peptide (BNP):* volume receptors in ventricles detect stretching → BNP secreted by cells in ventricles
  - *Urodilatin:* synthesized in distal tubular cells → paracrine actions on kidney
- Peritubular Starling forces
  - ↑ ECF volume → ECF dilution, ↓ π_c (capillary oncotic pressure); ↓ proximal tubule Na^+ reabsorption
  - ↓ ECF volume → ↑ ECF concentration, ↑ π_c; ↑ proximal tubule Na^+ reabsorption
- *Renin-angiotensin-aldosterone system (RAAS):* ↓ arterial blood pressure (BP) → ↓ renal perfusion → juxtaglomerular apparatus secretes renin → angiotensinogen (plasma protein) converted to angiotensin I → angiotensin I converted to angiotensin II → adrenal cortex secretes aldosterone, vasoconstriction → ↑ Na^+, Cl^-, water reabsorption → ↑ ECF volume, ↑ BP

Excess Na^+ intake response

- → Na^+ ECF distribution → ↑ ECF, ↑ EABV, ↓ π_c → ↓ sympathetic activity, ↑ ANP (and other natriuretic hormones), ↓ RAAS → ↑ Na^+ excretion

Decreased Na^+ intake response

- → ↓ ECF, ↓ EABV, ↑ π_c → ↑ sympathetic activity, ↓ ANP (and other natriuretic hormones), ↑ RAAS → ↓ Na^+ excretion

Na^+ HANDLING

Filtration

- Freely filtered across glomerular capillaries

Filtered load reabsorption

- 67% reabsorbed by proximal tubule
  - Isosmotic reabsorption of water, Na^+
  - Water reabsorption coupled with Na^+ reabsorption ($[TF/P]_{Na+} = 1$)
- 25% reabsorbed by thick ascending limb
  - Na^+ reabsorbed without water (impermeable to water) via Na^+-K^+-$2Cl^-$ cotransporter
  - Influenced by ADH, loop diuretics
- 5% reabsorbed by early distal convoluted tubule
  - Na^+ reabsorbed without water (impermeable to water) via Na^+-$2Cl^-$ cotransporter
  - Influenced by thiazide diuretics
- 3% reabsorbed by late distal convoluted tubule
  - Influenced by aldosterone

Excretion

- < 1% excreted (99% net Na^+ reabsorption)

NOTES
RENAL REABSORPTION & SECRETION

TUBULAR REABSORPTION & SECRETION

osms.it/tubular-reabsorption-secretion

- Blood chemistry balanced, urine formed through glomerular filtration, tubular reabsorption, secretion
  - Filtered blood continues through glomerulus, substances reabsorbed/ secreted according to body's needs
  - Entire plasma volume filtered approx. 60 times/day

REABSORPTION

- Retention of substances contained in filtrate back into peritubular capillary blood

Filtration only/no reabsorption

- *Occurs with:* products of metabolism (e.g. urea, creatinine), foreign substances (e.g. drugs)

Filtration with partial reabsorption

- Electrolytes (e.g. sodium, bicarbonate) easily reabsorbed, may be partially reabsorbed, secreted

Filtration with complete reabsorption

- Nutritional substances (e.g. glucose, amino acids) completely reabsorbed

SECRETION

- Substances not reabsorbed (e.g. organic acids), secreted into tubular fluid to become urine

TUBULAR REABSORPTION OF GLUCOSE

osms.it/tubular-reabsorption-glucose

- *Filtration rate of glucose:* mass of glucose filtered through kidneys per day (depends on plasma glucose concentration)
- Kidney filtrate passes through renal tubules in nephron before becoming urine
  - Tubules lined by brush border cells with apical surface (lined with microvilli), basolateral surface; peritubular capillaries surround tubules

GLUCOSE REABSORPTION

- Occurs primarily in proximal convoluted tubule

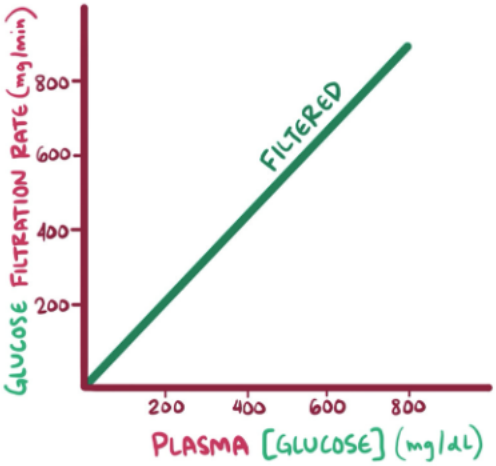


Figure 62.1 Graph showing glucose filtration rate as a function of plasma glucose. As the plasma glucose concentration increases, the filtered load of glucose increases linearly.

Two steps

1. Glucose moves across apical membrane into brush border cells
   - Glucose concentration inside cells typically higher than outside → sodium-glucose linked transporters use energy from existing sodium concentration gradient to move glucose against concentration gradient
2. Glucose diffuses across basolateral membrane into peritubular capillaries (facilitated diffusion with GLUT1/GLUT2)

- *Normal plasma glucose levels (< 200mg/dL)*: glucose reabsorption matches filtration
- *High plasma glucose levels (> 200mg/dL)*: limited number of glucose transporter proteins prevents reabsorption from keeping up with filtration
- *Higher glucose levels (> 350mg/dL)*: glucose transporter proteins fully saturated, reabsorption cannot go faster; transport maximum (T_m)

GLUCOSE EXCRETION

- Excess glucose excreted in urine
  - *Threshold:* plasma glucose level at which glucose excretion starts
  - *Splay:* initial, nonlinear increase in urine excretion
- Glycosuria (glucose excreted in urine) may be caused by diabetes mellitus (↓ insulin → ↑ plasma glucose)/hormonal changes during pregnancy (↑ renal blood flow → ↑ glucose filtration)

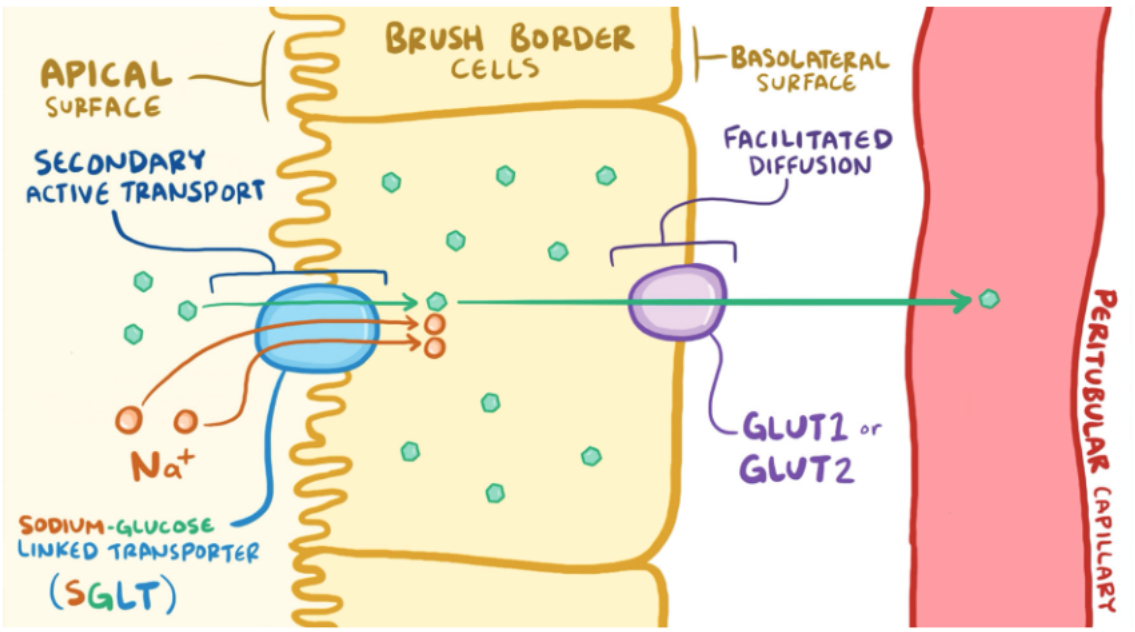


Figure 62.12 An illustration depicting the two steps of glucose reabsorption that occur in the proximal convoluted tubule: transport across the apical membrane of the brush border cells, followed by transport across the basolateral membrane of the brush border cells by GLUT1 or GLUT2.

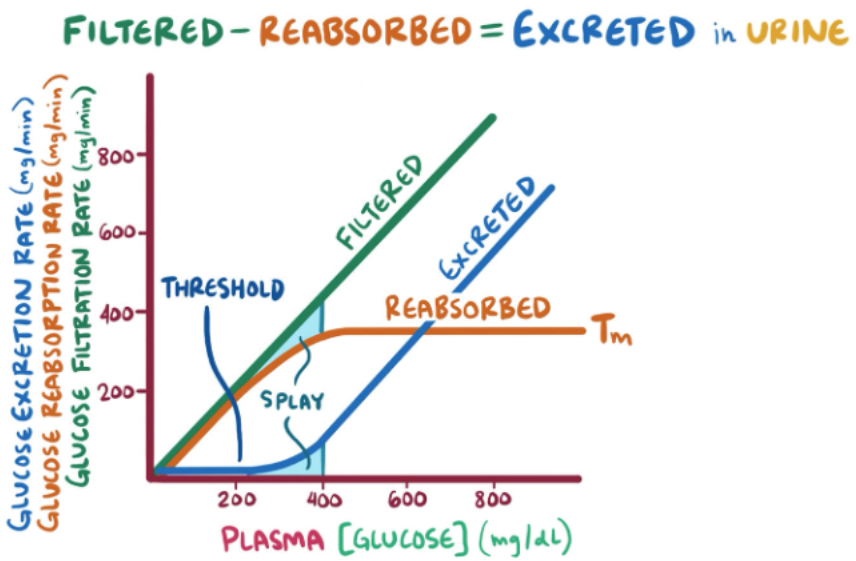


Figure 62.2 A graph showing glucose reabsorption and secretion rates as a function of plasma glucose. The glucose reabsorption line plateaus because the plasma [glucose] has been reached where all the GLUT1/GLUT2 transporters in virtually all the nephrons are occupied by glucose molecules.

TUBULAR SECRETION OF PARA-AMINOHIPPURIC ACID (PAH)

osms.it/tubular-secretion-PAH

- Body's entire plasma volume, including some para-aminohippuric acid (PAH), filtered approx. 60 times/day
  - *PAH:* organic acid; approx. 90% bound to plasma proteins, cannot be filtered
  - *Filtration rate of PAH:* mass of PAH filtered through kidneys per day (depends on plasma concentration of unbound PAH)
- Kidney filtrate passes through renal tubules in nephron before becoming urine
  - Tubules lined by brush border cells with apical surface (lined with microvilli), basolateral surface; peritubular capillaries surround tubules

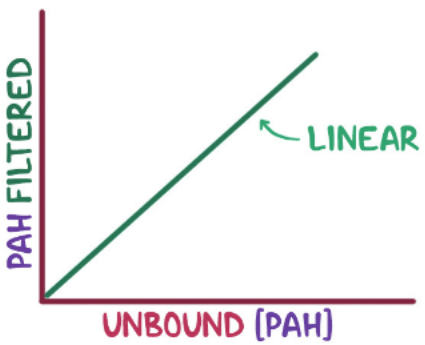


Figure 62.3 Graph showing PAH filtration rate as a function of unbound plasma PAH.

- No renal reabsorption of PAH
- PAH secretion occurs primarily in proximal convoluted tubule
  - Special carrier proteins on basolateral membrane transport PAH, other organic anions directly into tubules
- *Low plasma PAH levels:* PAH secretion increases linearly with PAH concentration
- *Higher plasma PAH levels:* limited number of carrier proteins prevents secretion from increasing, even with increasing PAH concentration (T_m) → some PAH left behind in peritubular capillaries
- Both filtered, secreted PAH excreted in urine

Using PAH to estimate renal plasma flow (RPF)

- *Fick's principle:* $PAH_{entering} = PAH_{leaving}$
- PAH enters kidney via renal artery; leaves via renal vein/urine
- *Low PAH concentrations (< T_m):* all PAH leaves via urine
- $PAH_{entering} = PAH_{excreted}$
- $[PAH]R.A. \times RPF = [PAH]_{urine} \times$ urine flow rate (UFR)
  - Renal, urine concentrations of PAH both measured in milligrams per millilitre
  - RPF, urine flow rate (UFR) both measured in liters per minute
- $RPF = ([PAH]_{urine} \times UFR)/[PAH]_{R.A.}$ (milliliters of plasma per minute)
- Some PAH may remain in renal vein → estimate usually accurate to 10% of true RPF
- Renal plasma flow can be used to calculate renal blood flow (RBF)
  - RBF = RPF/(1-Hct)
  - *Hematocrit (Hct):* volume of blood occupied by red blood cells (RBCs)

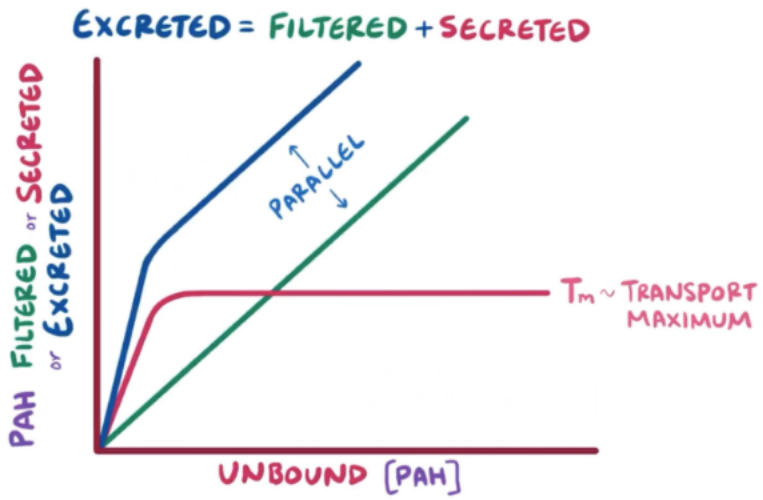


Figure 62.4 Graph showing PAH secretion and excretion rates as a function of plasma PAH.

UREA RECYCLING

osms.it/urea-recycling

- *Urea:* one of body's waste products (byproduct of amino acid breakdown)
- Freely filtered across kidneys' glomerular capillaries, travels through renal tubule
- Part of reabsorbed urea secreted back into loop of Henle → "urea recycling"
  - Helps establish corticopapillary gradient (reabsorbs water from kidneys back into blood)

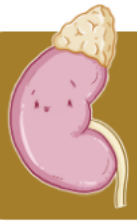
Four steps to urea recycling

- 50% of urea reabsorbed by simple diffusion in proximal convoluted tubule (leaving behind 50% of initial urea), together with water
- Urea from medullary interstitium secreted back into tubule in descending limb of loop of Henle (resulting in 110% of initial urea in bottom of loop of Henle)
  - Occurs due to higher urea concentration in medullary interstitium
- Ascending limb of loop of Henle, early distal convoluted tubule impenetrable to urea, water (urea levels stay same)
- 70% of initial urea reabsorbed into interstitium in late distal convoluted tubule, cortical, outer medullary collecting ducts (leaving behind 40% of initial urea to be excreted in urine)
  - Occurs due to antidiuretic hormone (ADH)-induced water reabsorption through aquaporins → concentration gradient of urea towards interstitium

WEAK ACIDS & BASES - NON-IONIC DIFFUSION

osms.it/non-ionic__diffusion

- Many substances secreted by proximal tubule weak acids/bases
- Exist in uncharged (nonionic)/charged (ionized) forms; amount depends on pH of tubular fluid
  - *Urine with low pH:* nonionic forms dominate
  - *Urine with higher pH:* ionized forms dominate
- Nonionic weak acids, bases lipid soluble, able to passively diffuse back into blood from urine
- Ionized weak acids, bases not lipid soluble, remain in tubular fluid to be excreted
- Excretion of unwanted substances, toxins accomplished by manipulating urine pH, promoting ionization



NOTES
WATER REGULATION

OSMOREGULATION

osms.it/osmoregulation

- Regulation of body fluid solute concentrations
  - Concentrations measured in osmolarity (mOsm/L)
  - Osmole: single ion in solution

BLOOD PLASMA OSMOLARITY

- 290–300 mOsm/L
- Main components
  - Sodium, glucose, urea
- Osmolarity = $2[Na^+]$ + [Glucose]/18 + [BUN]/2.8
  - Glucose, blood urea nitrogen (BUN) measured in mg/dL

HYDRATION

- Changes in hydration affect plasma osmolarity, blood pressure
  - Osmoreceptors in supraoptic nuclei of anterior hypothalamus detect changes in plasma osmolarity
  - Baroreceptors in cardiovascular system detect changes in blood pressure
- Osmoreceptors, baroreceptors regulate production of ADH in hypothalamus

Overhydration

- Plasma osmolarity decreases, blood pressure increases
- Osmoreceptors, baroreceptors fire less, stimulating less ADH production
- Less/no water reabsorbed from kidneys

Dehydration

- Plasma osmolarity increases, blood pressure decreases
- Osmoreceptors, baroreceptors fire more, stimulating greater ADH production
- More water reabsorbed from kidneys

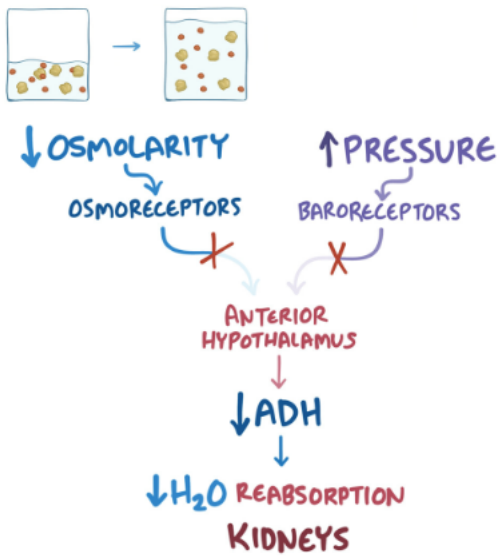


Figure 63.1 Body response to overhydration.

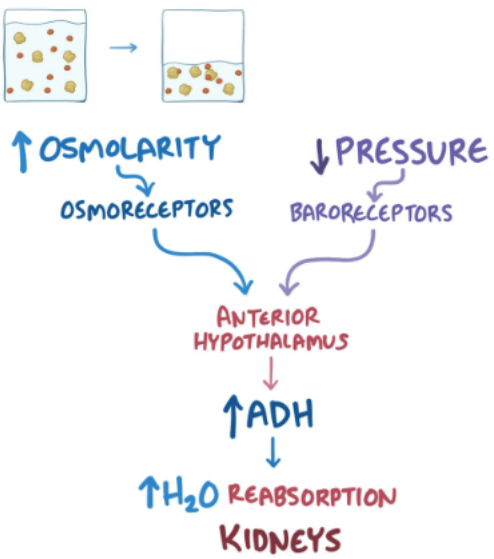


Figure 63.2 Body response to dehydration.

KIDNEY COUNTERCURRENT MULTIPLICATION

osms.it/kidney-countercurrent-multiplication

- Concentration gradient (corticopapillary gradient) established in medulla of kidney

TWO STEPS

- In nephron loop of Henle

Single effect

- Takes advantage of ascending limb being impermeable to water
- Sodium, potassium, chloride ions enter tubule cells along ascending limb via $Na^+K^+2Cl^-$ cotransporters on apical surface
- Na/K ATPase pumps sodium ions through basolateral surface into interstitium in exchange for potassium ions
- Potassium, chloride ions enter interstitium
- Osmosis → ions in interstitium diffuse into descending limb → fluid concentration

Flow of fluid

- Uses new fluid to distribute ions
- New fluid pushes existing fluid around loop
- Concentrated fluid (previously in descending limb) enters ascending limb
- Single effect recurs, fluid more concentrated at bottom of ascending limb → more ions enter interstitium at bottom

Two steps repeat

- Form concentration gradient of 1200mOsm/L at inner medulla, 300mOsm/L at outer cortex

COUNTERCURRENT EXCHANGE

- Important process for corticopapillary gradient
- Peritubular capillaries permeable to water, solutes
- Osmosis would destroy corticopapillary gradient if capillaries only ran along descending limb → peritubular capillaries run down descending limb, up ascending limb → allow extra solutes pulled from interstitium near descending limb to return to interstitium near ascending limb (as corticopapillary gradient decreases) → water diffused from capillary into interstitium returns

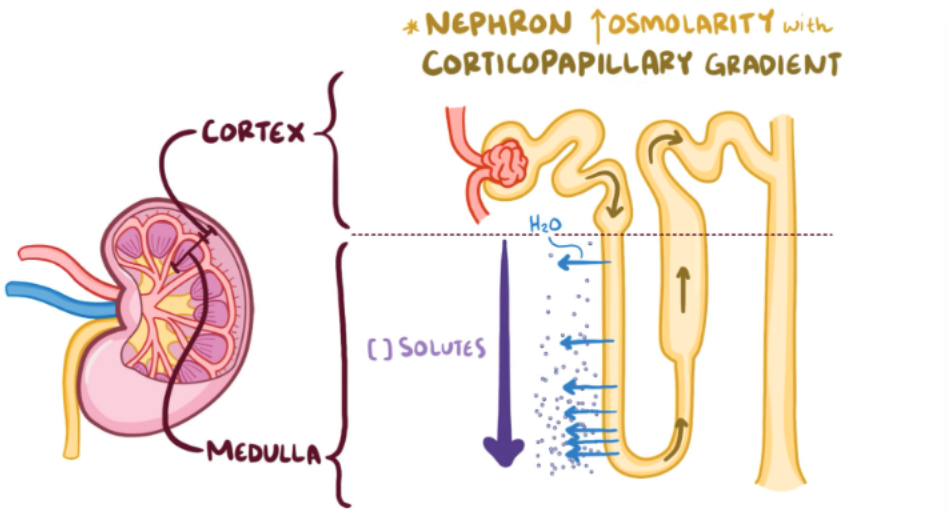


Figure 63.3 To increase urine osmolarity, nephrons rely on the corticopapillary gradient. The interstitium becomes increasingly hypertonic relative to the lumen of the tubule.

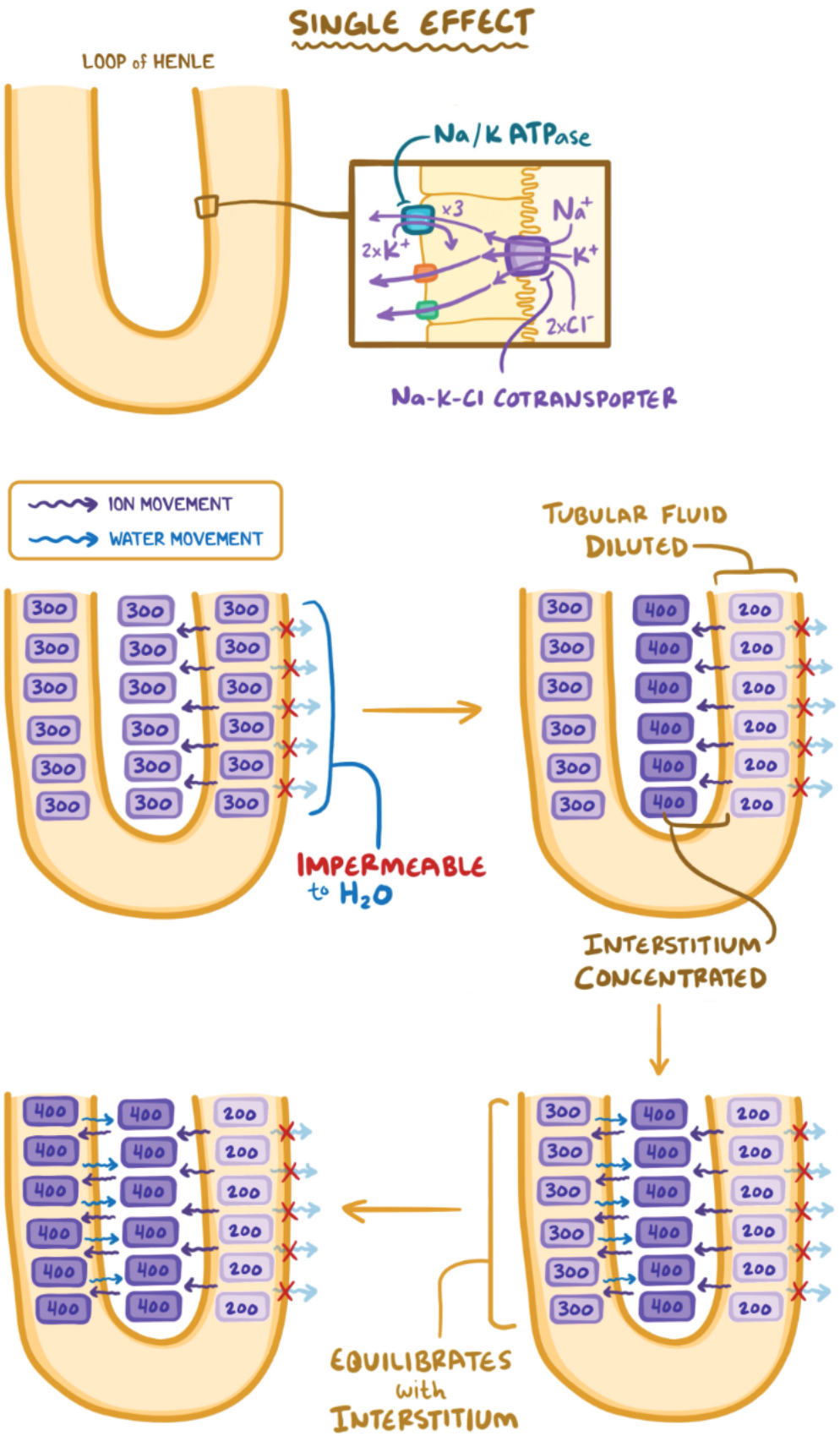


Figure 63.4 *Single effect:* ions leave ascending limb, but water can't follow → urine osmolarity in ascending limb decreases. Water can pass through descending limb → descending limb equilibrates with the interstitium. Numeric values = number of mOsm/L (e.g. 300 = 300mOsm/L).

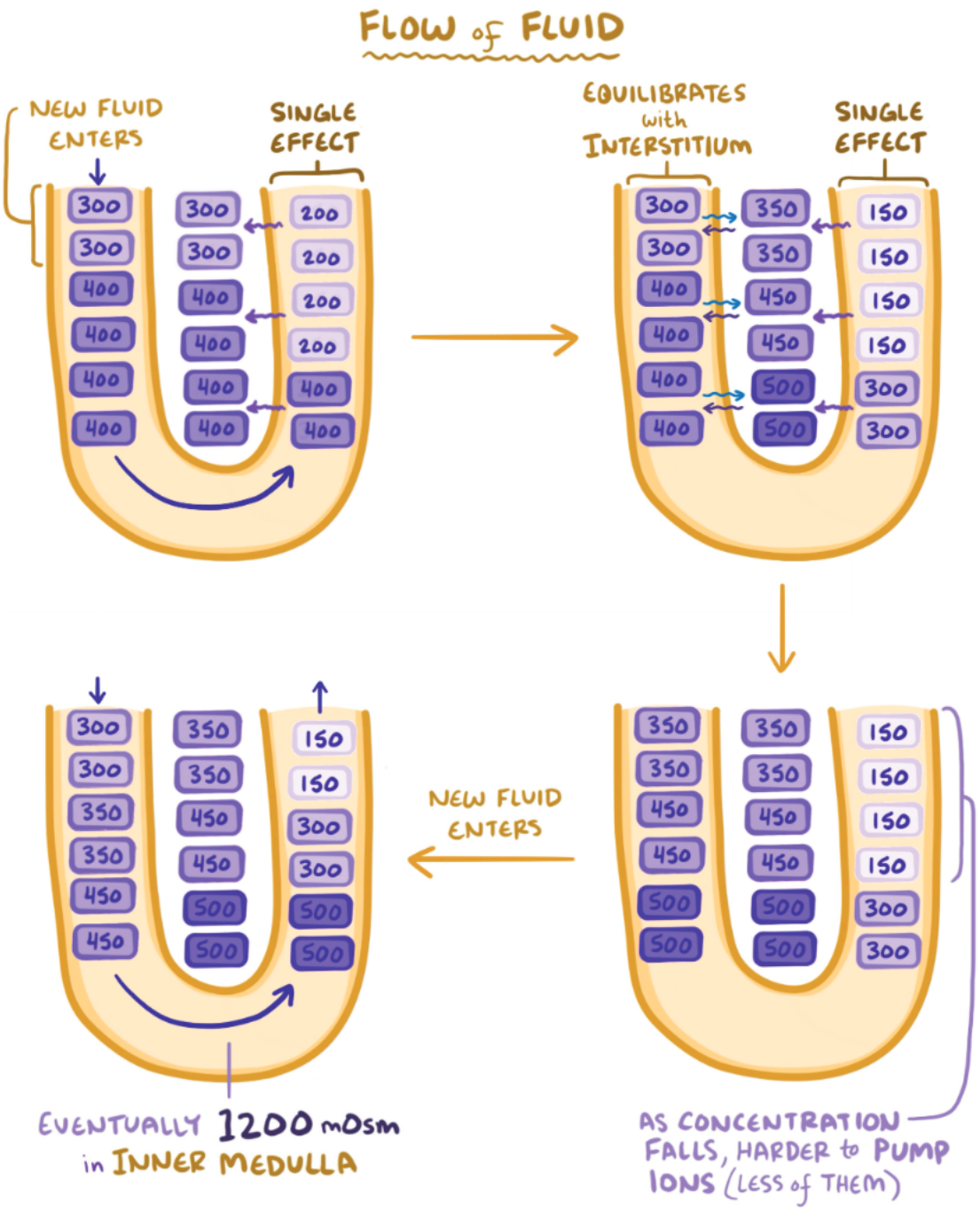


Figure 63.5 Flow of new fluid into the loop of Henle + single effect = corticopapillary gradient. Numeric values = number of mOsm/L (e.g. 300 = 300mOsm/L).

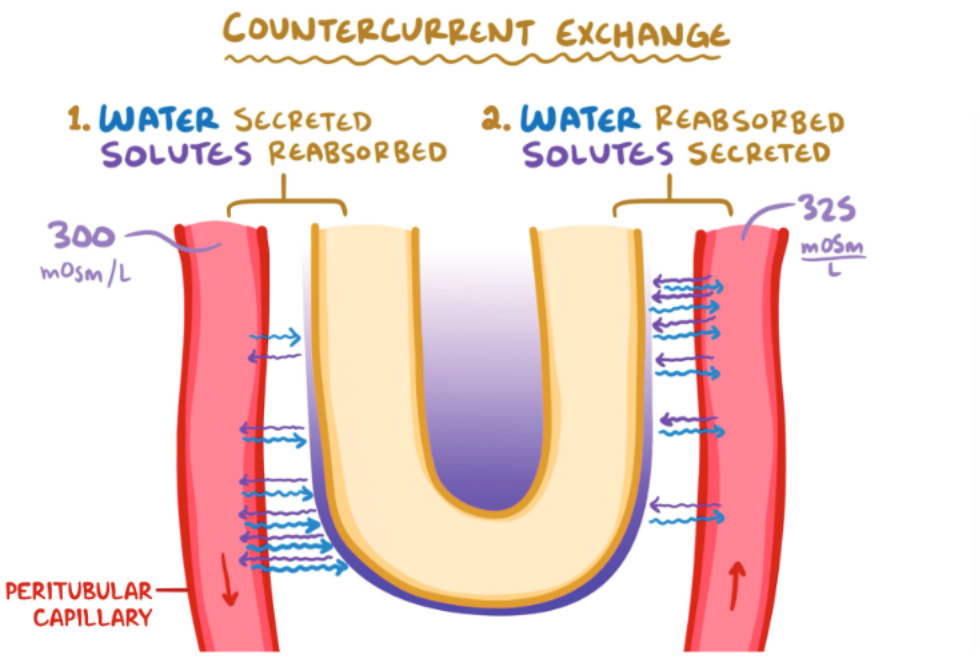


Figure 63.6 *Countercurrent exchange:* peritubular capillaries run down the descending limb and up the ascending limb to maintain the corticopapillary gradient.

ANTIDIURETIC HORMONE

osms.it/antidiuretic-hormone

- Peptide hormone prevents excessive urine production by reabsorbing water from kidneys
- Allows body to control amount of fluid retention
- Antidiuretic hormone (ADH) production triggered by osmoreceptors in supraoptic nuclei of anterior hypothalamus, baroreceptors in cardiovascular system; stimulated by angiotensin II
- ADH (AKA vasopressin) also causes smooth muscles cells in arteries to constrict

ADH PATHWAY

- Produced in paraventricular, supraoptic neurons of hypothalamus → travels down axons through infundibulum → stored in posterior pituitary gland
- When needed, released into blood, travels to kidneys
- In kidneys, travels through peritubular capillaries → binds to V2 receptors (AVPR2) on basolateral membrane of principal cells (along collecting ducts of nephrons)
- AVPR2 signals adenylyl cyclase to convert ATP to cAMP → cell produces water protein channels called aquaporins, opens existing aquaporins (in apical membrane) of principal cells → osmosis pulls water from lumen of ducts into interstitium, reabsorbed into circulation

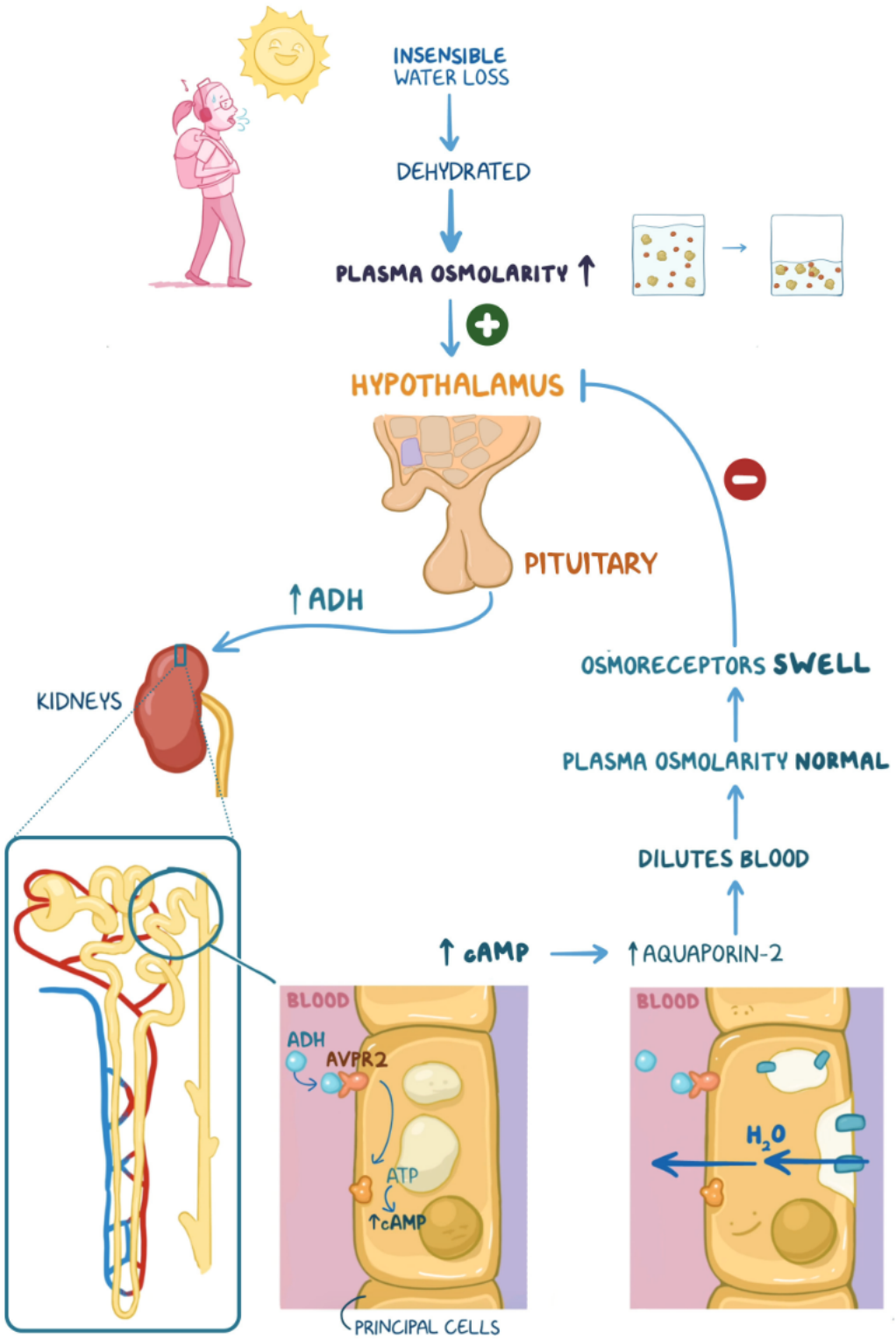


Figure 63.7 The ADH pathway. Increased plasma osmolarity triggers ADH release from the posterior pituitary. ADH acts on the principal cells of the distal convoluted tubule, collecting ducts → ↑ aquaporins in the cell membranes → ↑ water reabsorption → ↓ plasma osmolarity.

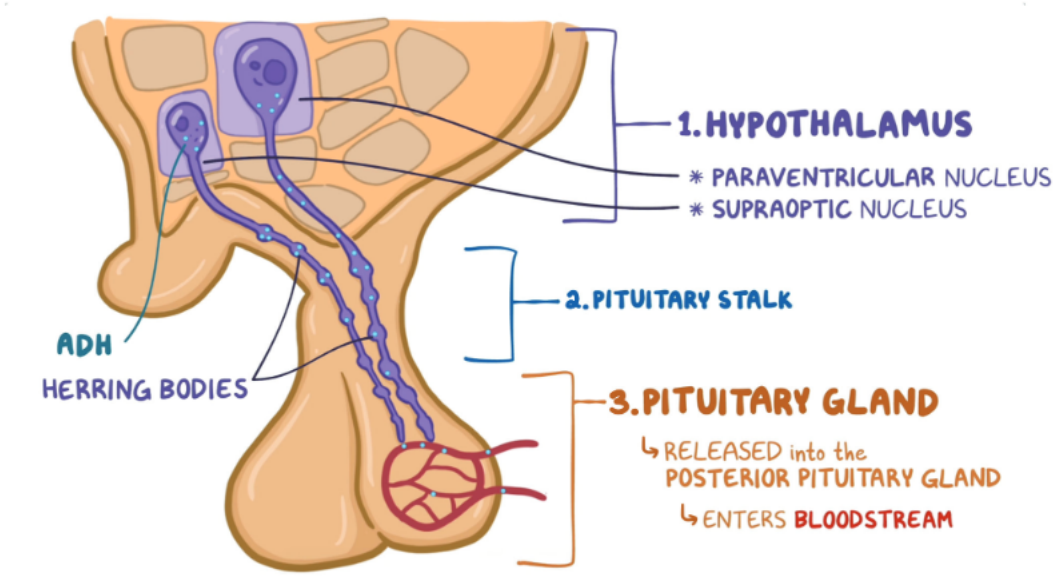


Figure 63.8 ADH is produced in the paraventricular and supraoptic nuclei in the hypothalamus, stored in Herring bodies in paraventricular and supraoptic neurons, and released into the bloodstream from the posterior pituitary gland.

FREE WATER CLEARANCE

osms.it/free-water-clearance

- *Free water*: water without solutes
- *Free water clearance*: rate at which kidneys filter free water out of blood plasma

PATHWAY

- Free water filtered out of blood plasma in ascending limbs, distal convoluted tubules of kidneys' nephrons, solutes removed
- Free water reabsorbed into circulation through aquaporin protein channels in collecting ducts

ANTIDIURETIC HORMONE EFFECTS

- High amounts of ADH → lots of free water reabsorbed, retained (negative free water clearance) → hyperosmotic urine
- Low amounts of ADH → little free water reabsorbed, excreted (positive free water clearance) → hypoosmotic urine
- *Free water clearance, 0*: excreted urine has same osmolarity as blood plasma
- $C_{H2O} = V - (U_{osm}/P_{osm})V$
  - V: urine flow rate (mL/min)
  - U_{osm}: urine osmolarity
  - P_{osm}: plasma osmolarity