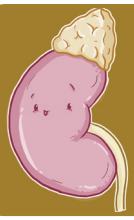

NOTES
RENAL ELECTROLYTE REGULATION

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

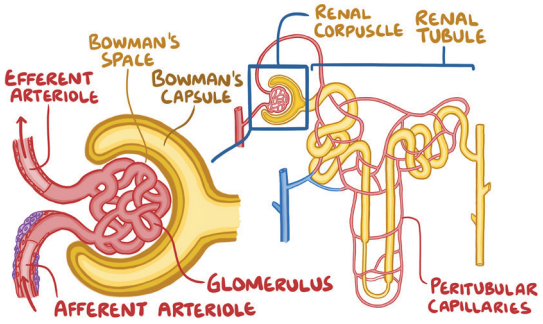

Figure 8.1 An illustration depicting the glomerulus and its relationship to the rest of the nephron.

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

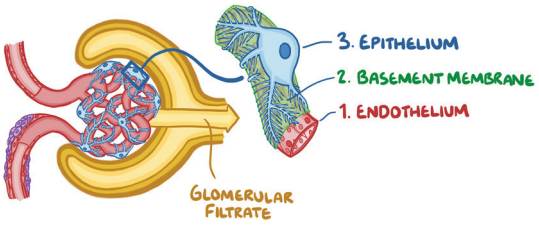

Figure 8.2 The three layers of the glomerular filtration barrier.

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)

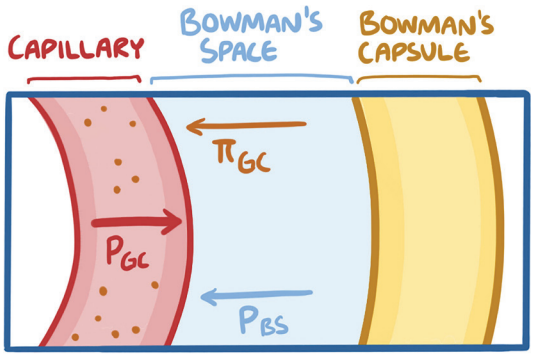

Figure 8.3 Illustration depicting the three Starling forces at play in the glomerular filtration barrier.

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 capilary'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

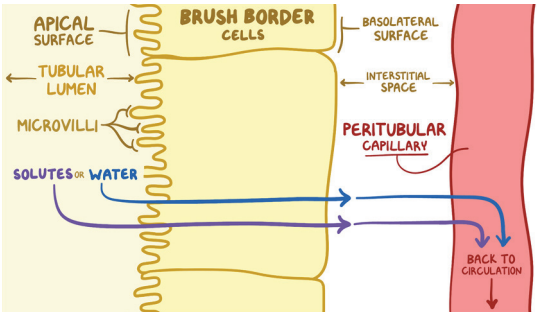

Figure 8.4 The relationship between the proximal convoluted tubule's brush border cells and a peritubular capillary.

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 $H_2CO_3 \rightarrow H_2O + CO_2$

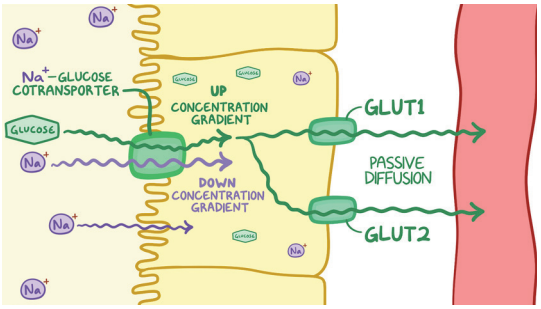

Figure 8.5 The Na^+-glucose cotransporter uses the concentration gradient of Na^+ to transport glucose against its concentration gradient.

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)

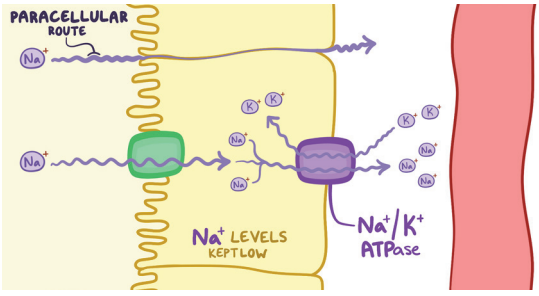

Figure 8.6 Na^+/K^+ ATPase and the paracellular route of Na^+ movement.

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

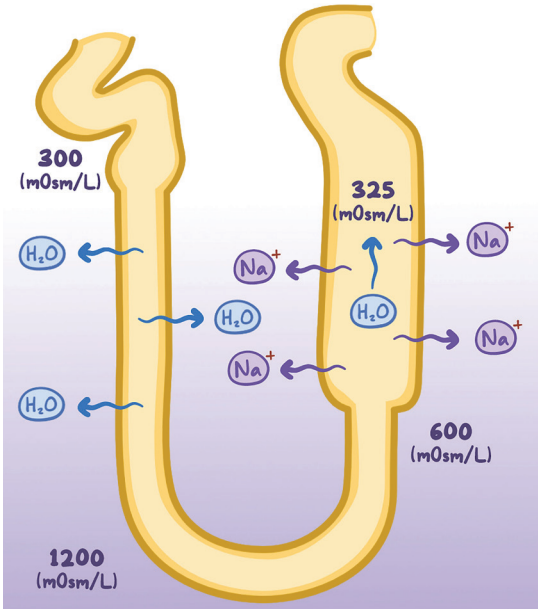

Figure 8.7 Countercurrent multiplication is the process of creating the concentration gradient along the loop of Henle. It uses ATP.

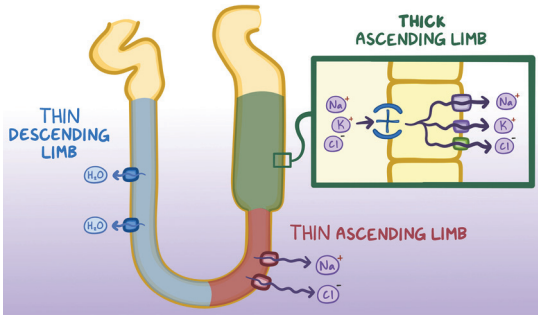

Figure 8.8 Aquaporins transport H_2O out of the thin descending limb; channel proteins transport Na^+ and Cl^- out of the thin ascending limb; Na-K-2Cl cotransporters and channels transport Na^+, K^+, and Cl^- out of the thick ascending limb.

DISTAL CONVOLUTED TUBULE

osms.it/distal-convoluted-tubule

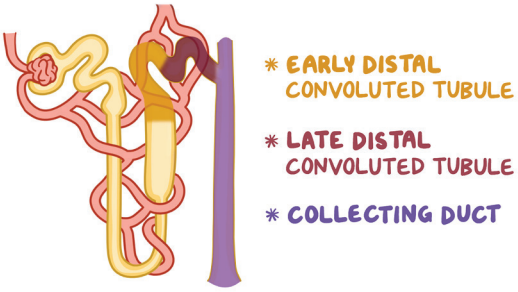

Figure 8.9 Filtrate passes through the early and late portions of the distal convoluted tubule, then reaches the collecting duct.

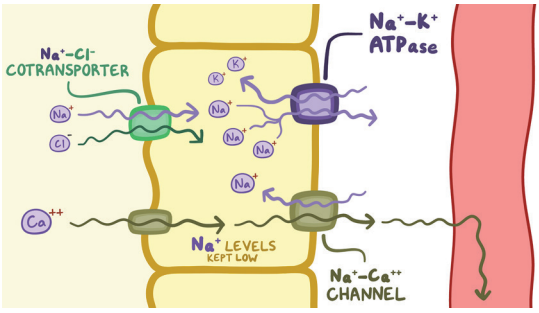

Figure 8.10 An illustration of the transporters present in the early distal convoluted tubule.

- 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

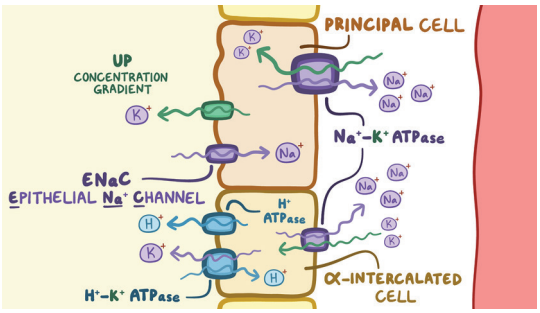

Figure 8.11 An illustration of the transporters present in the late distal convoluted tubule.

TF/P_x RATIO & TF/P_{INULIN}

osms.it/TFPx-ratio-TFPinulin

$[TF/P]_x$ 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 Mg2+ 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 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)