Functional Anatomy and Urine Formation by the Kidneys

Functions of Kidney

- *Excretion of wastes, foreign chemicals, drugs, hormone metabolites, food additives, pesticides*
- *Maintaining the proper osmolarity of body fluids*
- *Regulating the quantity and concentration of most ECF ions*
- *Excreting the end products of bodily metabolism, such as urea (from proteins), uric acid (from nucleic* acids), creatinine (from muscle creatine), bilirubin (from hemoglobin)

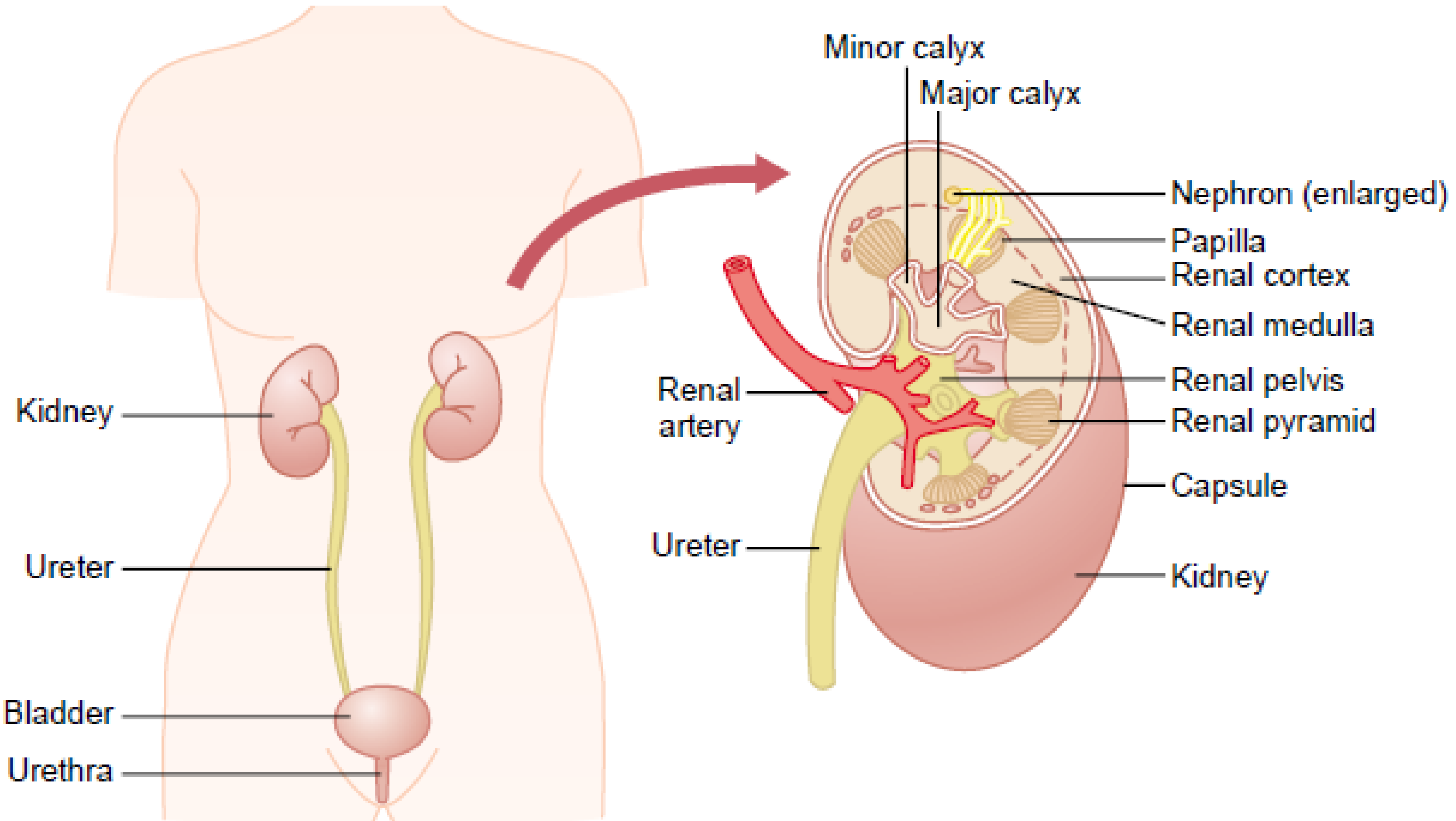
- **Regulation of**
  - **Water & electrolytes**
  - **Arterial pressure (by maintaining plasma volume)**
  - **Acid-Base balance**

  Producing ertytrpoeitin

  Producing renin

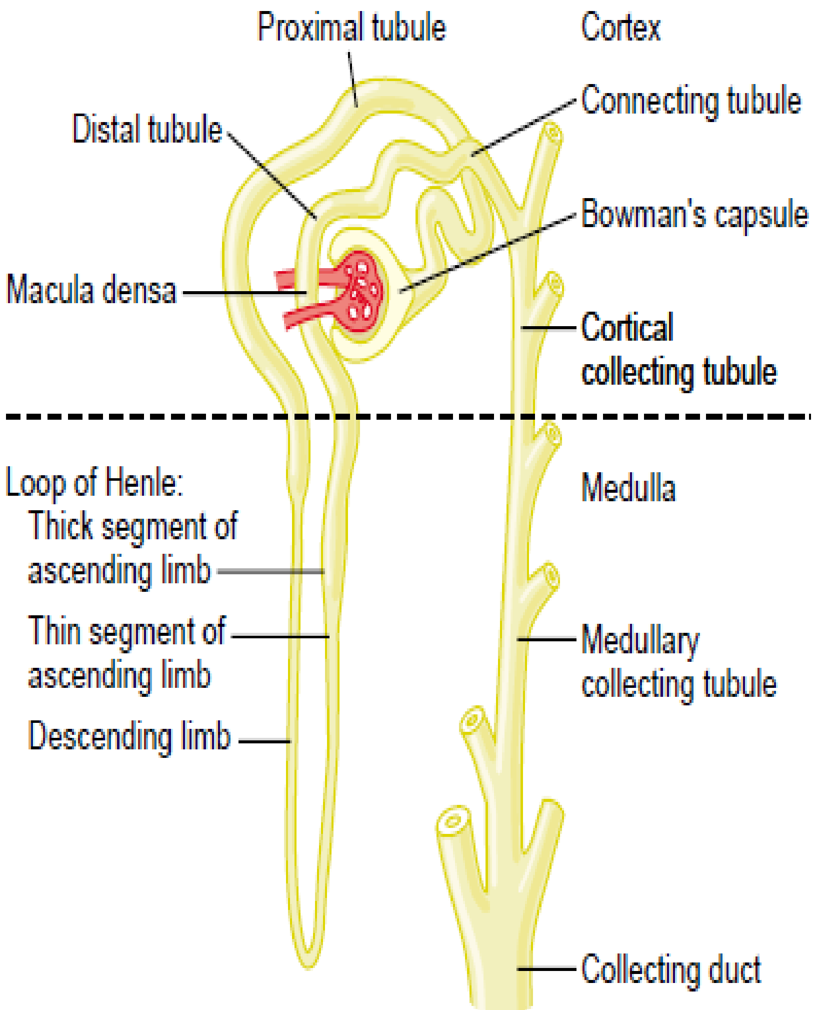
  1,25-Dihydroxycholecalciferol production
- **Glucose synthesis**

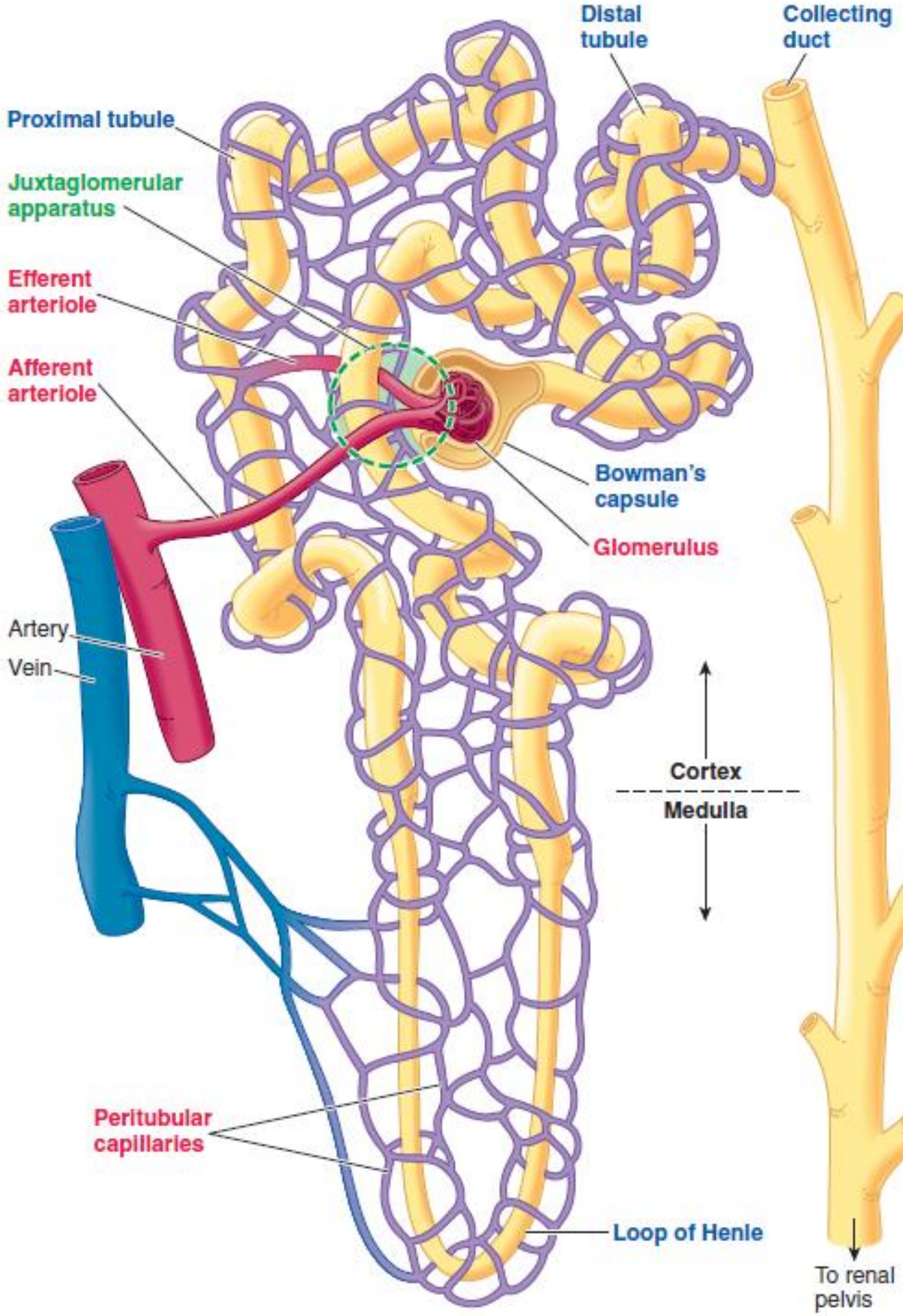
Physiological Anatomy of Kidneys

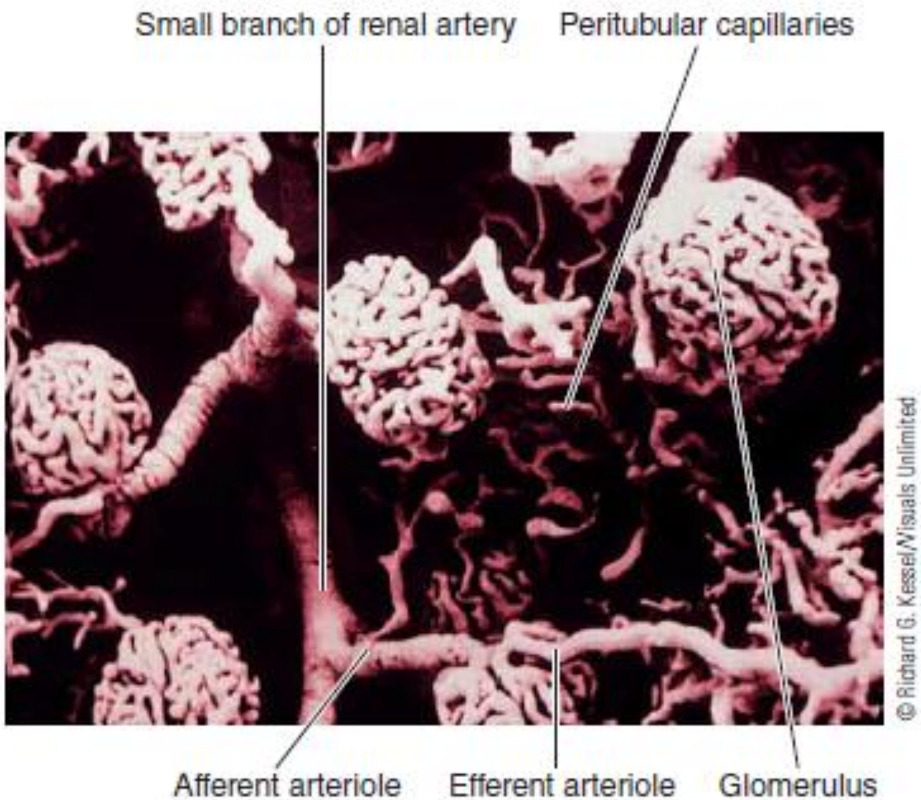


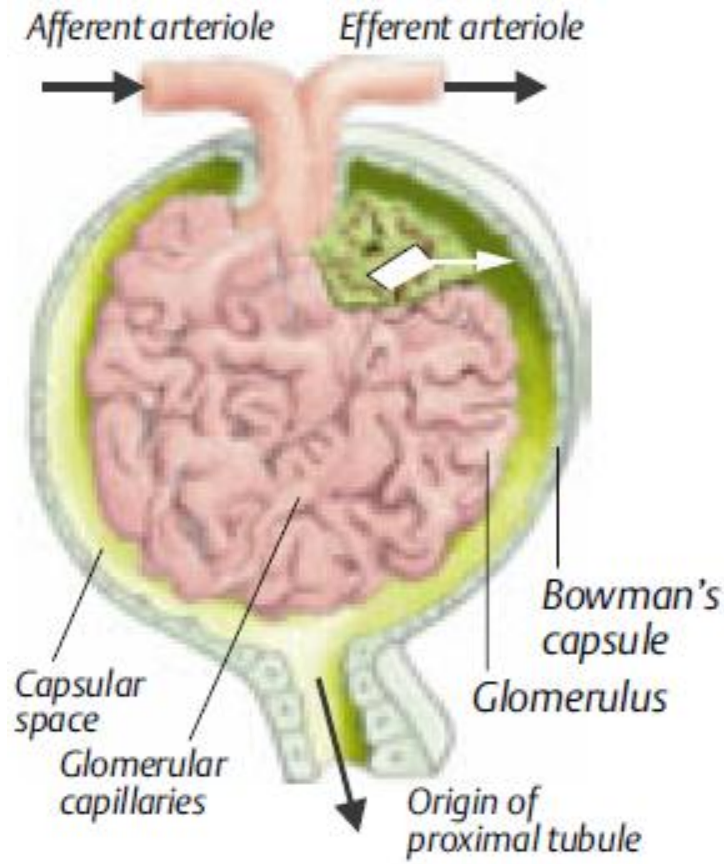
- Two kidneys lying on post. Abd. wall
- Each weighing **150gms**
- Enclosed in a thin, tough capsule
- Medial indentation called **Hilum**
- On Cross sectional view Kidney has two zones
  - Outer **CORTEX** & inner **MEDULLA**
- Renal pyramids
- Major & Minor **Calyces**
- Renal pelvis

The functional unit of the kidney: Nephron




Distal tubule
Collecting duct
Proximal tubule
Juxtaglomerular apparatus
Efferent arteriole
Afferent arteriole
Bowman's capsule
Glomerulus
Artery
Vein
Cortex
Medulla
Peritubular capillaries
Loop of Henle
To renal pelvis


Small branch of renal artery
Peritubular capillaries
Afferent arteriole
Efferent arteriole
Glomerulus
© Richard G. Kessel/Visuals Unlimited


Afferent arteriole
Efferent arteriole
Bowman's capsule
Glomerulus
Capsular space
Glomerular capillaries
Origin of proximal tubule

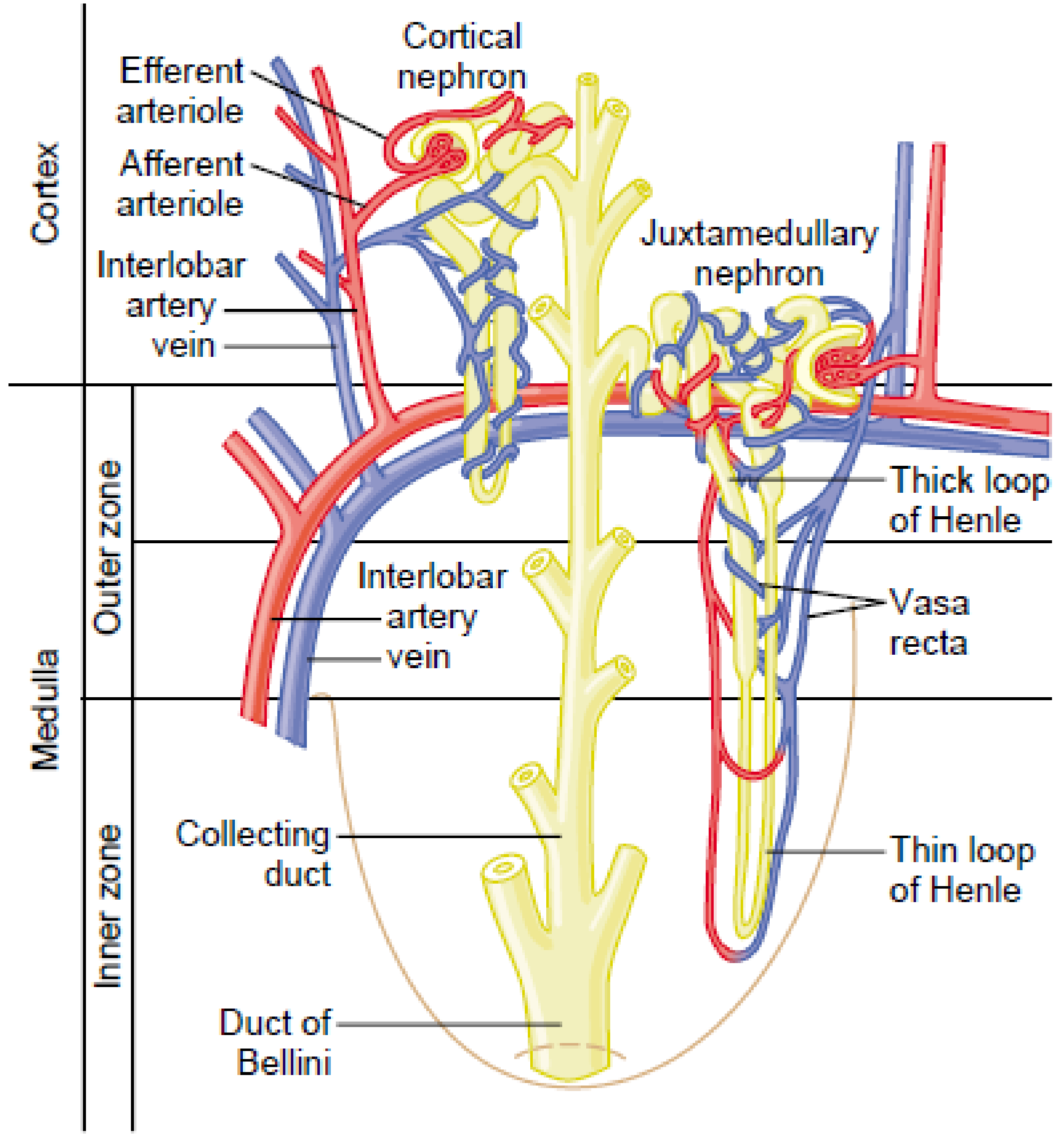
REGIONAL DIFFERENCES IN NEPHRON STRUCTURE

CORTICAL

- 60-70%
- Glomeruli lie in cortex
- Short loops of Henle penetrating partly into medulla
- PTC surround the entire tubular system
- Smaller Glomruli
- Afferent arterioles are larger

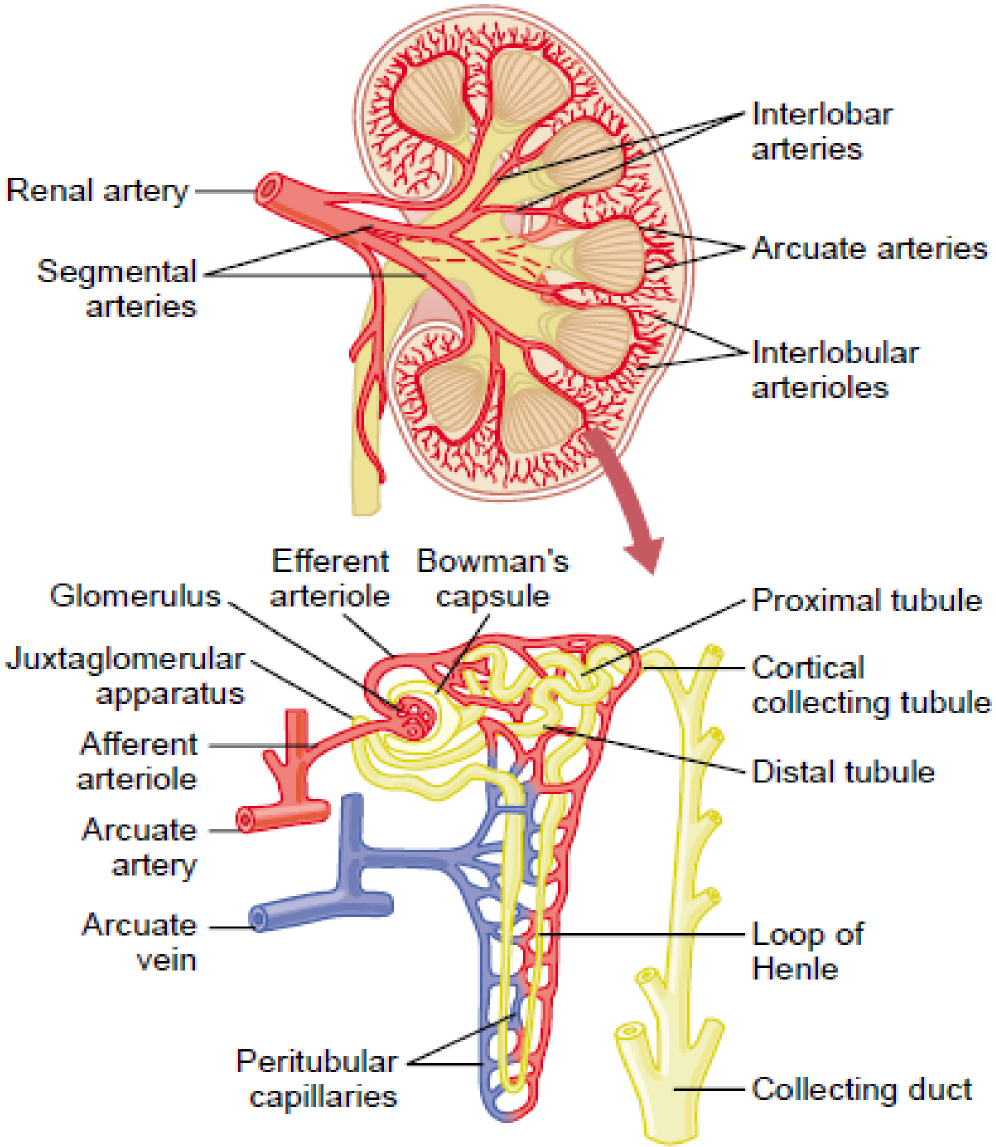
JUXTAMEDULLARY

- 20-30%
- Glomeuli lie deep in cortex near medulla
- Long loops of Henle penetrating deep into medulla
- Efferent arterioles extend deep into medulla to give specialize PTC called VASA RECTA
- Larger Glomeruli
- Efferent arterioles are larger
  - Fenestrations present in Ascending VASA RECTA
- VASA RECTA are important in formation of concentrated urine
- Descending (non fenestrated)

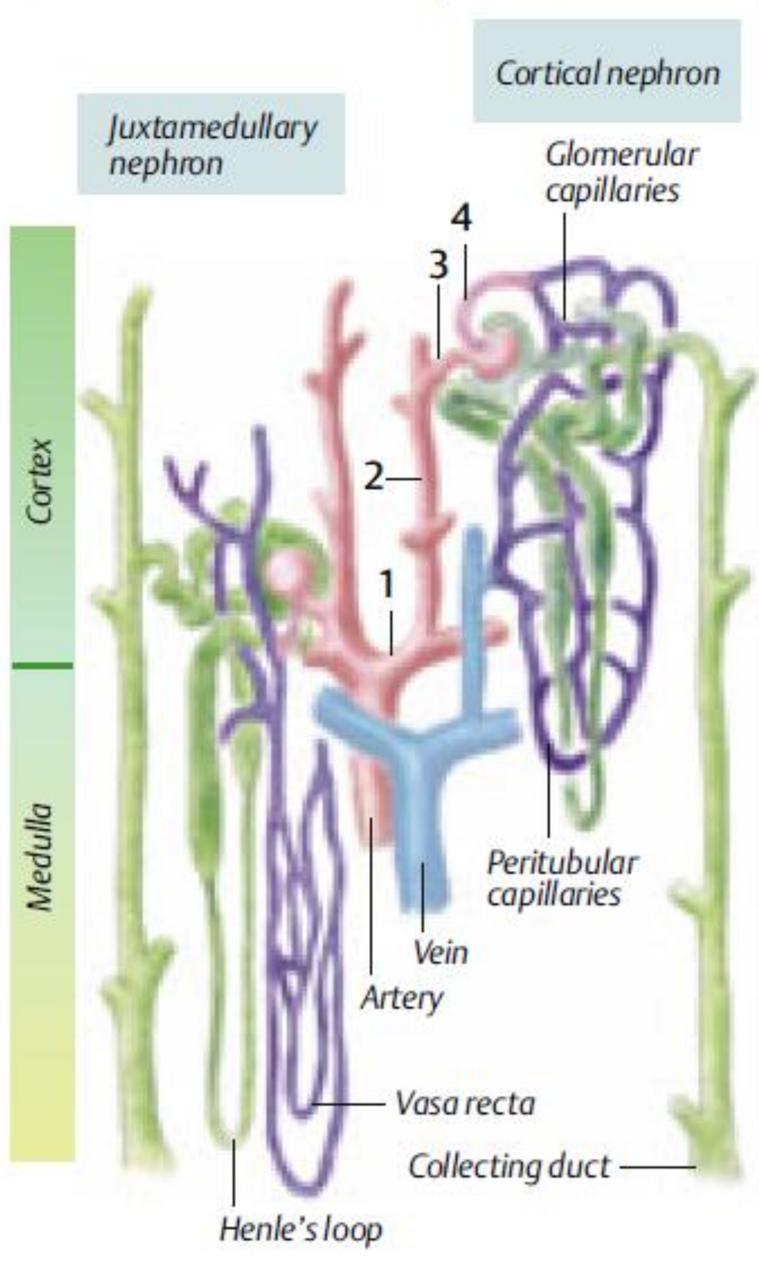


Cortex
Medulla
Outer zone
Inner zone
Efferent arteriole
Afferent arteriole
Interlobar artery
vein
Cortical nephron
Juxtamedullary nephron
Thick loop of Henle
Vasa recta
Interlobar artery
vein
Collecting duct
Thin loop of Henle
Duct of Bellini

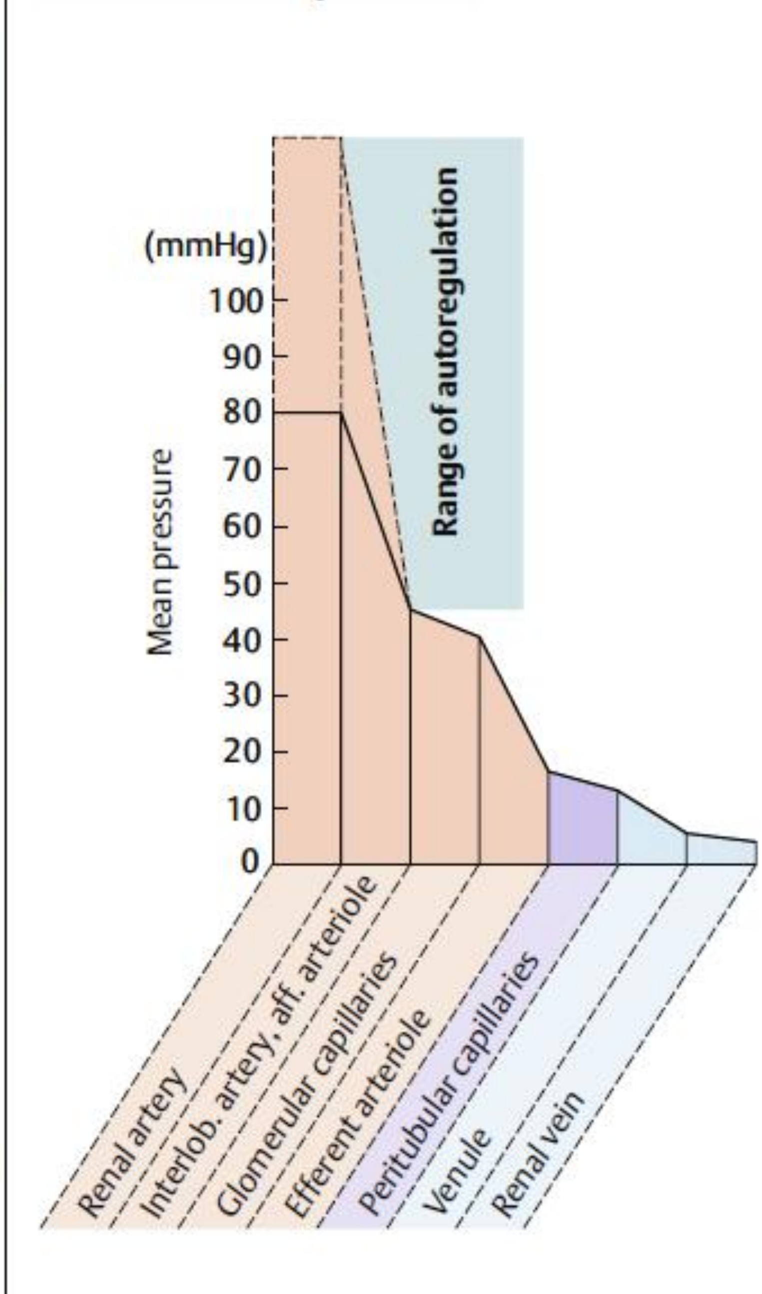
Renal Blood Supply



A. Renal blood vessel system



B. Renal blood pressure



- Kidneys have excellent blood supply: **0.5%** total body weight but ~**22%** of C.O. (**1100ml**)
- Renal artery direct branch of **Abd. Aorta**
- Renal artery → Segmental A. → Interlobar A. → Arcuate A. → Interlobular A. (Radial A.) → Afferent arterioles → Glomerular capillaries → Efferent arterioles → Peritubular capillaries
- Renal circulation is unique ---- Has **TWO capillary beds**.

- Glomerular capillary hydrostatic pressure --- 60 mmHg
- Peritubular capillary hydrostatic pressure --- 13 mmHg
- Pressure regulated by resistance of afferent & efferent arterioles

VENOUS DRAINAGE

- Interlobular vein → Arcuate vein → Interlobar vein → Renal vein.

URINE

- Daily production --- 1-2 liters/day
- Anuria: less than 100ml/day
- Oliguria: less than 400ml/day
- Polyuria: More than 2.5L/day
- Color: Colorless to deep yellow (effected by drugs, chemicals, disease conditions)
- PH: 5-6 (maximum 4.5-8)
- Glucose & Proteins: Present only in Pathological states

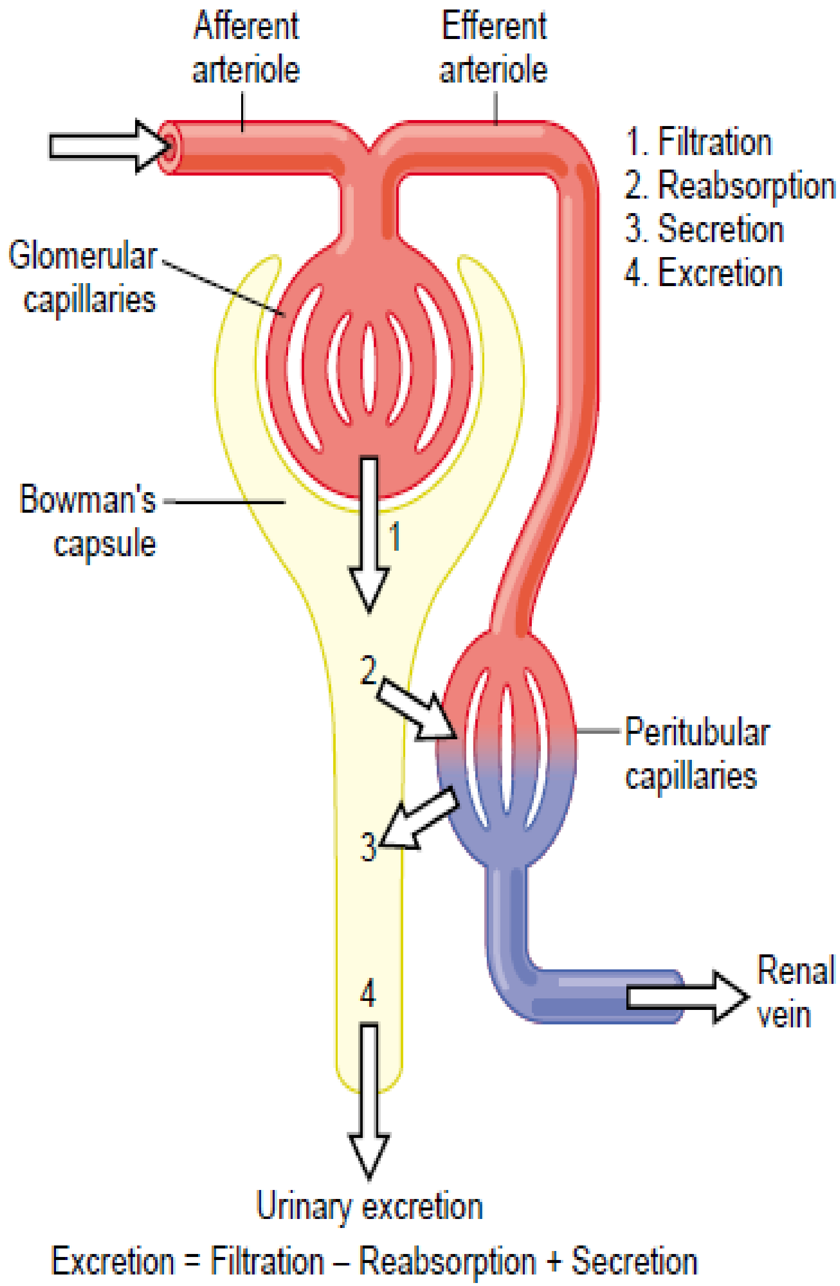
Normal concentrations

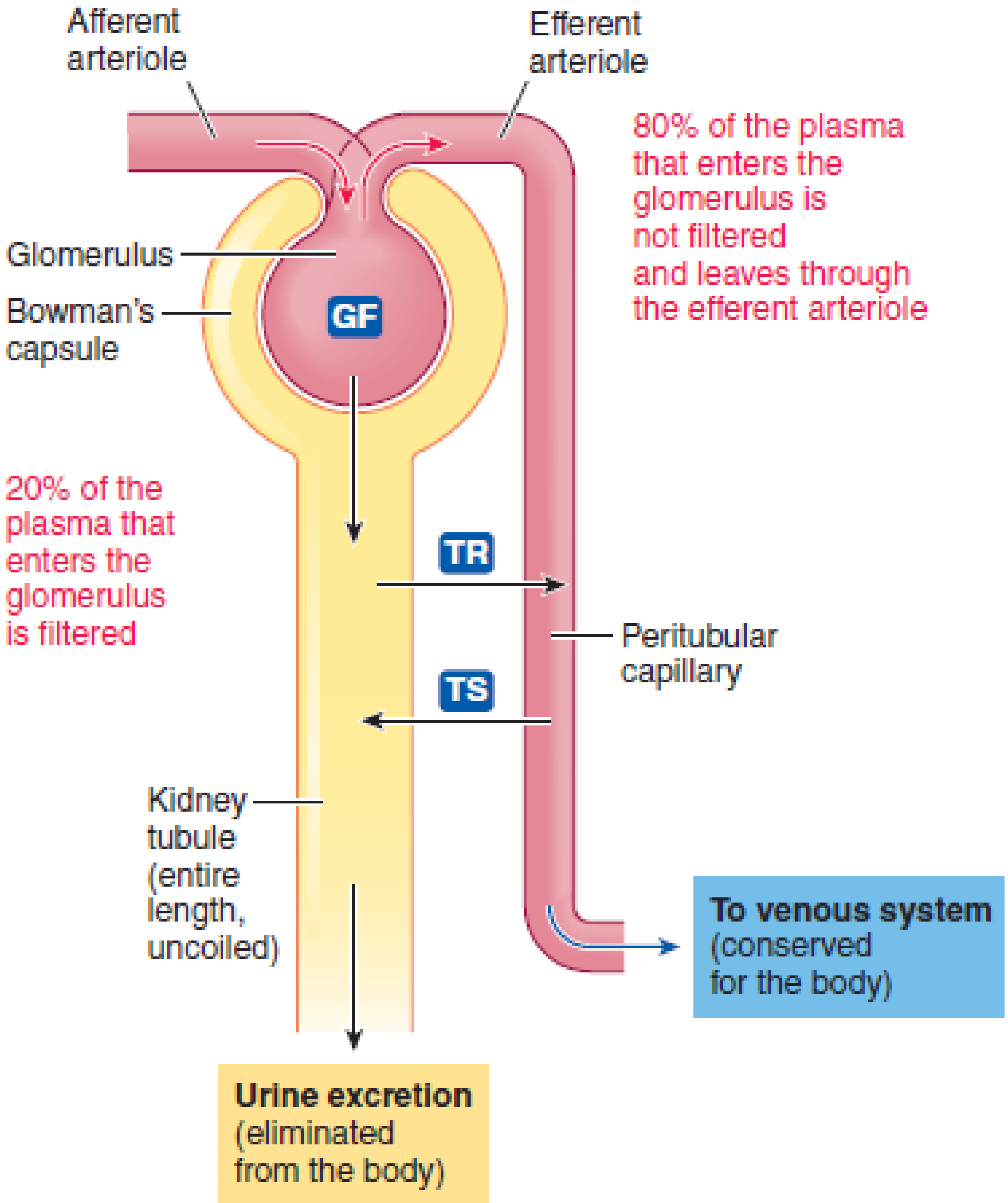
- Glucose : NIL
- Proteins : NIL
- Sodium : 90 mEq/L (50-130)
- Potassium : 20-70 mEq/L
- Calcium : 5-12 mEq/L
- Magnesium : 2-18 mEq/L
- Chloride : 50-130 mEq/L
- Ammonium : 30-50 mEq/L
- Urea : 900 mg/dL
- Creteanine : 150 mg/dL

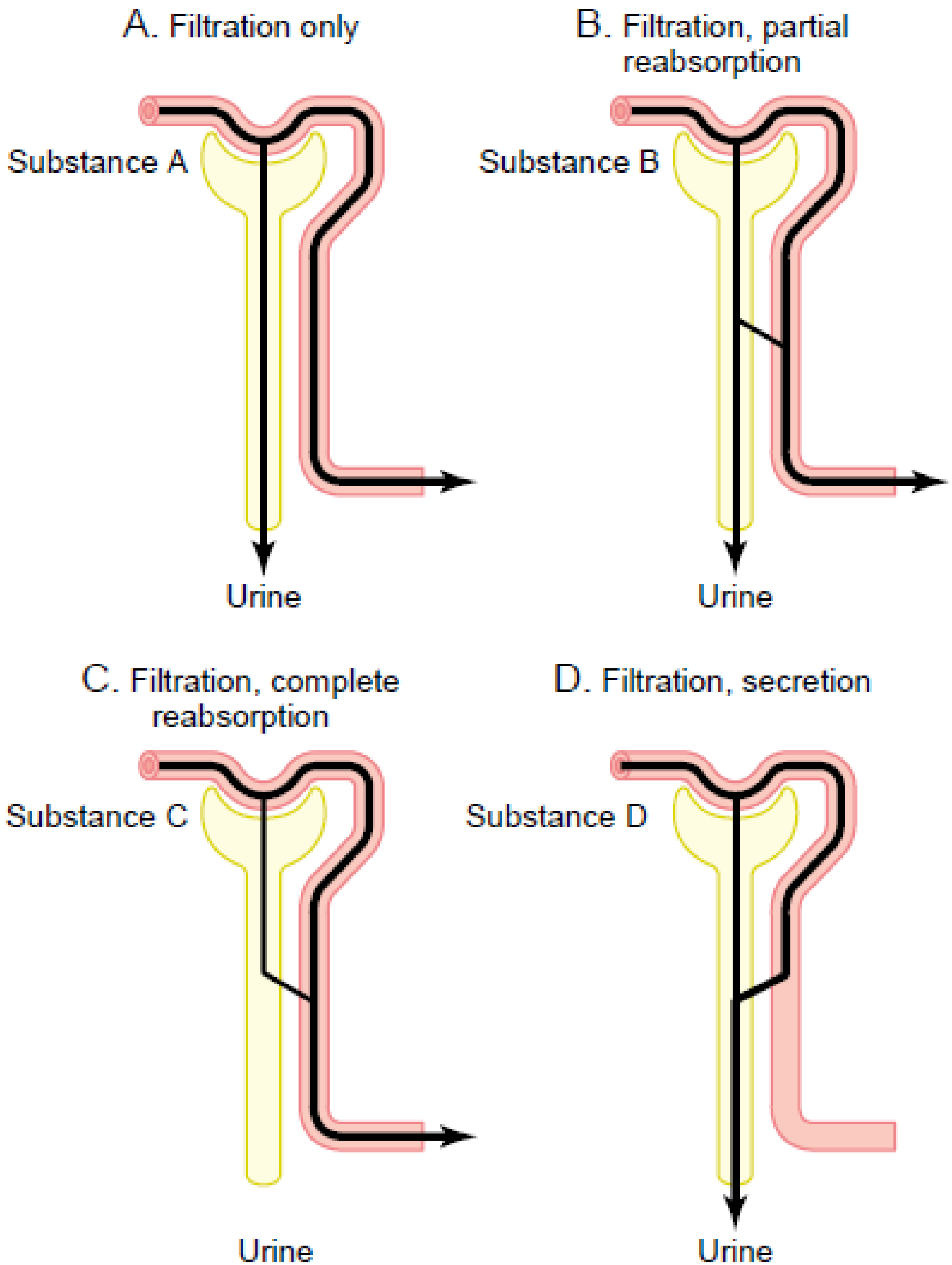
The three basic renal processes

- **Glomerular filtration**
- **Tubular reabsorption**
- **Tubular secretion**
- **Urinary excretion rate**

  Filtration rate - Reabsorption rate + Secretion rate


Afferent arteriole
Efferent arteriole
1. Filtration
2. Reabsorption
3. Secretion
4. Excretion
Glomerular capillaries
Bowman's capsule
1
2
3
4
Peritubular capillaries
Renal vein
Urinary excretion
Excretion = Filtration – Reabsorption + Secretion


Afferent arteriole
Efferent arteriole
80% of the plasma that enters the glomerulus is not filtered and leaves through the efferent arteriole
Glomerulus
Bowman's capsule
GF
20% of the plasma that enters the glomerulus is filtered
TR
Peritubular capillary
TS
Kidney tubule (entire length, uncoiled)
To venous system (conserved for the body)
Urine excretion (eliminated from the body)


A. Filtration only
Substance A
Urine
B. Filtration, partial reabsorption
Substance B
Urine
C. Filtration, complete reabsorption
Substance C
Urine
D. Filtration, secretion
Substance D
Urine

- The three basic processes involved in urine formation are regulated as per body needs
- Increase or decrease in sodium intake changes its rate of filtration, reabsorption
- For example, 10% increase in GFR from 180 to 198 L/Day may increase urine volume to 13 fold keeping reabsorption same
- Advantages of high GFR
  - Efficient removal of wastes
  - Maintainance of homeostasis (whole plasma is filtered 60 times each day)

Glomerular Filtration—The First Step in Urine Formation

- Free filtration of large amounts of fluid
- Glomrular capillaries are impermeable to proteins
- Conc. of other constituents same as plasma except :
    - Calcium
    - Fatty acids
    - One half of these are bound to plasma proteins
- Normal GFR : 125ml/min or 180 L/Day
- GF is 20% of Renal Plasma Flow
- Determined by forces across the membrane & filtration coefficient

FILTRATION FRACTION

Fraction Of Renal Plasma That Is Filtered Each Minute

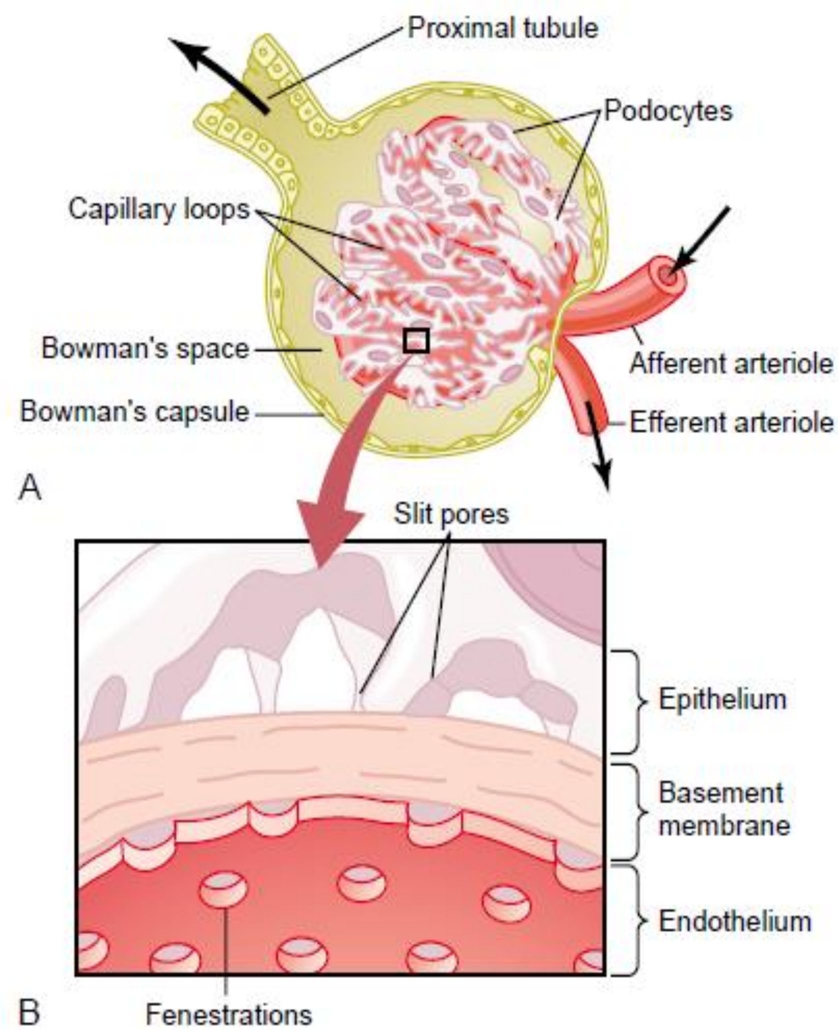
FF = GFR/Renal Plasma Flow

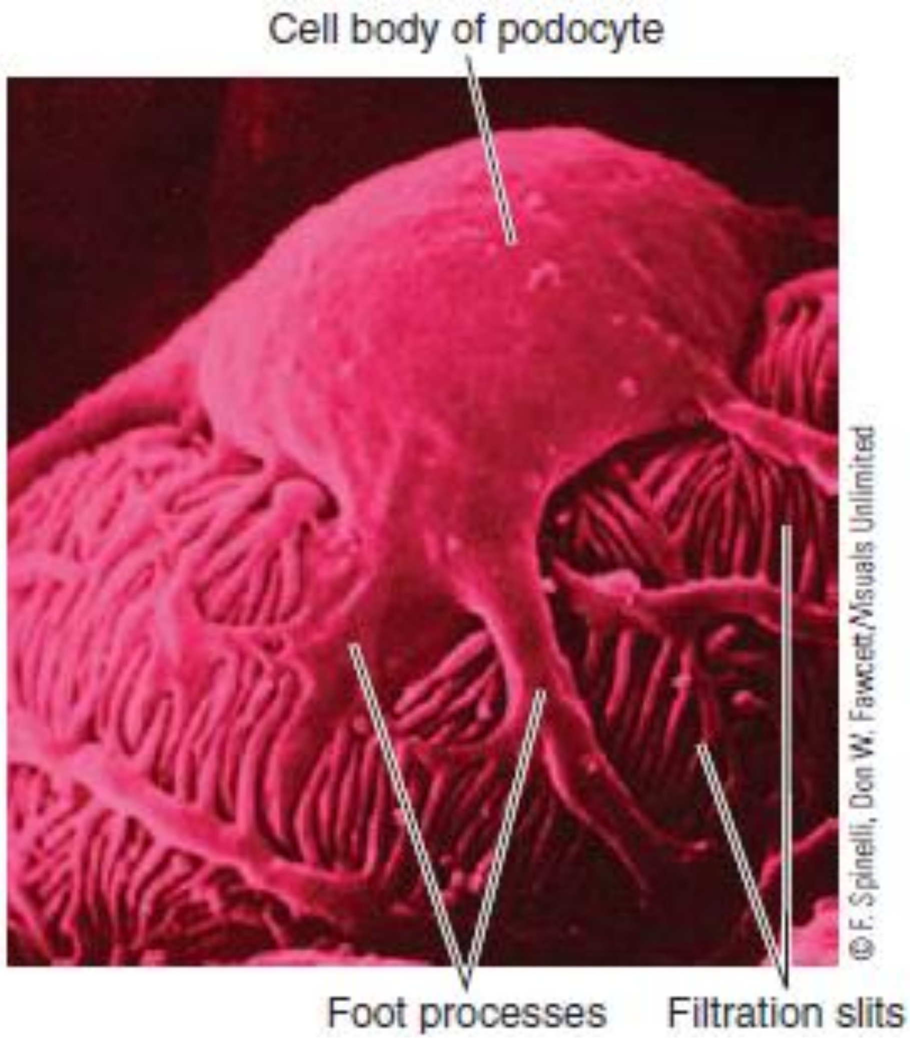
Normal FF = 0.2 or 20%

- Glomerular capillaries have high filtration coefficient

Glomerular Capillary Membrane

- Have 3 instead of 2 layers
  - **Endothelium**
  - **Basement membrane**
  - **Layer of epithelial cells (Podocytes)** surrounding the outer surface of B.M.
- Despite these three layers free filtration occurs **except** for **proteins**
- Endothelium has pores (**Fenestrations**) like liver
- Endothelium has –ve charge
- B.M. has a meshwork of collagen & proteoglycan (Gives –ve charge) **{Mesangial Cells}**
- Outer epithelial layer has foot like processes called Podocytes separated by gaps (slit pores)



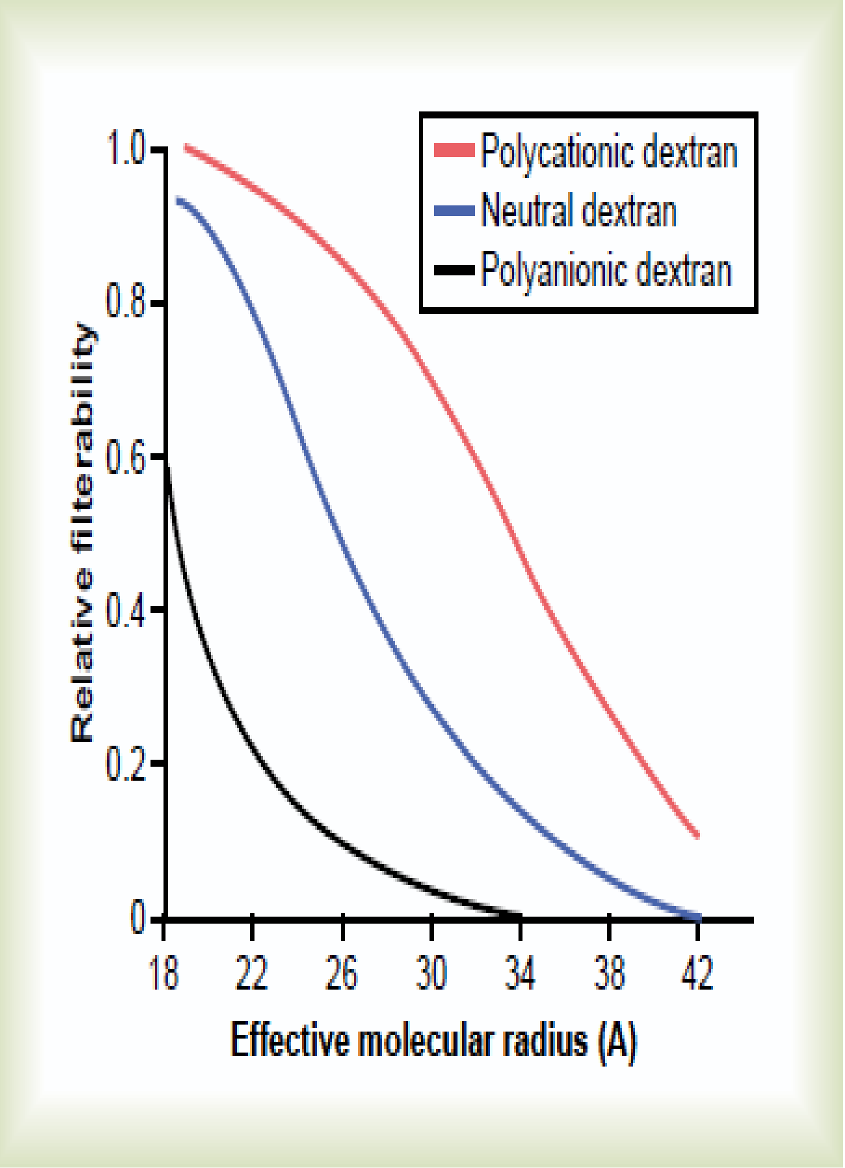

Cell body of podocyte
Foot processes
Filtration slits
© F. Spinelli, Don W. Fawcett/Visuals Unlimited

Filterability of Solutes Is Inversely Related to Their Size

Filterability of Substances by Glomerular Capillaries Based on Molecular Weight

Substance	Molecular Weight	Filterability
Water	18	1.0
Sodium	23	1.0
Glucose	180	1.0
Inulin	5,500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005

- Negatively charged large molecules are filtered less easily than positively charged molecules of equal molecular size
- Mol. Size of Albumin 6nm
- Dextrans
- Size of pores 8nm
- **Minimal change Nephropathy**
- **Proteinuria or Albuminuria**



DETERMINANTS OF GFR

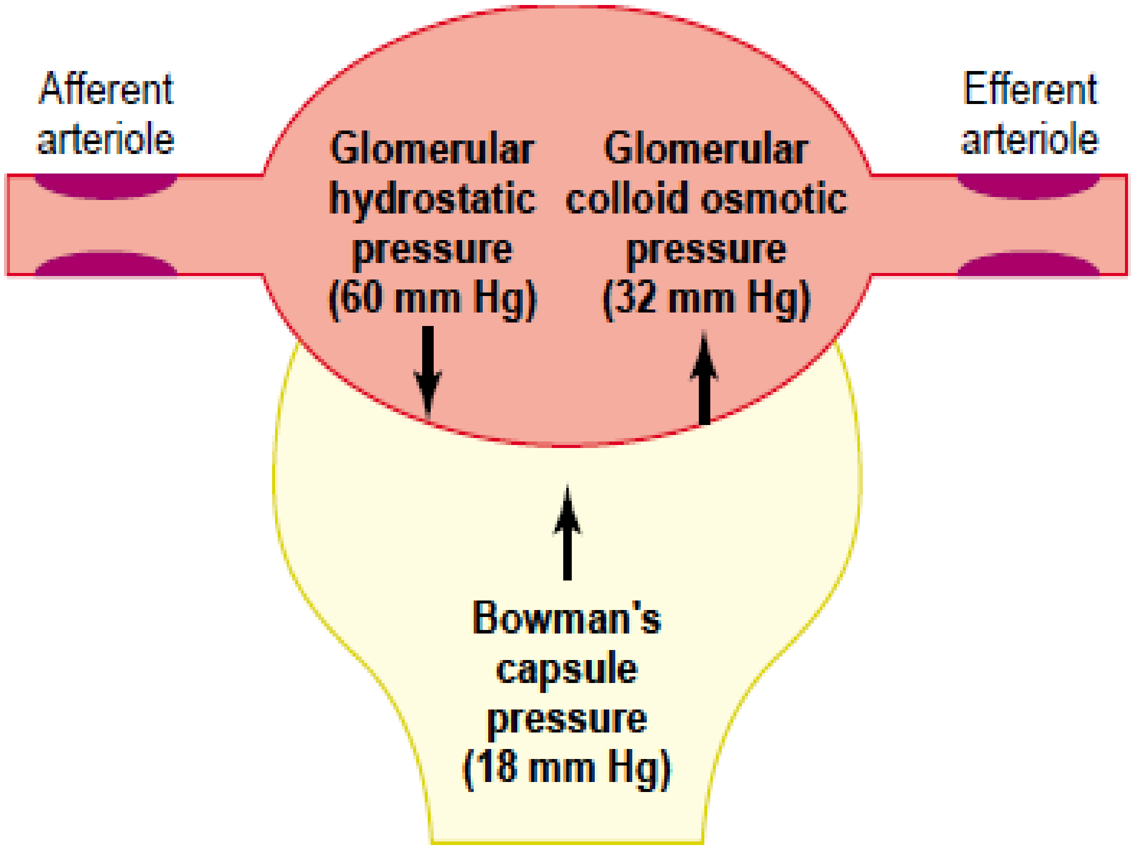
1. Net filtration Pressure
2. Glomerular capillary filtration coefficient

$$GFR = K_f \times \text{Net filtration pressure}$$

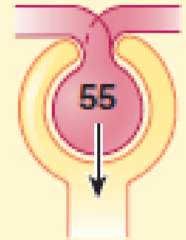
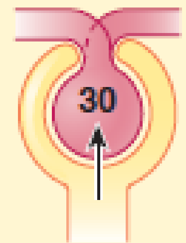
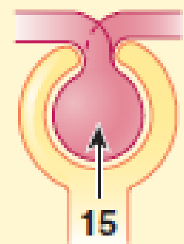
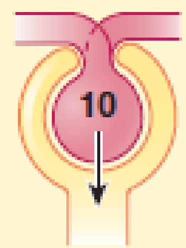
Net filtration Pressure:

- Glomerular capillary Hydrostatic pressure (P_G)
- Bowman's capsule Hydrostatic pressure (P_B)
- Glomerular capillary colloid osmotic pressure (π_G)
- Bowman's capsule colloid osmotic pressure (π_B)

$$GFR = K_f \times (P_G - P_B - \pi_G + \pi_B)$$



Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) – Bowman's capsule pressure (18 mm Hg) – Glomerular oncotic pressure (32 mm Hg)

Force	Effect	Magnitude (mm Hg)
Glomerular Capillary Blood Pressure	Favors filtration	
Plasma-Colloid Osmotic Pressure	Opposes filtration	
Bowman's Capsule Hydrostatic Pressure	Opposes filtration	
Net Filtration Pressure (Difference between Force Favoring Filtration and Forces Opposing Filtration)	Favors filtration	 $55 - (30 + 15) = 10$

Forces Favoring Filtration (mm Hg)

Glomerular hydrostatic pressure = 60

Bowman's capsule colloid osmotic pressure = 0

Forces Opposing Filtration (mm Hg)

Bowman's capsule hydrostatic pressure = 18

Glomerular capillary colloid osmotic pressure = 32

Net filtration pressure = 60 – 18 – 32 = +10 mm Hg

Increased Glomerular Capillary Filtration Coefficient Increases GFR

K_f = Product of hydraulic conductivity & Surface Area

K_f = GFR/Net filtration pressure

K_f = 125/10

= 12.5 ml/min/mm Hg

In terms of per 100gms

K_f = 4.2 ml/min/mm Hg

K_f of other tissues is 400 times less than that of kidney = 0.01 ml/min/mmHg

Increased Bowman's Capsule Hydrostatic Pressure Decreases GFR

- Normal pressure = 18 mm Hg
- Increased pressure reduces GFR
- Normally remains constant
- Not a primary mean of GFR regulation
- Increased in urinary tract obstruction
- E.g. Precipitation of Ca or Uric acid may lead to stone formation in urinary tract leading to obstruction

Increased Glomerular Capillary Colloid Osmotic Pressure Decreases GFR

- Conc. of proteins increases by 20% as blood passes from afferent arterioles to efferent
- Colloid osmotic pressure in afferent arterioles = 28 mm Hg
- Colloid osmotic pressure in efferent arterioles = 36 mm Hg

Average Colloid osmotic pressure in

Glomerular capillaries = 32 mm Hg

- Two factors change the COP :
  - » **The arterial plasma colloid osmotic pressure**
  - » **Fraction of plasma filtered by the glomerular capillaries (filtration fraction)**

Increased Glomerular Capillary Hydrostatic Pressure Increases GFR

- Normal pressure = 60 mm Hg
- Primary mean for physiological regulation of GFR
- Determined by three main factors:
  - » Arterial pressure
  - » Afferent arteriolar resistance
  - » Efferent arteriolar resistance

Factors That Can Decrease the Glomerular Filtration Rate (GFR)

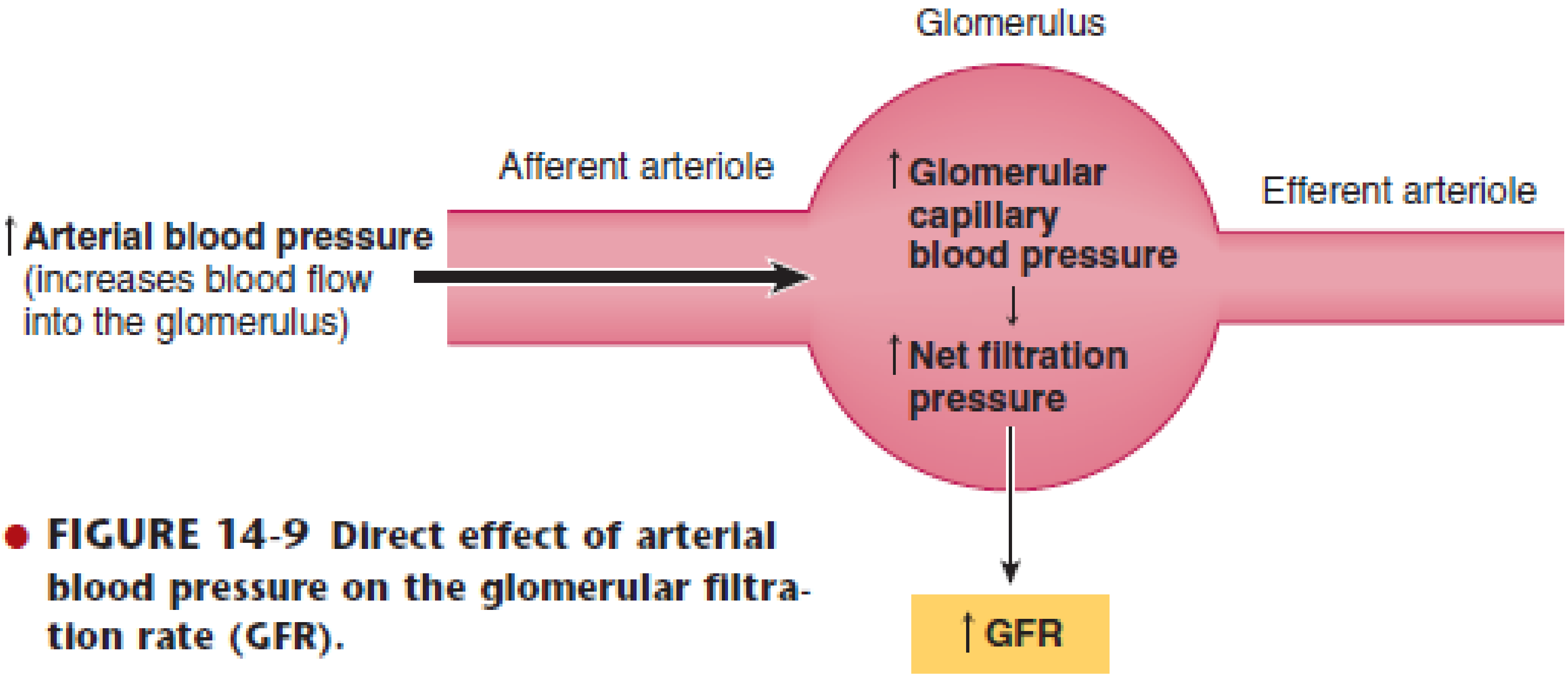
Physical Determinants*	Physiologic/Pathophysiologic Causes
$\downarrow K_f \rightarrow \downarrow$ GFR	Renal disease, diabetes mellitus, hypertension
$\uparrow P_B \rightarrow \downarrow$ GFR	Urinary tract obstruction (e.g., kidney stones)
$\uparrow \pi_G \rightarrow \downarrow$ GFR	↓ Renal blood flow, increased plasma proteins
$\downarrow P_G \rightarrow \downarrow$ GFR	
$\downarrow A_P \rightarrow \downarrow P_G$	↓ Arterial pressure (has only small effect due to autoregulation)
$\downarrow R_E \rightarrow \downarrow P_G$	↓ Angiotensin II (drugs that block angiotensin II formation)
$\uparrow R_A \rightarrow \downarrow P_G$	↑ Sympathetic activity, vasoconstrictor hormones (e.g., norepinephrine, endothelin)

Physiological Control of GFR & RBF

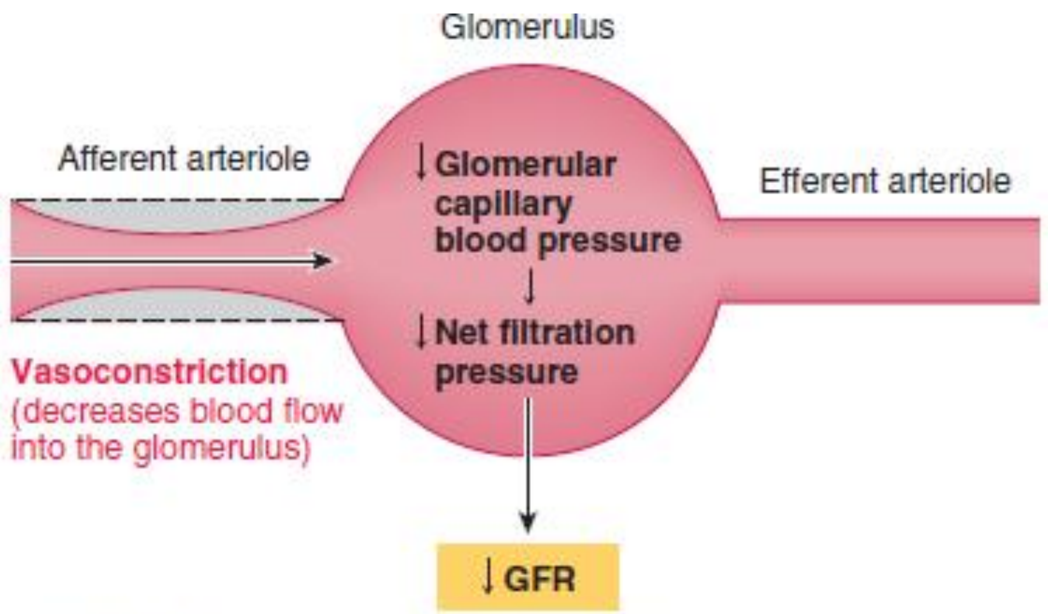
- **Glomerular capillary Hydrostatic pressure**
- Bowman's capsule Hydrostatic pressure
- **Glomerular capillary colloid osmotic pressure**
- Bowman's capsule colloid osmotic pressure

FACTORS AFFECTING CAPILLARY HYDROSTATIC & ONCOTIC PRESSURE

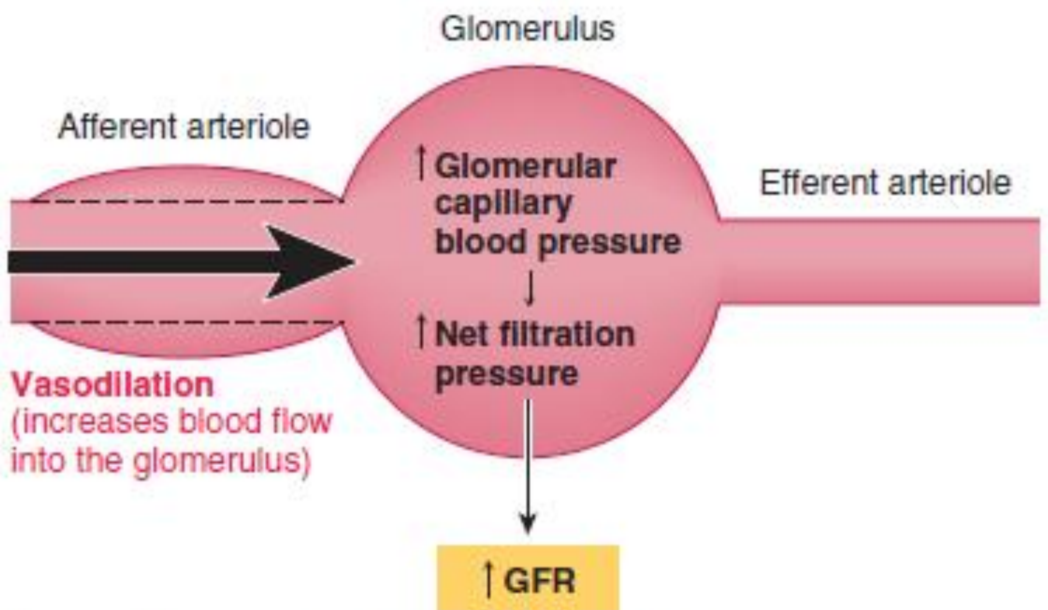
- Sympathetic nervous system
- Hormones
- Autacoids --- vasoactive substances that are released in the kidneys act locally
- Intrinsic renal feedback mechanisms



● **FIGURE 14-9 Direct effect of arterial blood pressure on the glomerular filtration rate (GFR).**



(a) Arteriolar vasoconstriction decreases the GFR



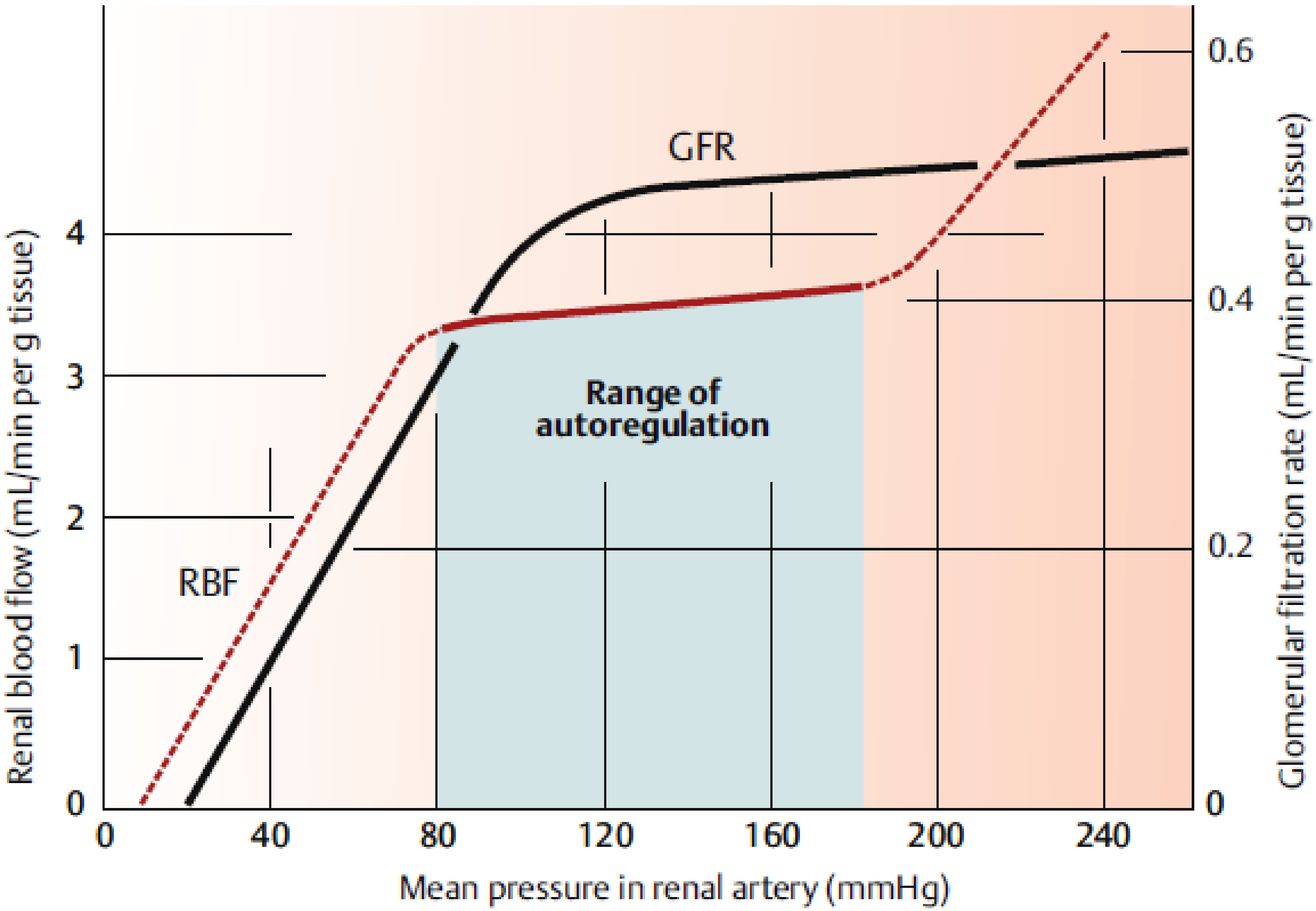
(b) Arteriolar vasodilation increases the GFR

SYMPATHETIC STIMULATION DECREASES GFR

- Renal blood vessels especially the afferent & efferent arterioles have abundant sympathetic nerve supply
- Strong sympathetic stimulation → Renal arteriolar constriction → Decreased RBF & GFR
- Mild to moderate sympathetic stimulation → Little or no influence on RBF & GFR

Autoregulation of GFR and Renal Blood Flow

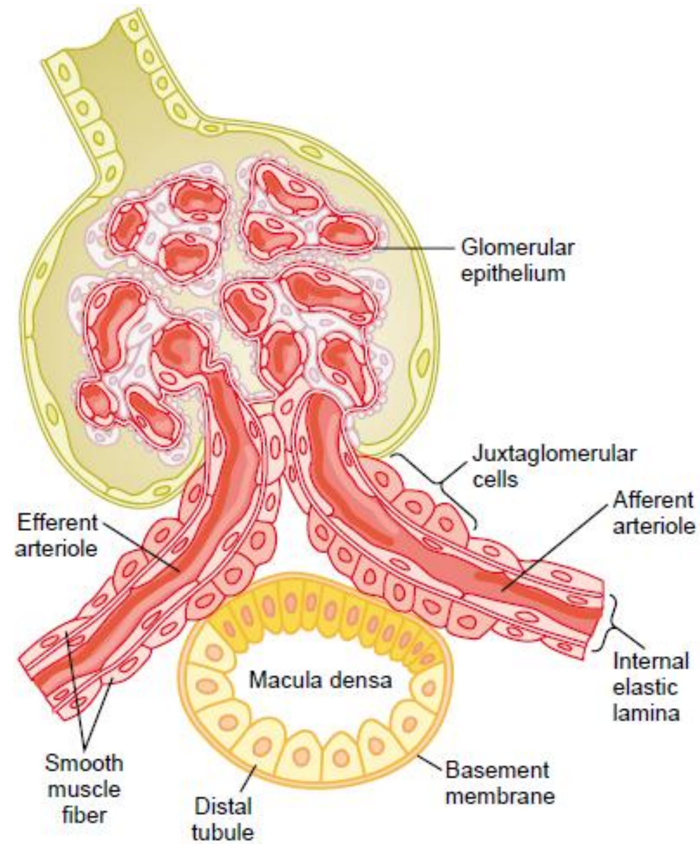
- Relative constancy of RBF & GFR is referred as AUTOREGULATION
- Intrinsic renal feedback back mechanisms that keep the RBF & GFR relatively constant despite marked changes in Arterial blood pressure
- Major function of autoregulation is to maintain adequate GFR & precise control of renal excretion of salt & water
- GFR remains relatively constant in a wide range of Arterial pressure (75 mmHg --- 160 mmHg)

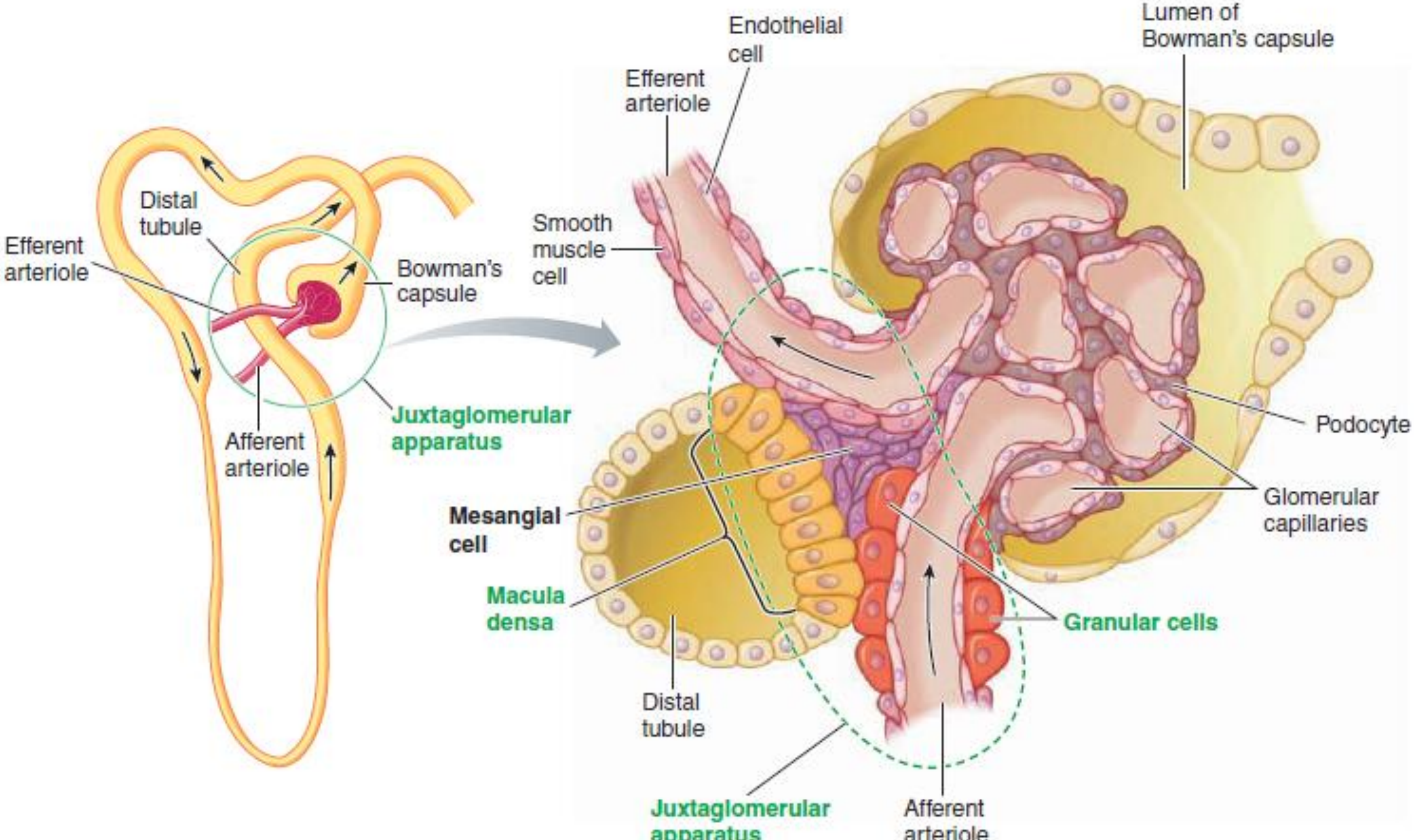


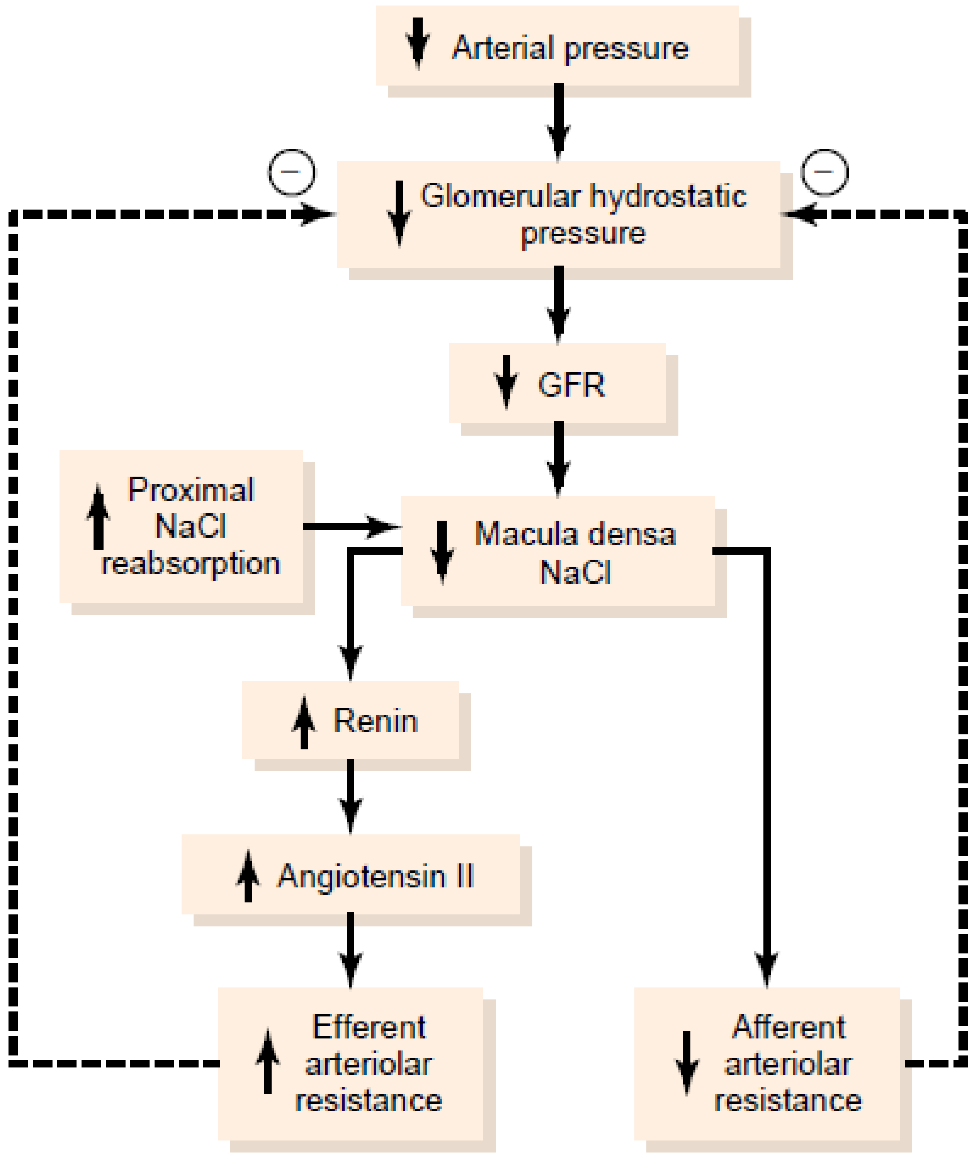
GFR
RBF
Range of autoregulation
Renal blood flow (mL/min per g tissue)
Glomerular filtration rate (mL/min per g tissue)
Mean pressure in renal artery (mmHg)
0
1
2
3
4
0
40
80
120
160
200
240
0
0.2
0.4
0.6

Role of Tubuloglomerular Feedback in Autoregulation of GFR

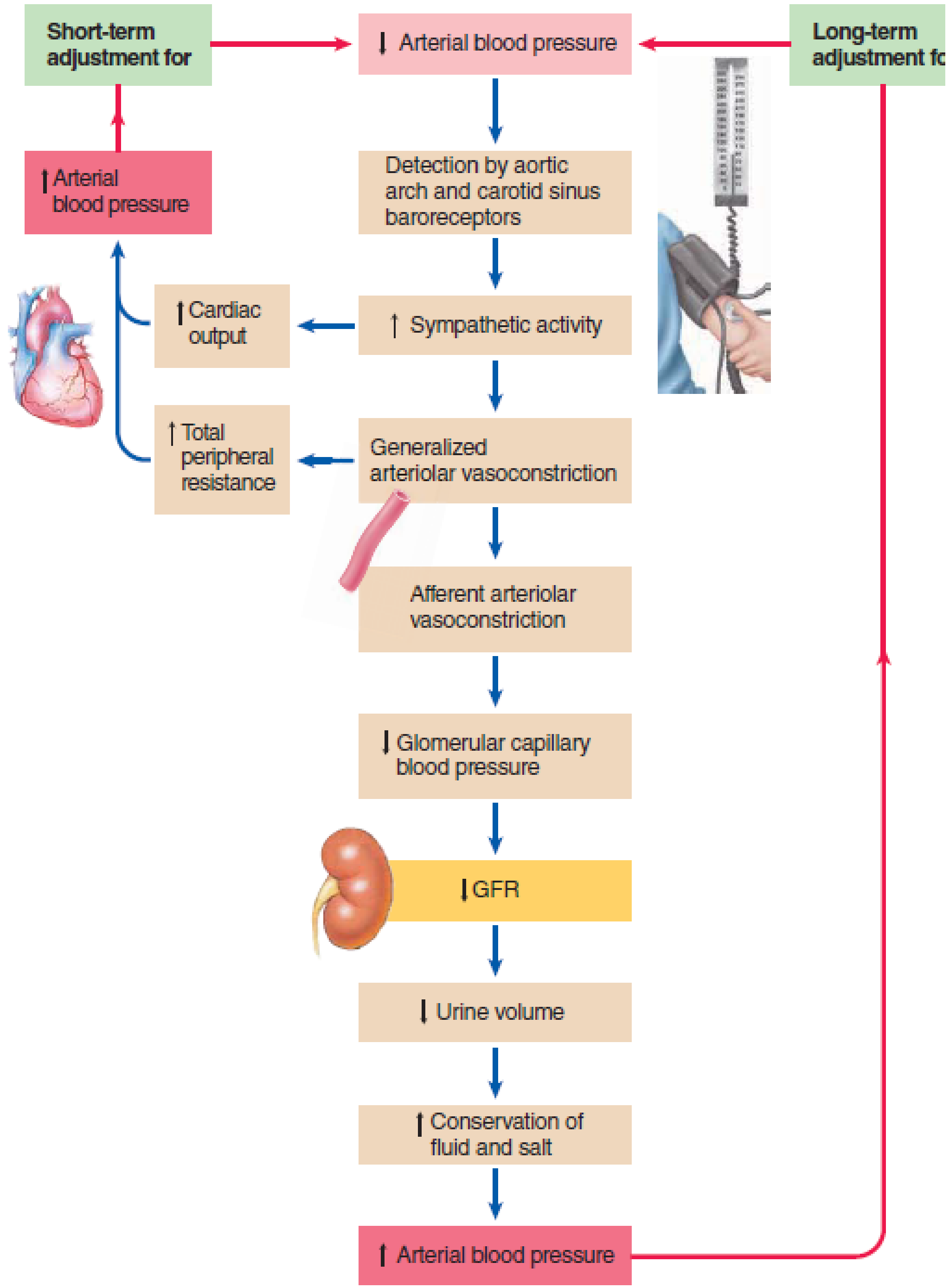
- Changes in NaCl conc at **MACULA DENSA** & control of arteriolar resistance
- TG feedback mechanism autoregulates RBF & GFR
- TG feedback mechanism has two components
  - AFFERENT ARTEROLAR FEEDBACK MECHANISM &
  - EFFERENT ARTEROLAR FEEDBACK MECHANISM
- **JUXTAGLOMERULAR APPARATUS**




Distal tubule
Efferent arteriole
Bowman's capsule
Afferent arteriole
Juxtaglomerular apparatus
Endothelial cell
Efferent arteriole
Lumen of Bowman's capsule
Smooth muscle cell
Podocyte
Mesangial cell
Glomerular capillaries
Macula densa
Granular cells
Distal tubule
Juxtaglomerular apparatus
Afferent arteriole



Arterial pressure
Glomerular hydrostatic pressure
GFR
Proximal NaCl reabsorption
Macula densa NaCl
Renin
Angiotensin II
Efferent arteriolar resistance
Afferent arteriolar resistance



Short-term adjustment for
↓ Arterial blood pressure
Long-term adjustment fo
Detection by aortic arch and carotid sinus baroreceptors
↑ Arterial blood pressure
↑ Sympathetic activity
↑ Cardiac output
↑ Total peripheral resistance
Generalized arteriolar vasoconstriction
Afferent arteriolar vasoconstriction
↓ Glomerular capillary blood pressure
↓ GFR
↓ Urine volume
↑ Conservation of fluid and salt
↑ Arterial blood pressure

Blockade of Angiotensin II Formation Further Reduces GFR During Renal Hypoperfusion

Myogenic Autoregulation of Renal Blood Flow and GFR

MYOGENIC MECHANISM

Renal Blood Flow

- 22% of Cardiac Output (1100ml)
- 0.4-0.5% of total body weight
- On per gram basis kidney consumes oxygen twice the rate of brain but has blood supply 7 times that of brain
- Most of the oxygen consumed is utilized for Na reabsorption
- Increased RBF → Increased GFR → Increased Na Reabsorption → Increased oxygen consumption

Determinants of Renal Blood Flow

- Determined by **pressure gradient** across the renal vasculature divided by **total renal vascular resistance**
- Renal artery pressure = systemic pressure
- Renal vein pressure = 3-4 mm Hg
- Main resistance lies in the **interlobular arteries, afferent & efferent arterioles**
- Resistance in these channels is controlled by **sympathetic nervous system**
- Changes in systemic blood pressure does effect the RBF but this effect is minimized by autoregulatory mechanisms
- RBF remains almost same in blood pressure b/w 80-170 mmHg

Blood Flow in the Vasa Recta of the Renal Medulla Is Very Low Compared with Flow in the Renal Cortex

Cortex --- 98-99% of RBF

Medulla --- 1-2% of RBF

HORMONAL AND AUTACOID CONTROL OF RENAL CIRCULATION

Nor-epinephrine & Epinephrine

- Released from adrenal medulla & sympathetic nerve endings during stressful conditions
- Potent constrictor of Afferent & Efferent arterioles
- Reduce RBF & GFR
- Blood levels of these hormones are parallel to sympathetic stimulation
- Have no influence under normal conditions

ENDOTHELIN

- **Peptide** in nature
- Released from damaged vasular endothelial cells of kidney & other tissues
- Contributes in hemostasis when endothelial cells are damaged
- Plasma endothelin levels are raised in **Pre-eclampsia** (Toxemia of Pregnancy), ARF, Chronic Uremia (leading to renal vasoconstriction & decreased GFR in these conditions)

ANGIOTENSIN II

- Powerful vasoconstrictor of Efferent arterioles
- Increased Angiotensin II → Increased GFR & decreased RBF
- Reduced AP or Volume depletion → Angiotensin II → Increased **efferent arteriolar tone** → prevents decrease in GFR & decreases RBF → Increased tubular reabsorption (due to reduced blood flow in PTC) of Na & water → restoration of depleted blood volume & AP

Endothelial-Derived Nitric Oxide

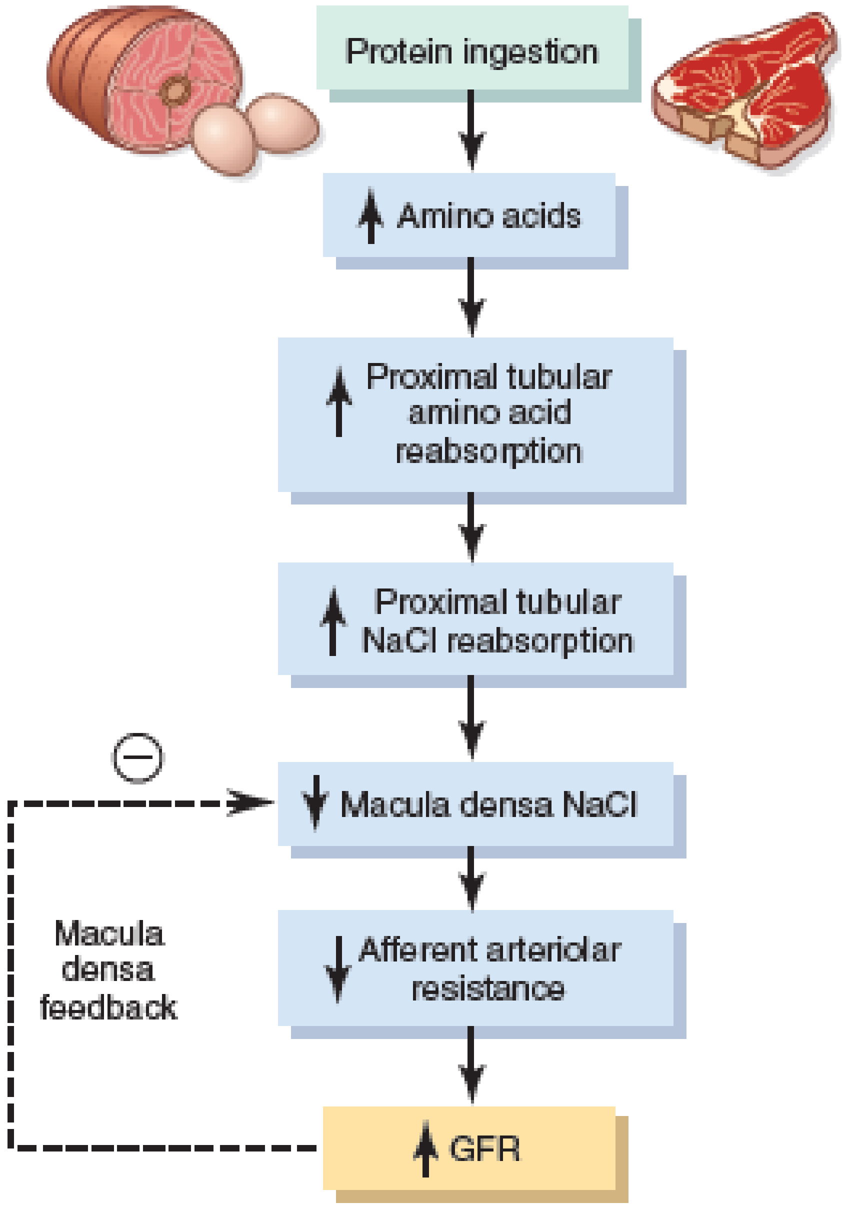
- Released by vascular endothelium throughout the body
- Decreases renal vascular resistance
- Basal level of NO important in maintaining the normal renal perfusion
- Drugs inhibiting formation of NO → increased renal vascular resistance → Decreased GFR & urinary Na excretion
- Impaired NO production cause of HYPERTENSION in some patients

Prostaglandins and Bradykinin

- Cause vasodilatation of renal vessels & increase the RBF & GFR
- Role in RBF regulation not important normally
- PG may help to prevent vasoconstriction of Afferent arterioles caused by sympathetic stimulation
- NSAIDs given in stressful conditions may reduce the renal perfusion and GFR

Other Factors That Increase Renal Blood Flow and GFR

High Protein Intake and Increased Blood Glucose


Protein ingestion
↑ Amino acids
↑ Proximal tubular amino acid reabsorption
↑ Proximal tubular NaCl reabsorption
↓ Macula densa NaCl
↓ Afferent arteriolar resistance
↑ GFR
Macula densa feedback

Renal Blood Flow

- 22% of Cardiac Output (1100ml)
- 0.4-0.5% of total body weight
- On per gram basis kidney consumes oxygen twice the rate of brain but has blood supply 7 times that of brain
- Most of the oxygen consumed is utilized for Na reabsorption
- Increased RBF → Increased GFR → Increased Na Reabsorption → Increased oxygen consumption

Determinants of Renal Blood Flow

- Determined by **pressure gradient** across the renal vasculature divided by **total renal vascular resistance**
- Renal artery pressure = systemic pressure
- Renal vein pressure = 3-4 mm Hg
- Main resistance lies in the **interlobular arteries, afferent & efferent arterioles**
- Resistance in these channels is controlled by **sympathetic nervous system**
- Changes in systemic blood pressure does effect the RBF but this effect is minimized by autoregulatory mechanisms
- RBF remains almost same in blood pressure b/w 80-170 mmHg

Blood Flow in the Vasa Recta of the Renal Medulla Is Very Low Compared with Flow in the Renal Cortex

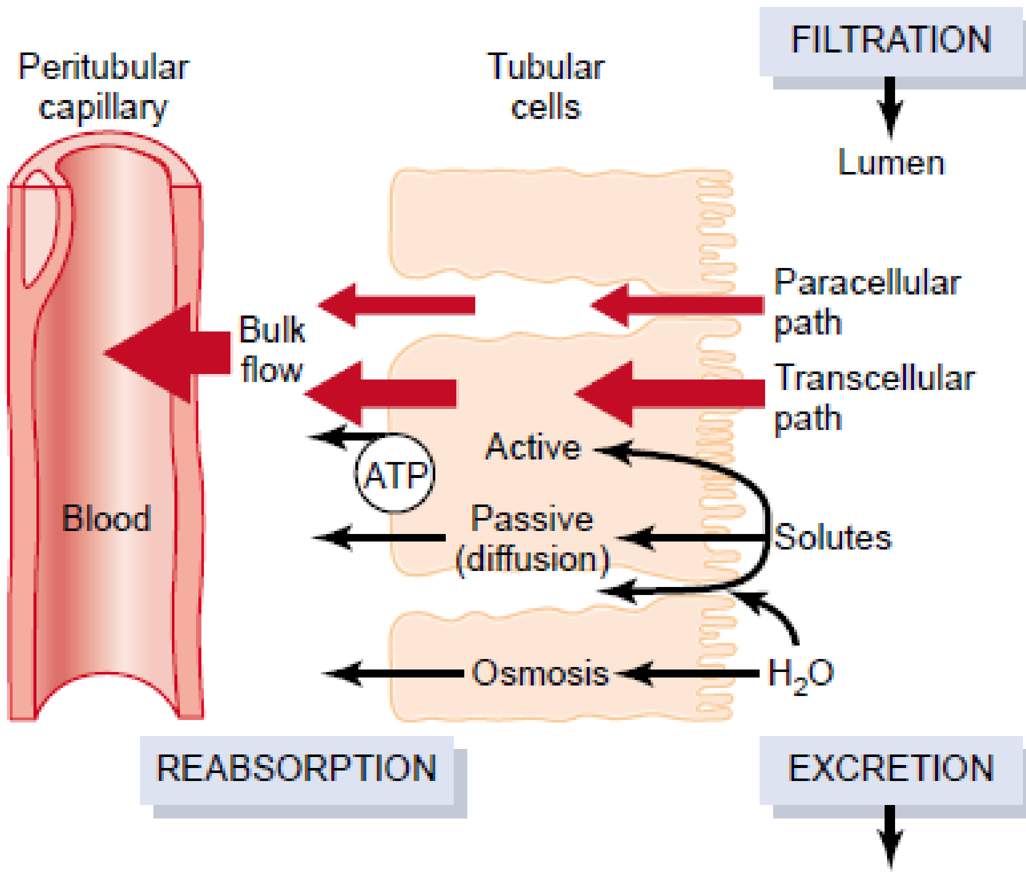
Cortex --- 98-99% of RBF

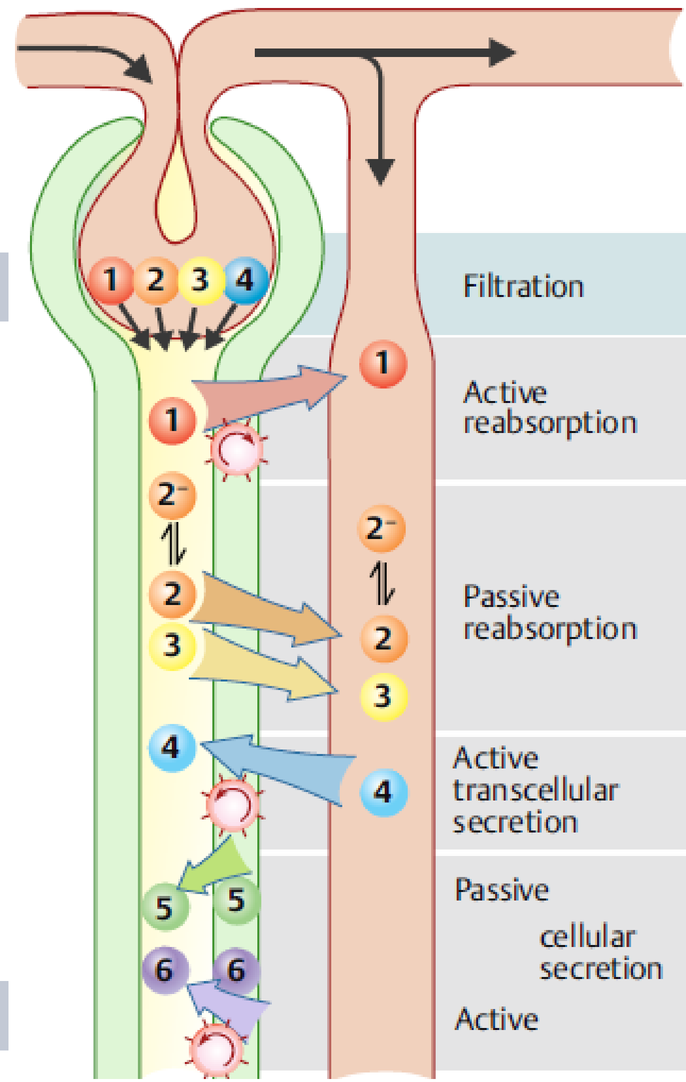
Medulla --- 1-2% of RBF

TUBULAR REABSORPTION

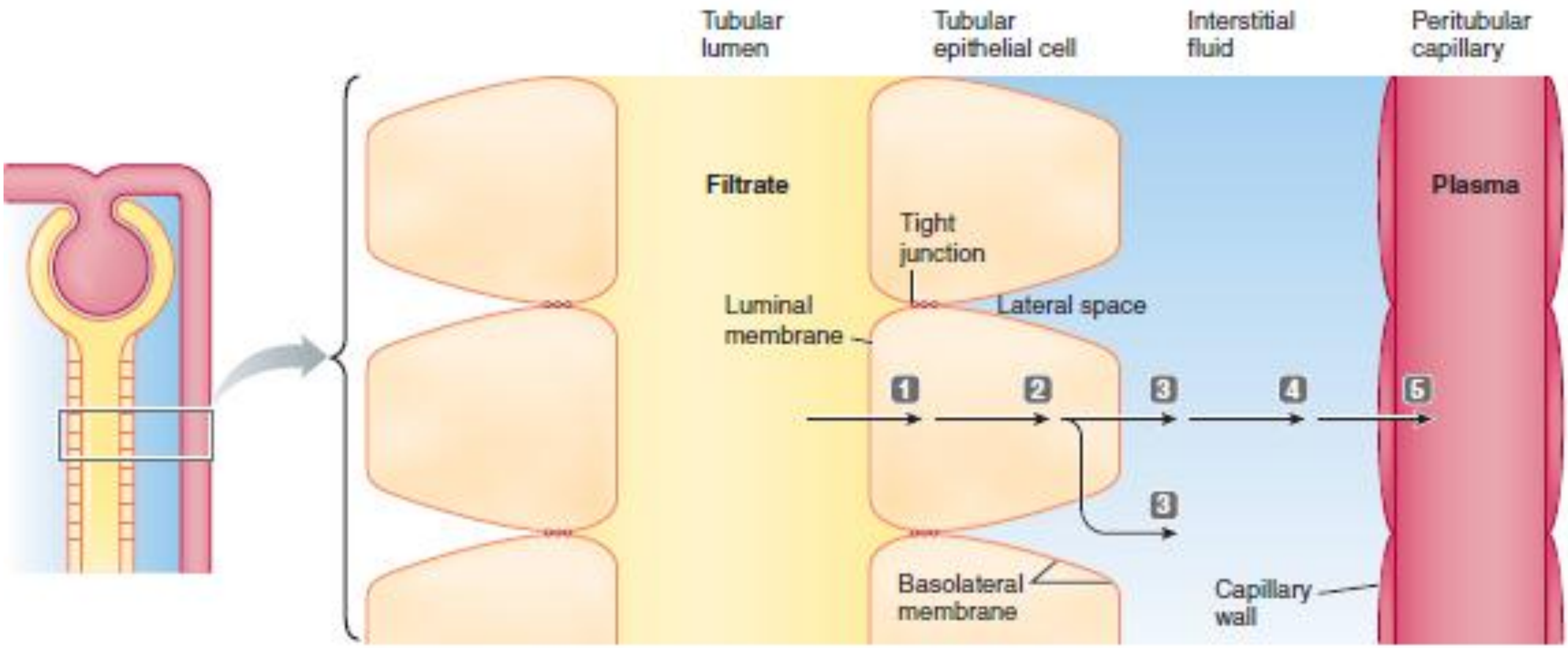
Tubular Processing of the Glomerular Filtrate

Tubular Reabsorption Includes Passive and Active Mechanisms



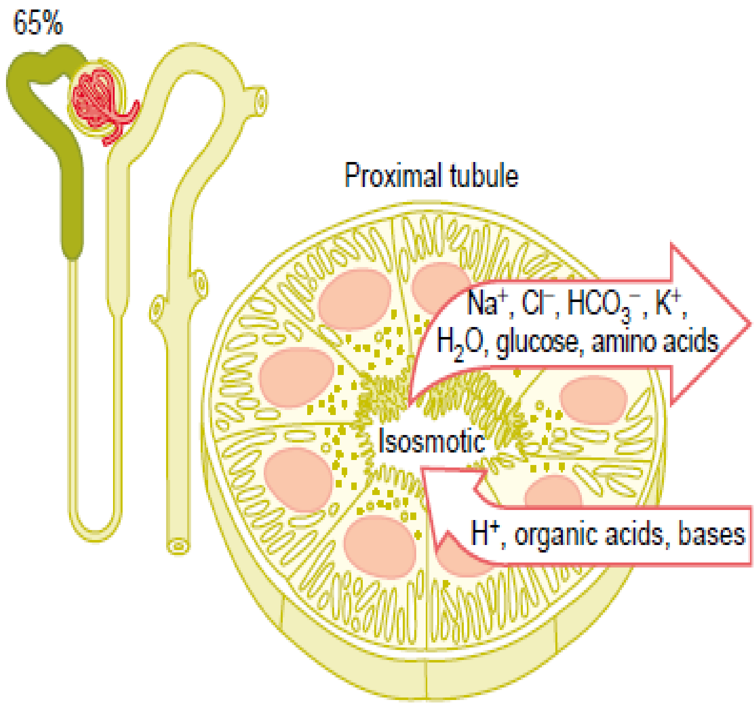


For a substance to be reabsorbed it must pass through

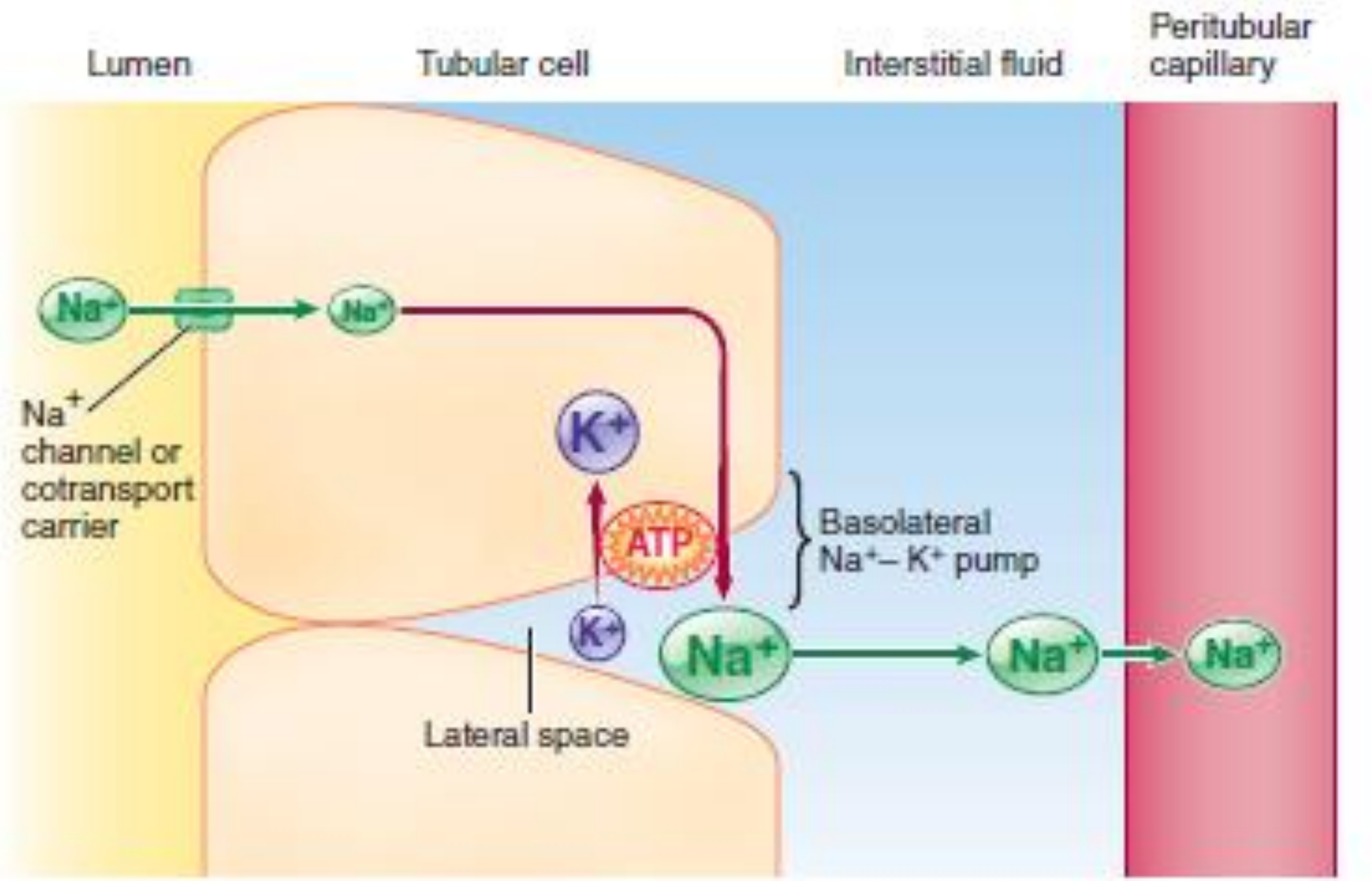


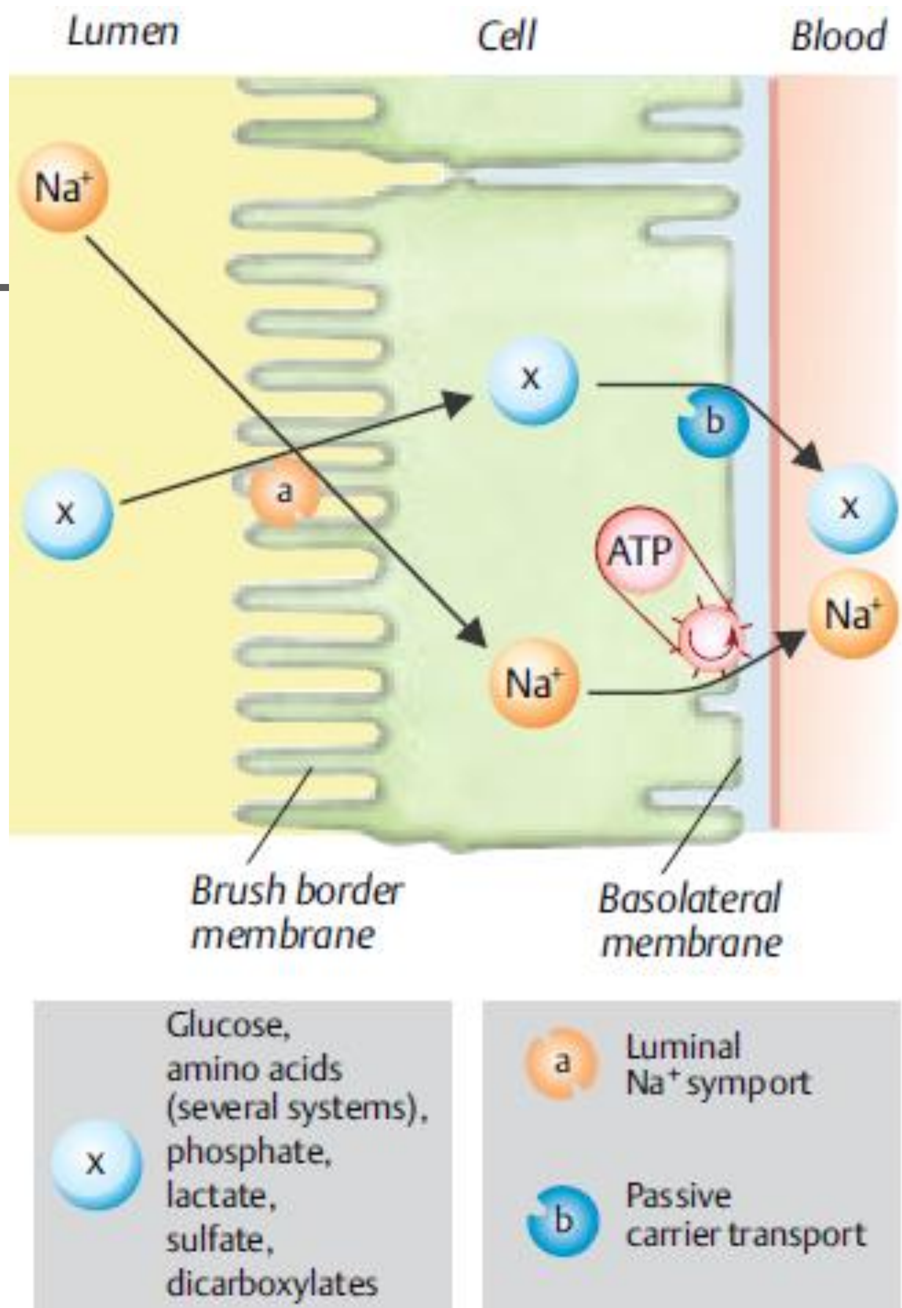
Proximal Tubular Reabsorption

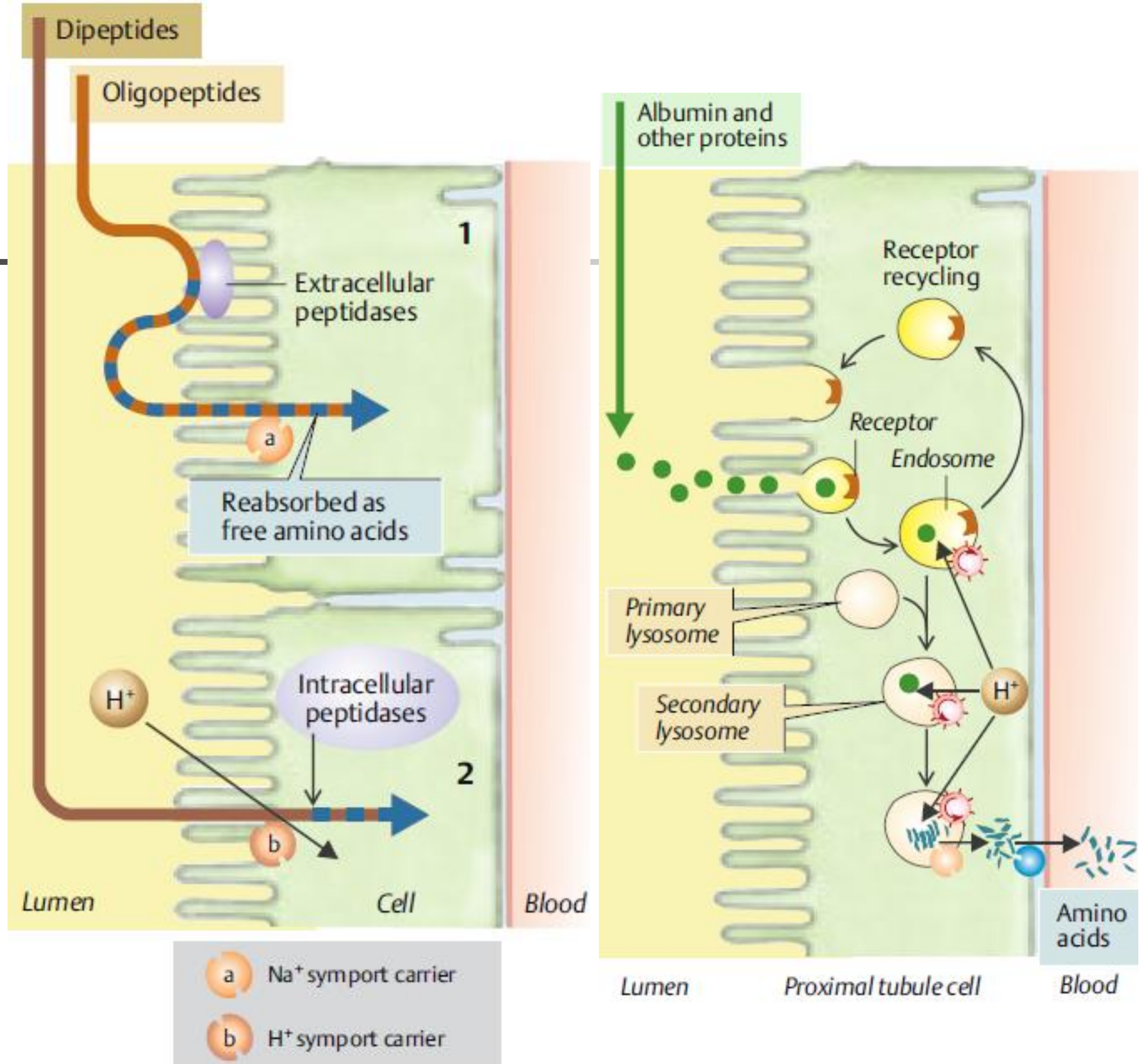
- Reabsorption of 65% of filtered load (Na & water)
- Special cellular arrangement
- Large no of mitochondria
- Extensive brush-border
- Large no of carrier proteins for co-transport & counter-transport of Na
- Difference b/w reab. of Na in 1st & 2nd part of PT



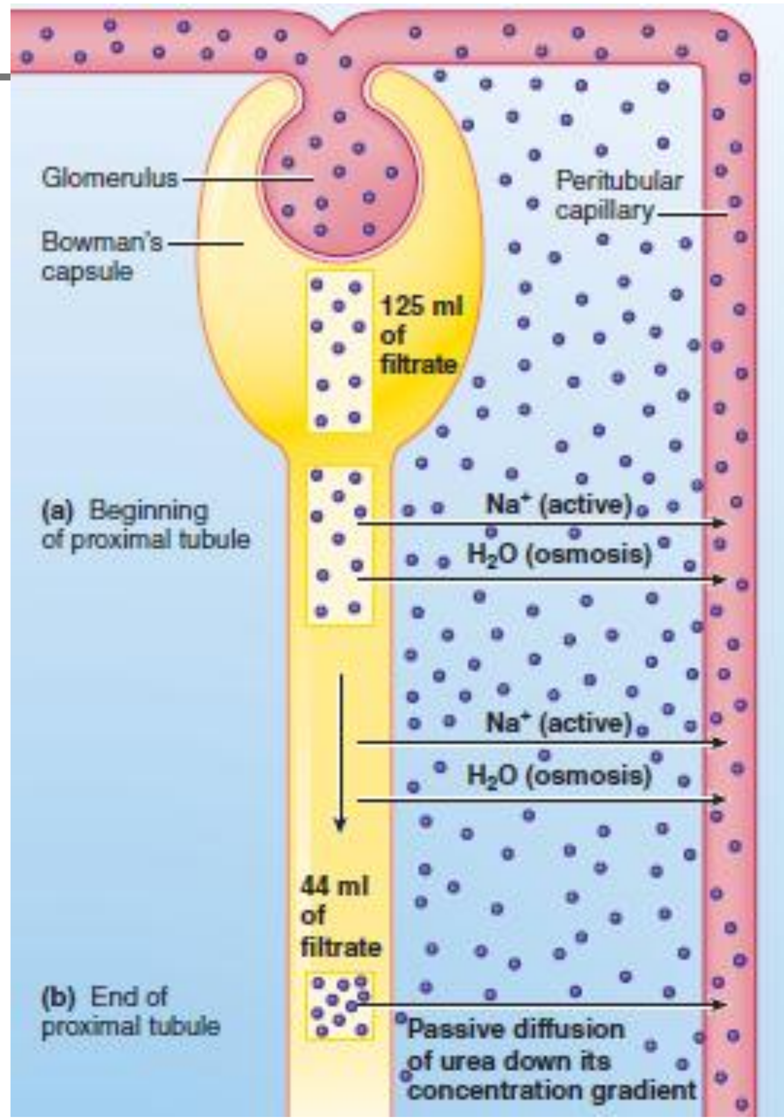
Sodium reabsorption



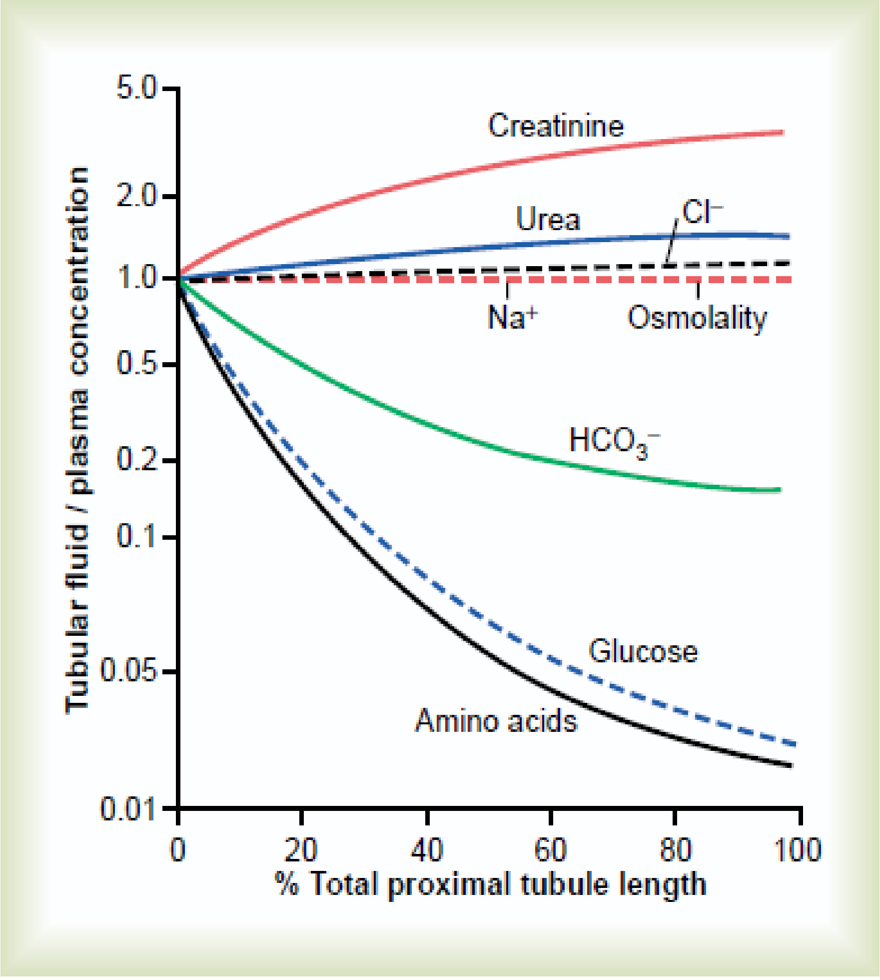

Lumen
Cell
Blood
Na+
x
a
x
b
x
ATP
Na+
Na+
Brush border membrane
Basolateral membrane
x
Glucose, amino acids (several systems), phosphate, lactate, sulfate, dicarboxylates
a
Luminal Na+ symport
b
Passive carrier transport


Dipeptides
Oligopeptides
1
Extracellular peptidases
a
Reabsorbed as free amino acids
H+
Intracellular peptidases
2
b
Lumen
Cell
Blood
a Na+ symport carrier
b H+ symport carrier
Albumin and other proteins
Receptor recycling
Receptor
Endosome
Primary lysosome
Secondary lysosome
H+
Amino acids
Lumen
Proximal tubule cell
Blood

Passive reabsorption of urea at the end of the proximal tubule



Concentration of solutes along PT



Secretion of organic acid & Bases

- Secretion of Bile salts, oxalate, urate & catecholamines
- Drugs & Toxins
- Rapid clearance of drugs may be a problem in maintaining adequate therapeutic levels
- PAH is also rapidly secreted by PT

Loop of Henle

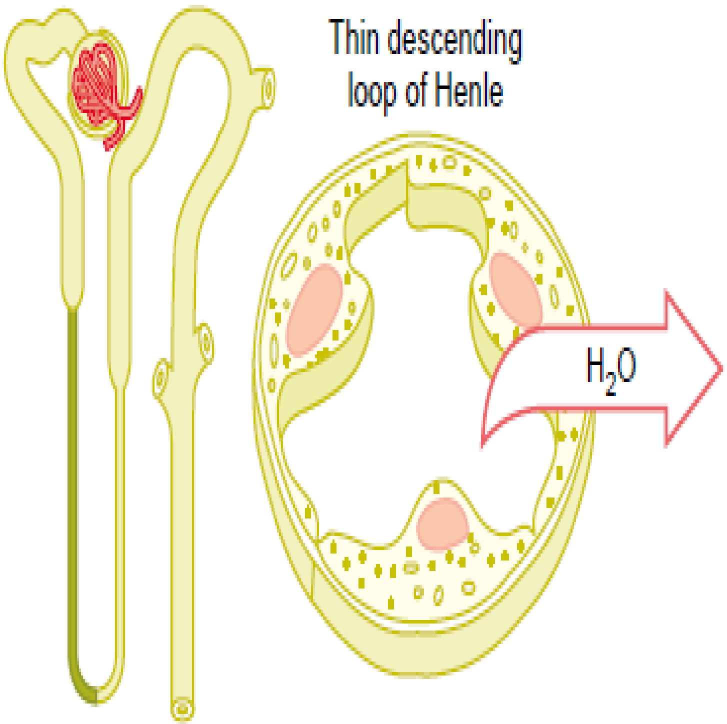
- Has three segments
  - Thin Descending segment
  - Thin Ascending segment
  - Thick Ascending segment

Thin Descending segment

- 20% of filtered load of water is reabsorbed
- Thin membrane
- Permeable to water, urea & Na

Thin Ascending segment

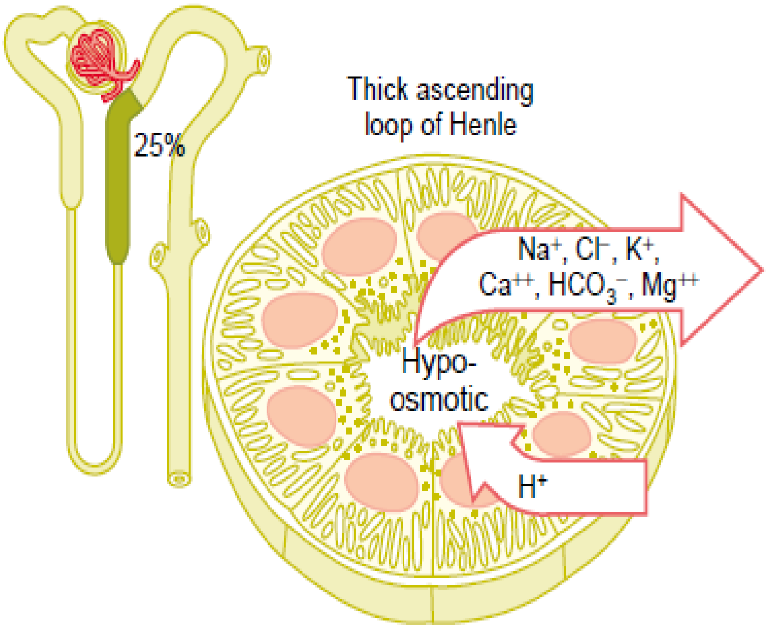
- Impermeable to water & very low permeability for solutes



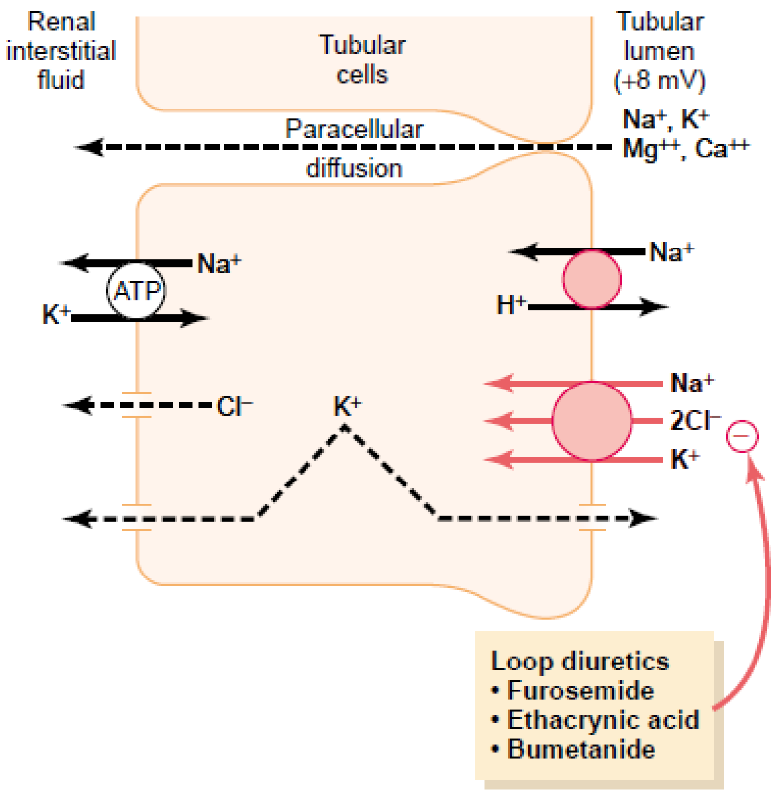
Thick Ascending segment

- Reab of 25% of filtered load of Na, Cl, K
- Impermeable to water
- Thick, metabolically active cells
- Na-K ATPase Pump
- **1-Na, 2-Cl, 1-K**

  Co- Transporter
- Site of action for Loop Diuretics (Frusemide, Bumetanide, Ethacrynic acid)

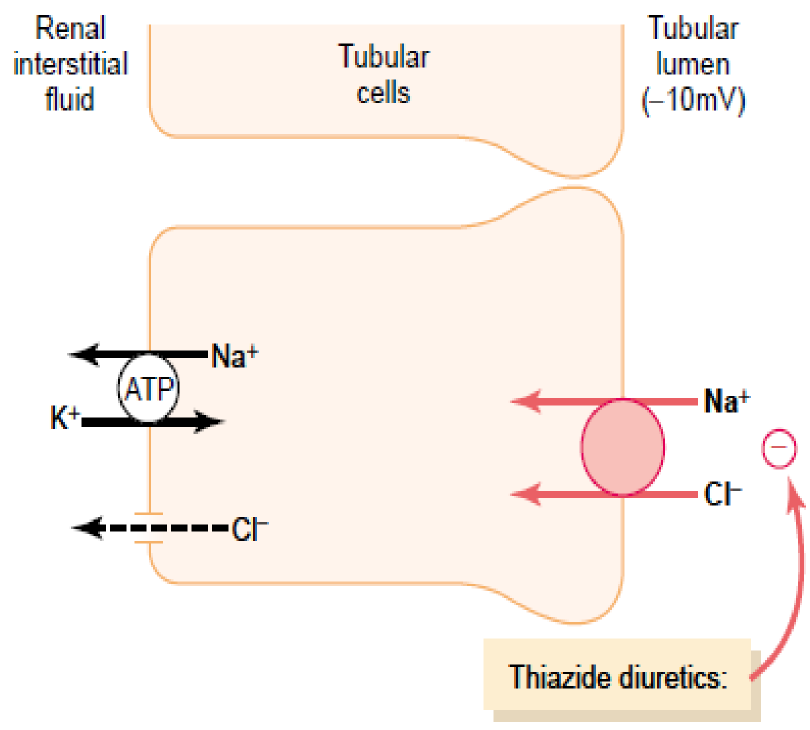


- Reabsorption of ions through paracellular pathway due to increased no of +ve charges
- Counter-transport of Na-H
- Due to reabsorption of large no of solutes the tubular fluid becomes dilute in the ascending segment



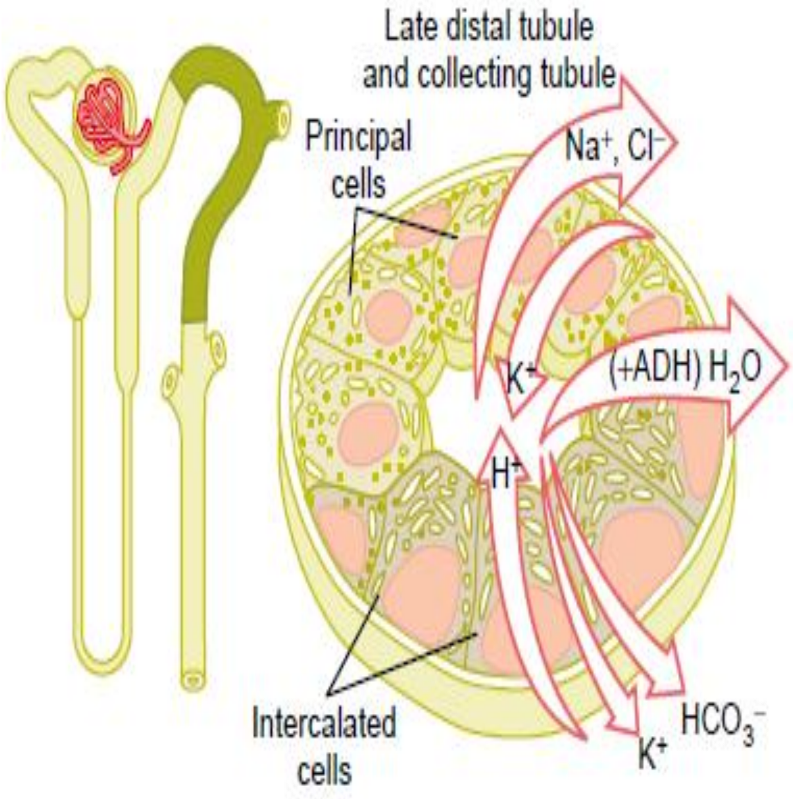
Distal Tubule

- Early part of DT has same reabsorptive properties as Thick segment
- Impermeable to water
- Reab of 5% of filtered load of Na & Cl
- **Na-Cl Co-Transport**
- Site of action for thiazide diuretics



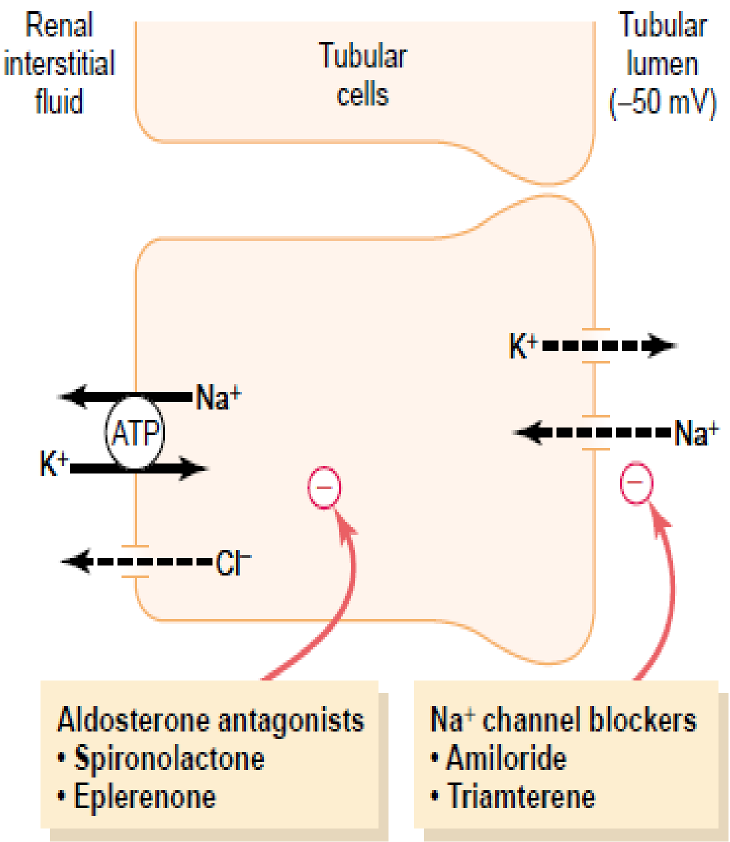
Late Distal Tubule & Cortical Collecting Ducts

- Similar cellular anatomy & functions
- Two specialized types of cells
    - Principal Cells
    - Intercalated Cells



Principal Cells

- Reabsorb Na & secrete K ions
- Site of action for K-sparing diuretics



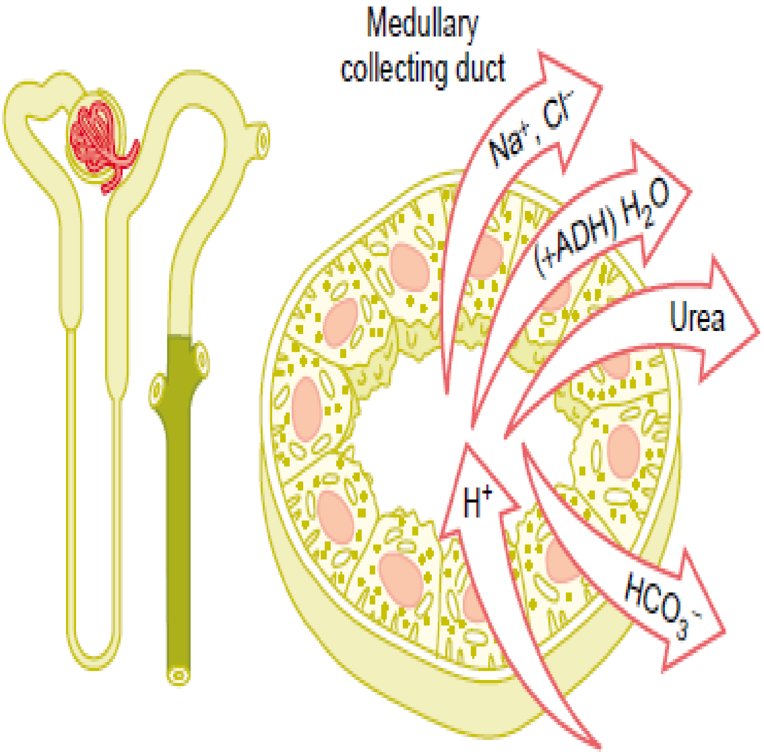
Intercalated Cells

- Reabsorb K & secrete H ions
- Carbonic Anhydrase

- Summary:
  - Reabsorption of Na & secretion of K ions in Late DT & CCD is Aldosterone dependant
  - Water Reabsorption is ADH dependant
  - Impermeable to Urea

Medullary Collecting Ducts

- Reabsorption of less than 10% of filtered of Na & water
- Cuboidal cells, smooth surface, very few mitochondria
- Permeability to water is controlled by ADH secretion
- High permeability for urea
- Can secrete H ions

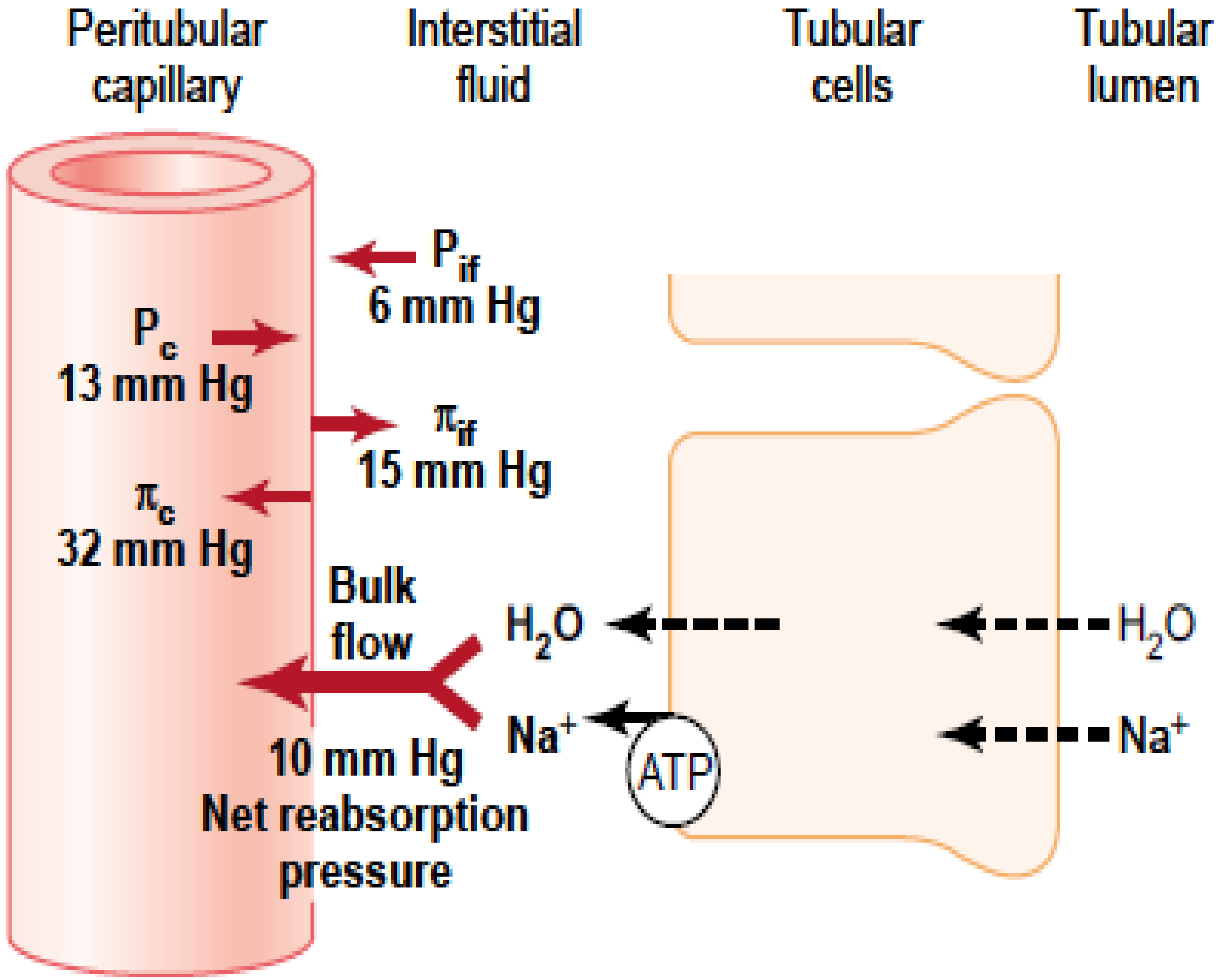


Regulation of Tubular Reabsorption

- Intrinsic Renal Regulation
- Hormonal Regulation
- Nervous Regulation

PTC & Renal I.F. Physical Forces

- Reabsorption = K_f × Net reabsorptive force
- Net absorptive force is the sum of:
  - Peritubular capillary hydrostatic pressure (P_c)
  - Peritubular capillary colloid osmotic pressure (□ $_c$)
  - Interstitial fluid hydrostatic pressure (P_{if})
  - Interstitial fluid colloid osmotic pressure (□ $_{if}$)
- Normal rate of Reabsorption : 99% of GFR or 124ml/min



Peritubular capillary
Interstitial fluid
Tubular cells
Tubular lumen
P_{if}
6 mm Hg
P_c
13 mm Hg
π_{if}
15 mm Hg
π_c
32 mm Hg
Bulk flow
H_2O
Na^+
ATP
H_2O
Na^+
10 mm Hg
Net reabsorption pressure

Regulation of forces across PTC

- PTC hydrostatic & COP directly influenced by Renal hemodynamic changes
- PTC hydrostatic pressure is regulated by
  - Arterial Pressure &
  - Afferent & Efferent arteriolar resistance
- PTC Colloid Osmotic Pressure is regulated by
  - Systemic Plasma COP
  - Filtration Fraction
- Filtration coefficient increases Reabsorption

Factors That Can Influence Peritubular Capillary Reabsorption

$\uparrow P_c \rightarrow \downarrow$ Reabsorption

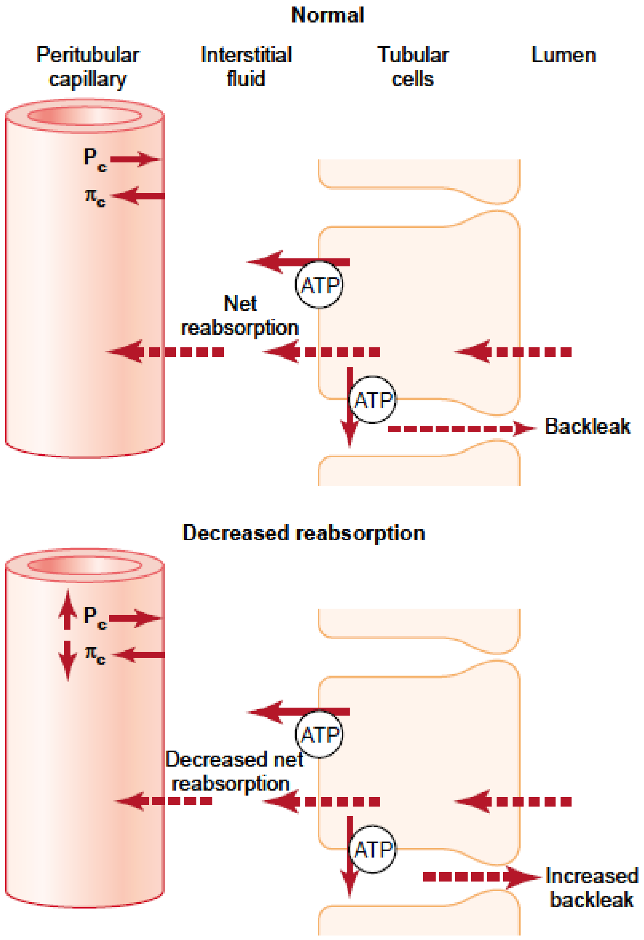
- $\downarrow R_A \rightarrow \uparrow P_c$
- $\downarrow R_E \rightarrow \uparrow P_c$
- $\uparrow$ Arterial Pressure $\rightarrow \uparrow P_c$

$\uparrow \pi_c \rightarrow \uparrow$ Reabsorption

- $\uparrow \pi_A \rightarrow \uparrow \pi_c$
- $\uparrow FF \rightarrow \uparrow \pi_c$

$\uparrow K_f \rightarrow \uparrow$ Reabsorption

Renal Interstitial hydrostatic & COP



Hormonal Regulation of reabsorption

ALDOSTERONE

- Zona glomerulosa cells of adrenal cortex
- Increases reabsorption of Na & secretion of K ions
- Site of action: Principal cells of CCT
- Mechanism: Increased Na-K ATPase activity &
  Increased Na permeability on luminal side
- Addison´s Disease: Reduced or absent secretion
- Conn´s Syndrome: Increased secretion

Angiotensin II

- Most potent Na retaining Hormone
- Increases Na & water reabsorption
- Mainly acts by three ways
  - Increases ALDOSTERONE secretion
  - Constriction of efferent arterioles
  - Stimulates Na reabsorption in PT, LOH, CT

Antidiuretic Hormone

- Realeased from Posterior Pituitary
- Site of action: DT, CT, CCT, MCD
- Specific receptors V_2 in epithelial cells
- Aquaporins --- Intracellular protein
- AQP-2, AQP-3, AQP-4

ANP

- Released from cardiac Atria
- Stimulus for release --- Increased Atrial strech due to increased plasma plasma volume or raised AP
- Inhibits reasorption of Na & water from CD

PTH

- Most powerful Ca regulating Hormone
- Increases tubular reabsorption of Ca from DT & LOH
- Also inhibits Phosphorus reabsorption from PT & increase s reabsorption of Mg

Sympathetic Nervous System

- Decreases Na & water excretion by constricting renal arterioles
- Also increases Na reabsorption from PT, Ascending thick segment of LOH, Distal tubules
- Increases renin & Angiotensin release

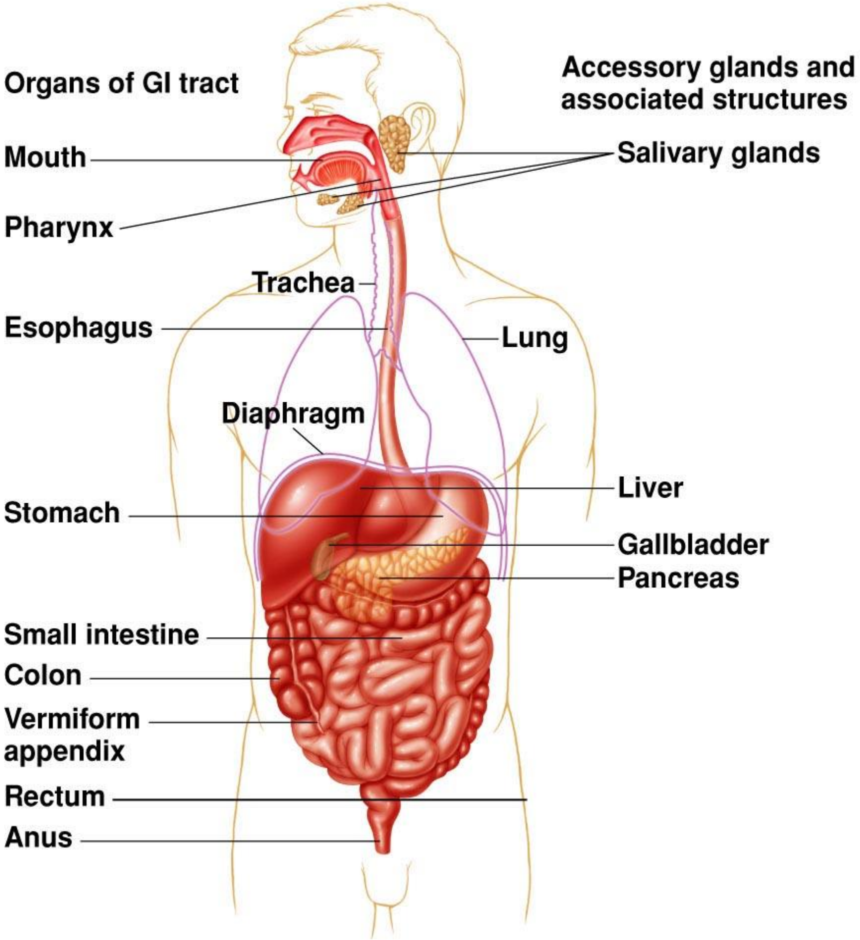
Hormone	Site of Action	Effects
Aldosterone	Collecting tubule and duct	↑ NaCl, H_2O reabsorption, ↑ K^+ secretion, ↑ H^+ secretion
Angiotensin II	Proximal tubule, thick ascending loop of Henle/distal tubule, collecting tubule	↑ NaCl, H_2O reabsorption, ↑ H^+ secretion
Antidiuretic hormone	Distal tubule/collecting tubule and duct	↑ H_2O reabsorption
Atrial natriuretic peptide	Distal tubule/collecting tubule and duct	↓ NaCl reabsorption
Parathyroid hormone	Proximal tubule, thick ascending loop of Henle/distal tubule	↓ PO_4^- reabsorption, ↑ Ca^{++} reabsorption

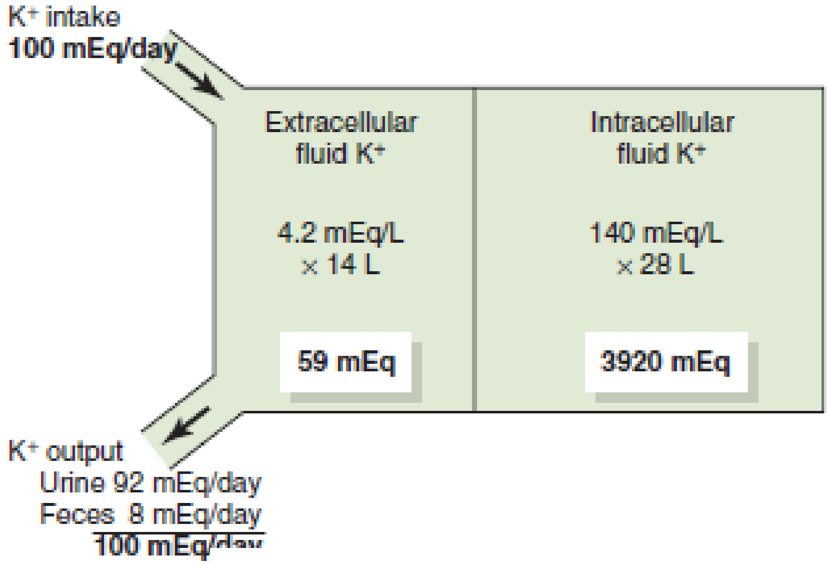
Renal Physiology; Secretion

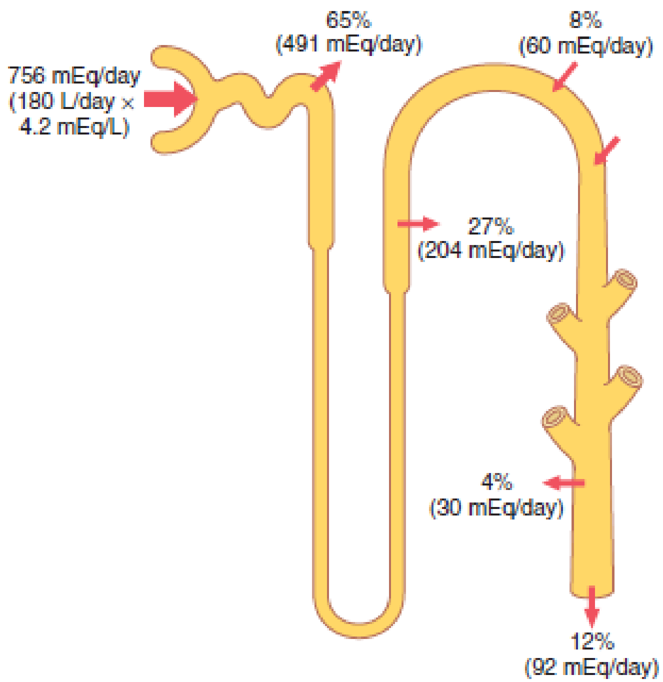
Dr.Shahid Javed
MBBS; PhD

Gastrointestinal system

- Overview
- Digestion of nutrients
- Absorption of nutrients and water
- Principles of GI regulation
- GI secretion and regulation
- GI motility and regulation
- Disorders of GIT

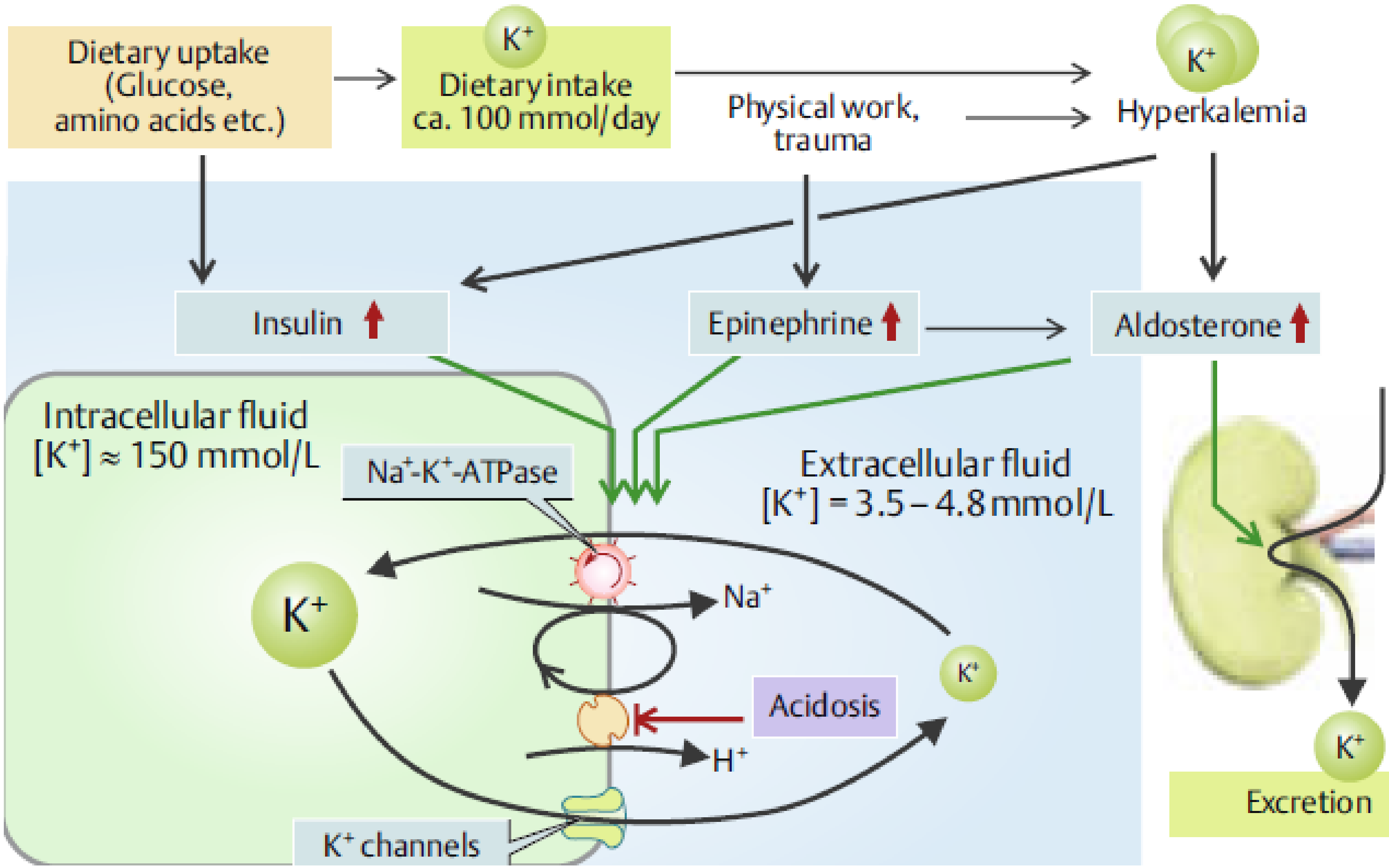




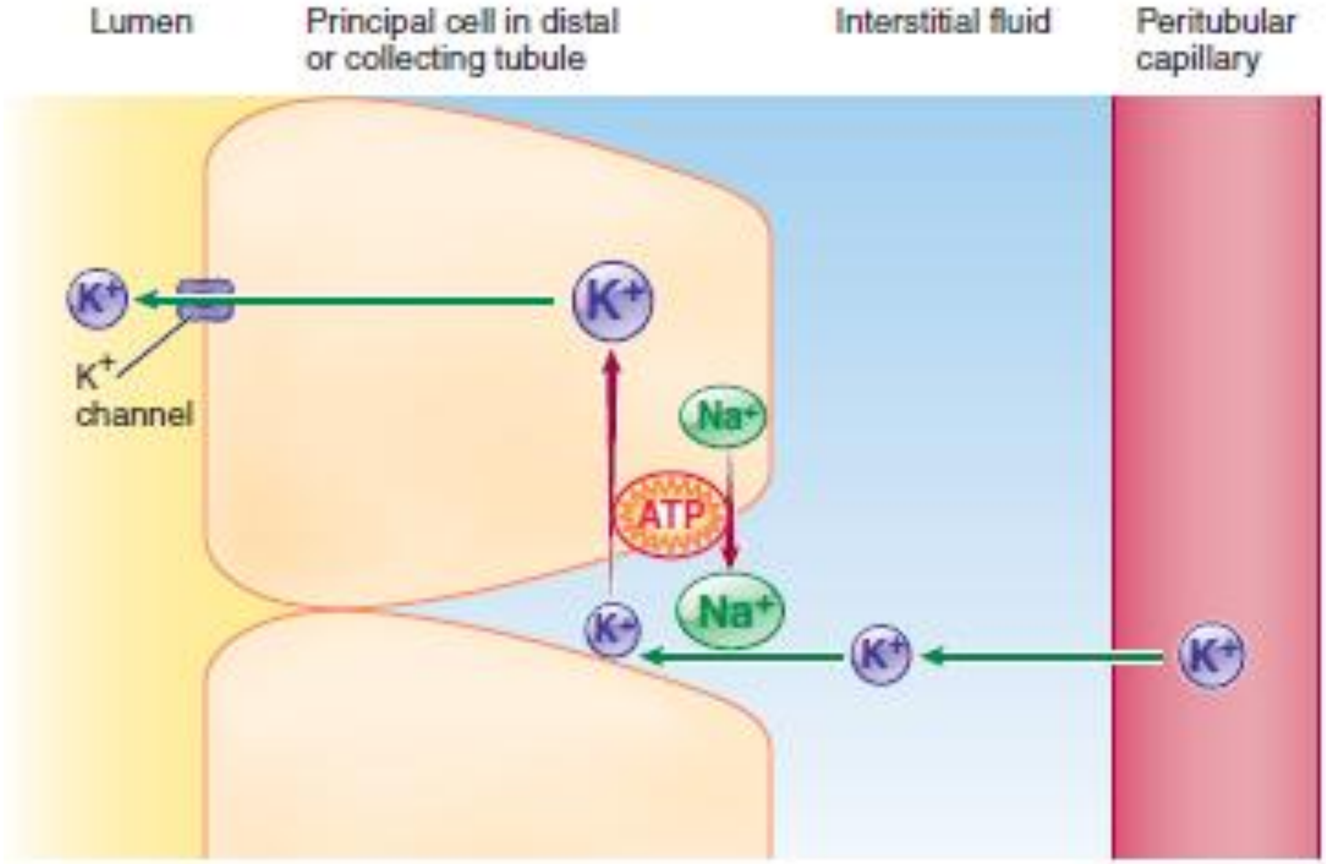


Factors That Shift K^+ Into Cells (Decrease Extracellular $[K^+]$)	Factors That Shift K^+ Out of Cells (Increase Extracellular $[K^+]$)
Insulin	Insulin deficiency (diabetes mellitus)
Aldosterone	Aldosterone deficiency (Addison's disease)
β-adrenergic stimulation	β-adrenergic blockade
Alkalosis	Acidosis
	Cell lysis
	Strenuous exercise
	Increased extracellular fluid osmolarity

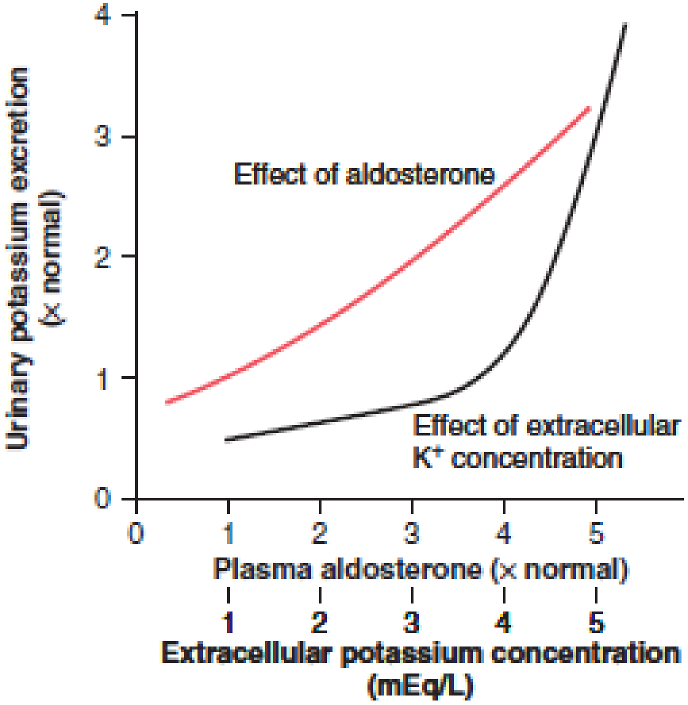
Regulation of extracellular K

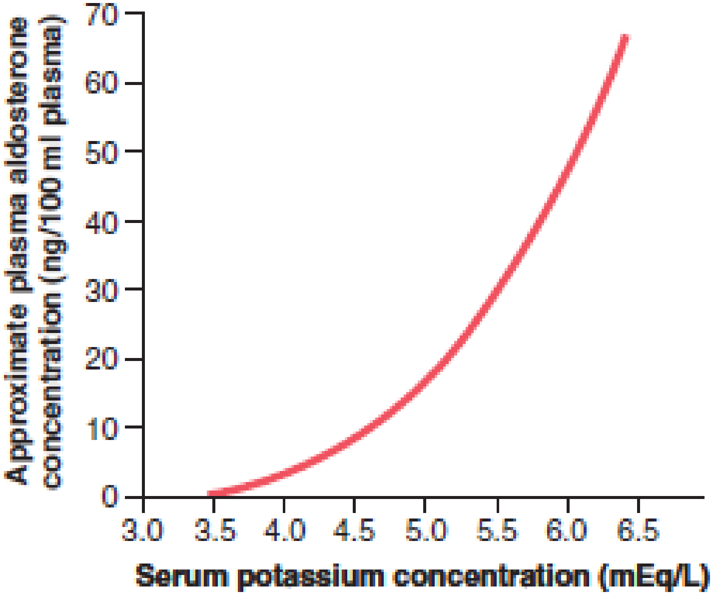


Potassium Secretion

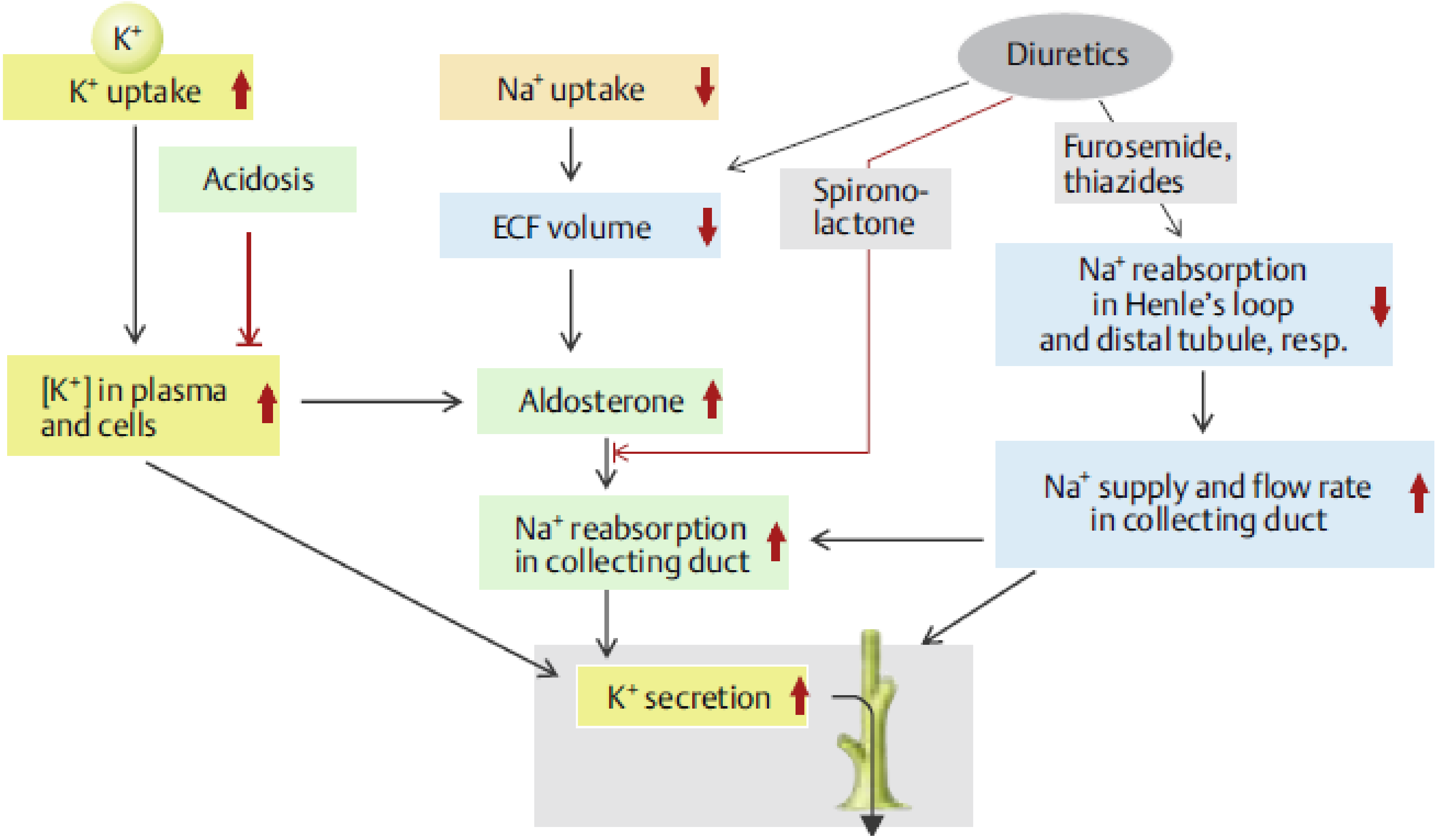


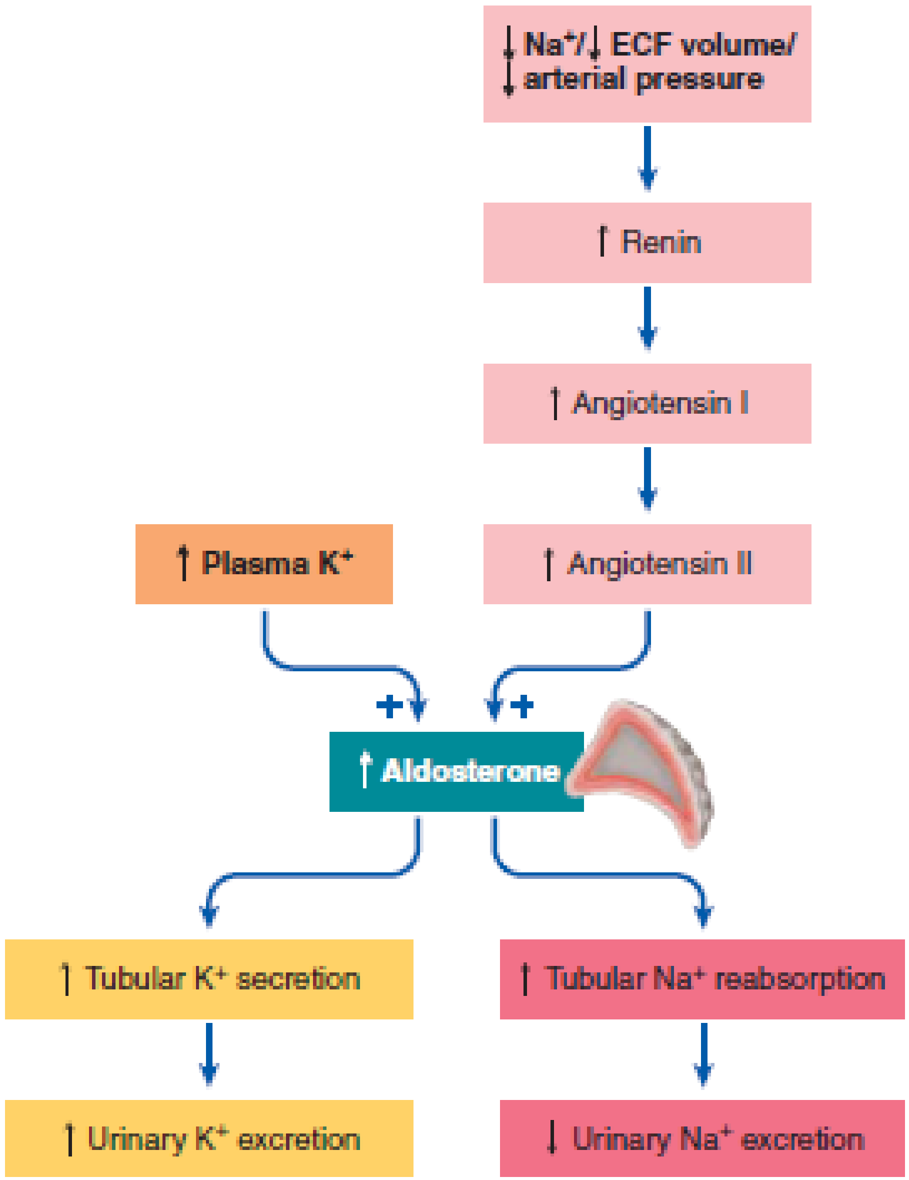
Potassium secretion is controlled by Aldosterone

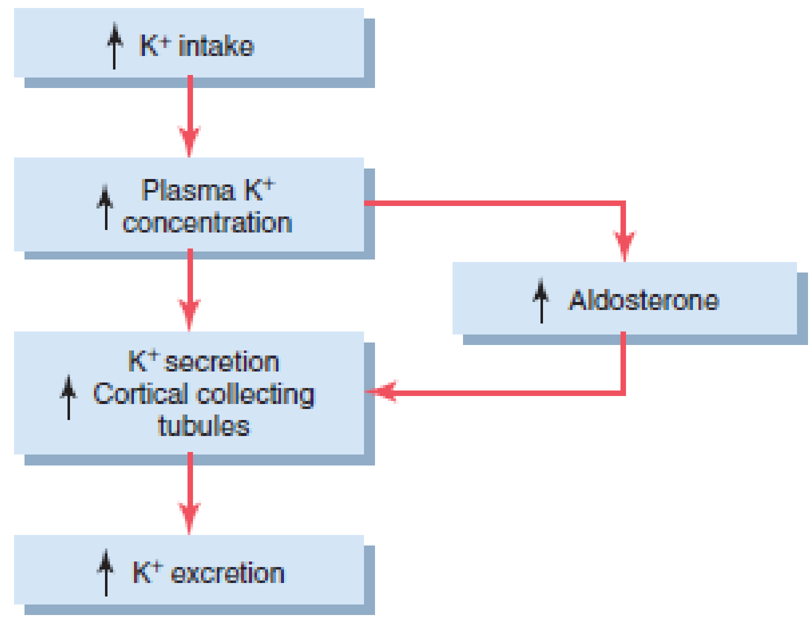




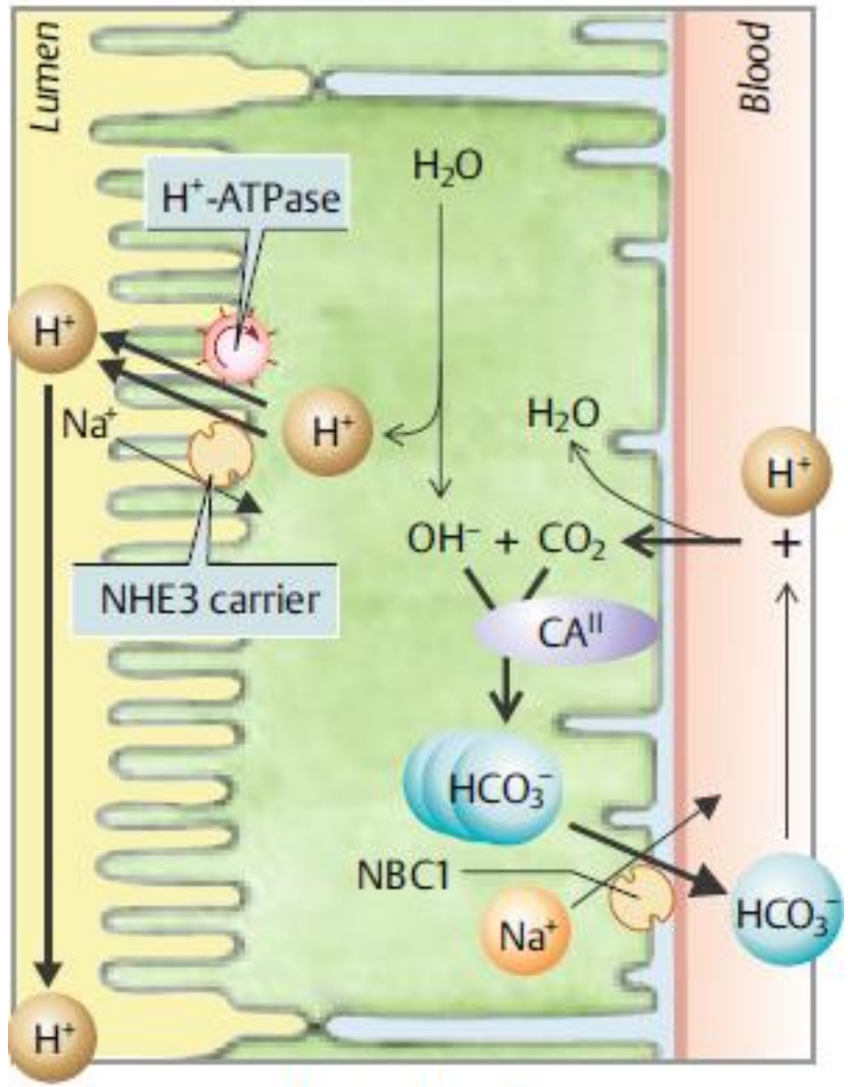
Factors affecting K secretion



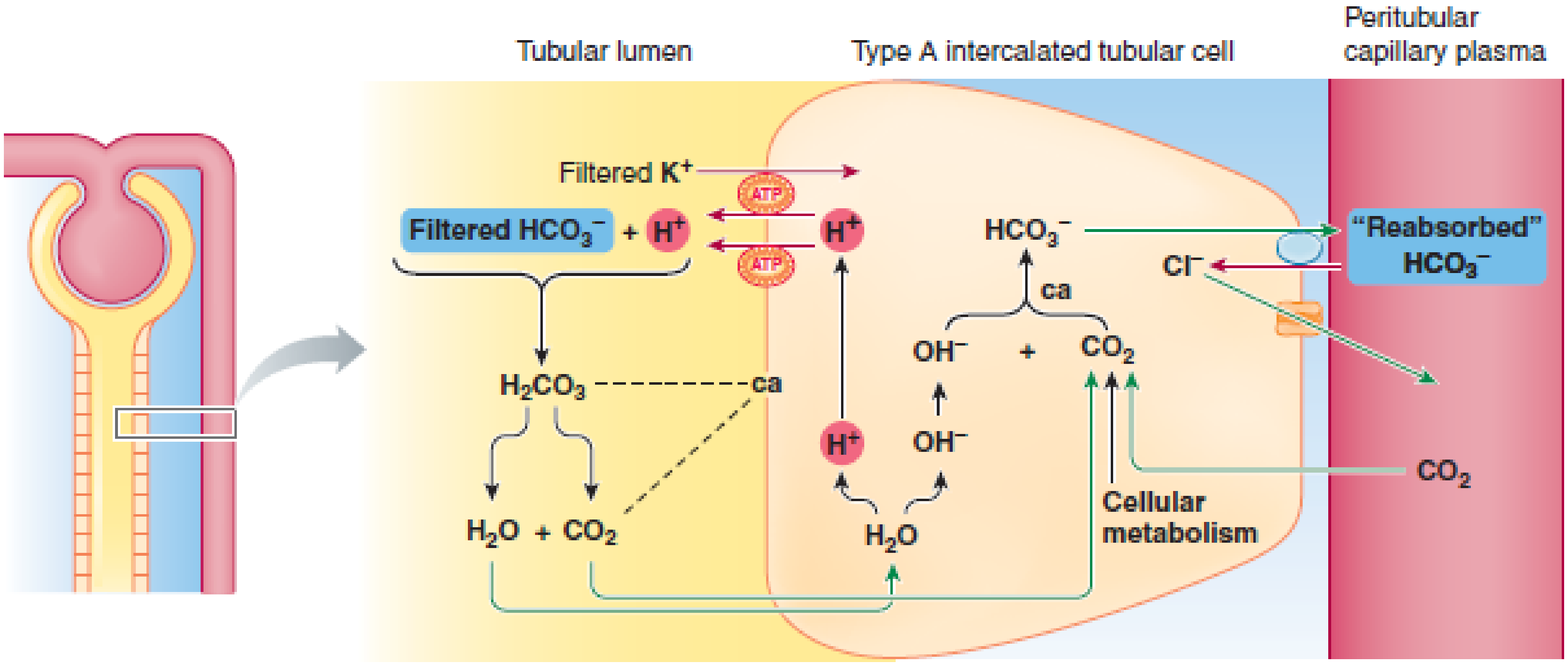

↓ Na+/↓ ECF volume/
↓ arterial pressure
↑ Renin
↑ Angiotensin I
↑ Angiotensin II
↑ Plasma K+
+
+
↑ Aldosterone
↑ Tubular K+ secretion
↑ Tubular Na+ reabsorption
↑ Urinary K+ excretion
↓ Urinary Na+ excretion


↑ K+ intake
↑ Plasma K+
concentration
↑ Aldosterone
↑ K+ secretion
Cortical collecting
tubules
↑ K+ excretion

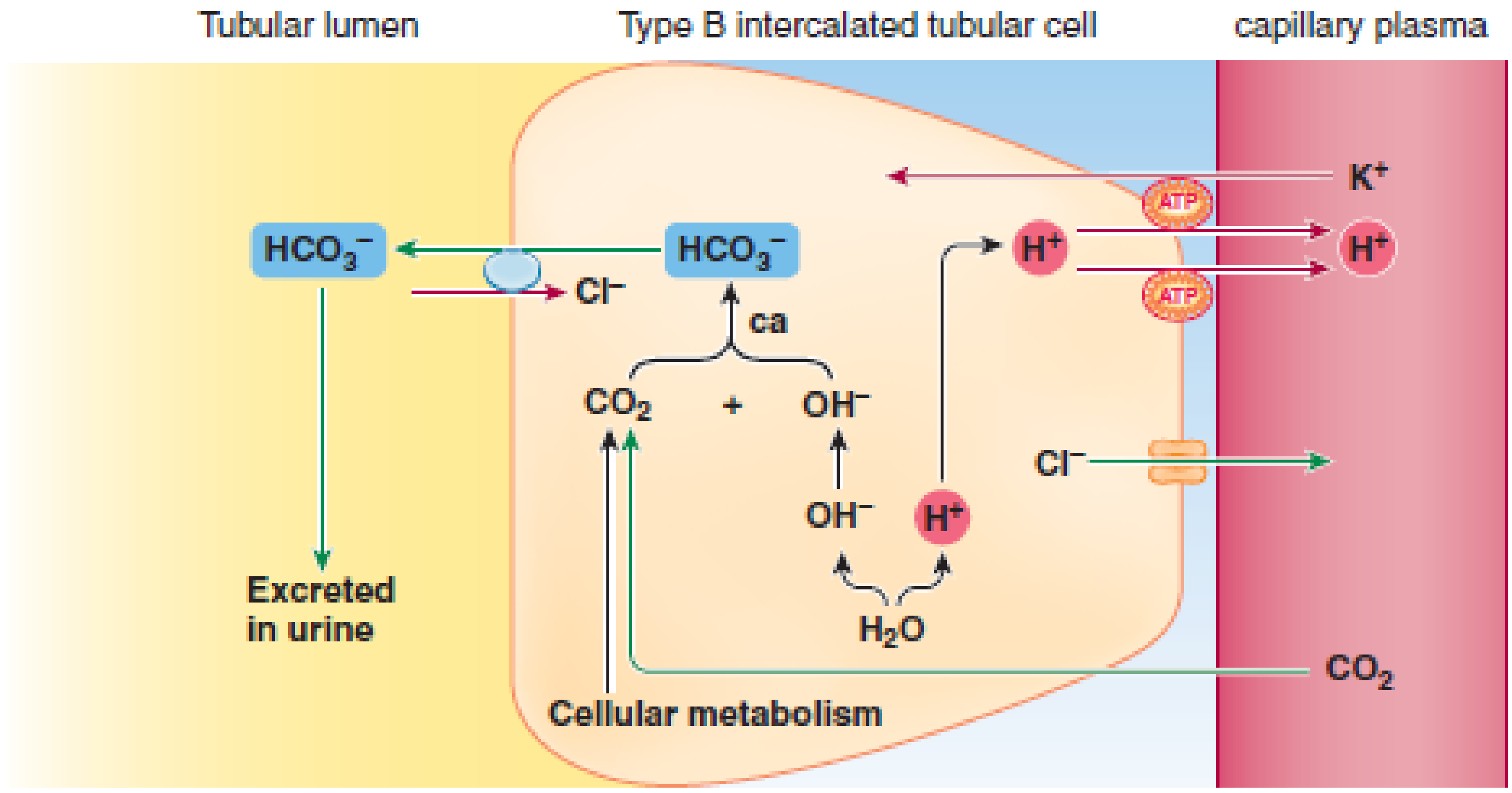
Hydrogen ion secretion in Proximal tubular cells



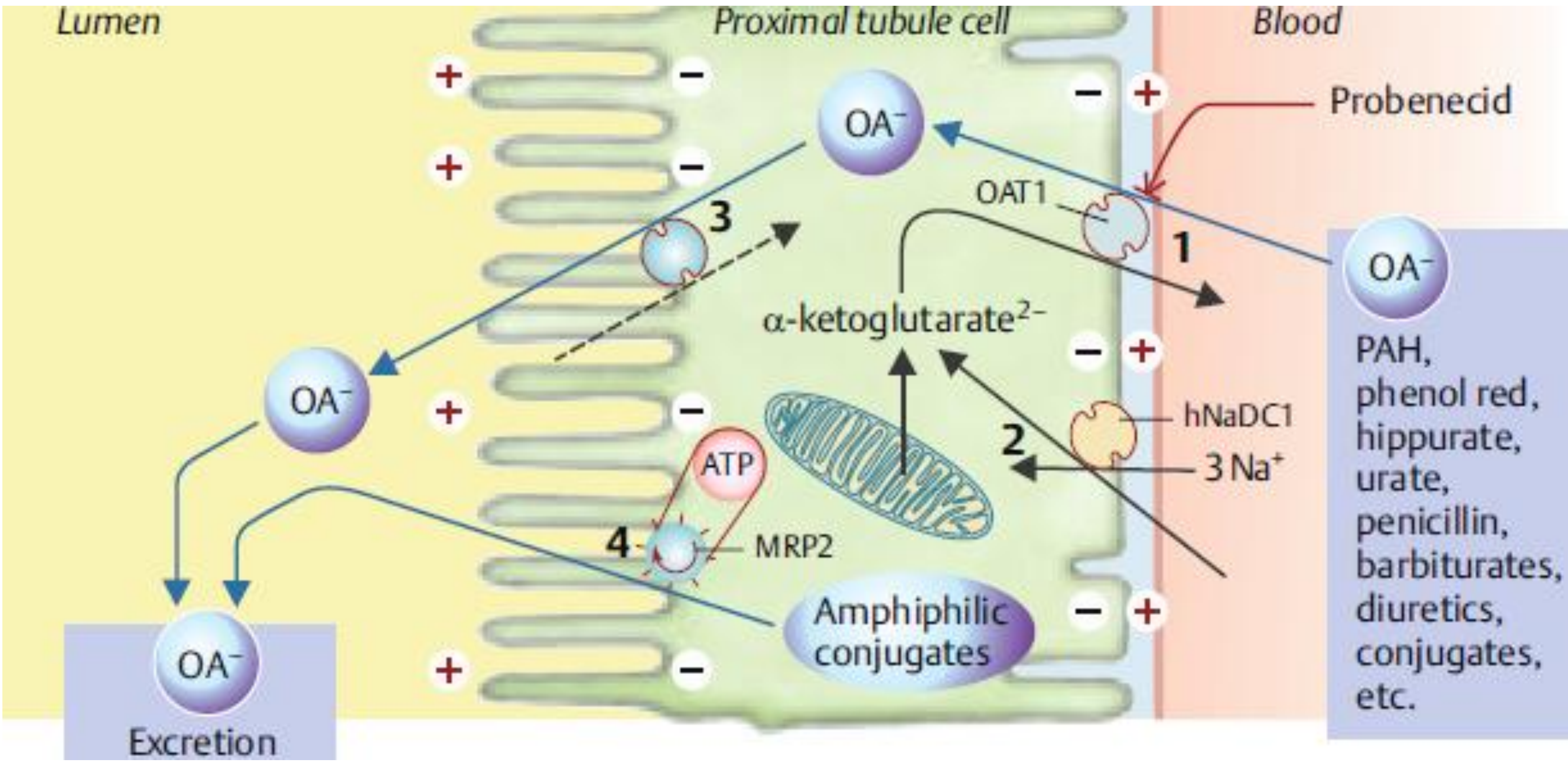
Hydrogen ion secretion in type A intercalated tubular cells



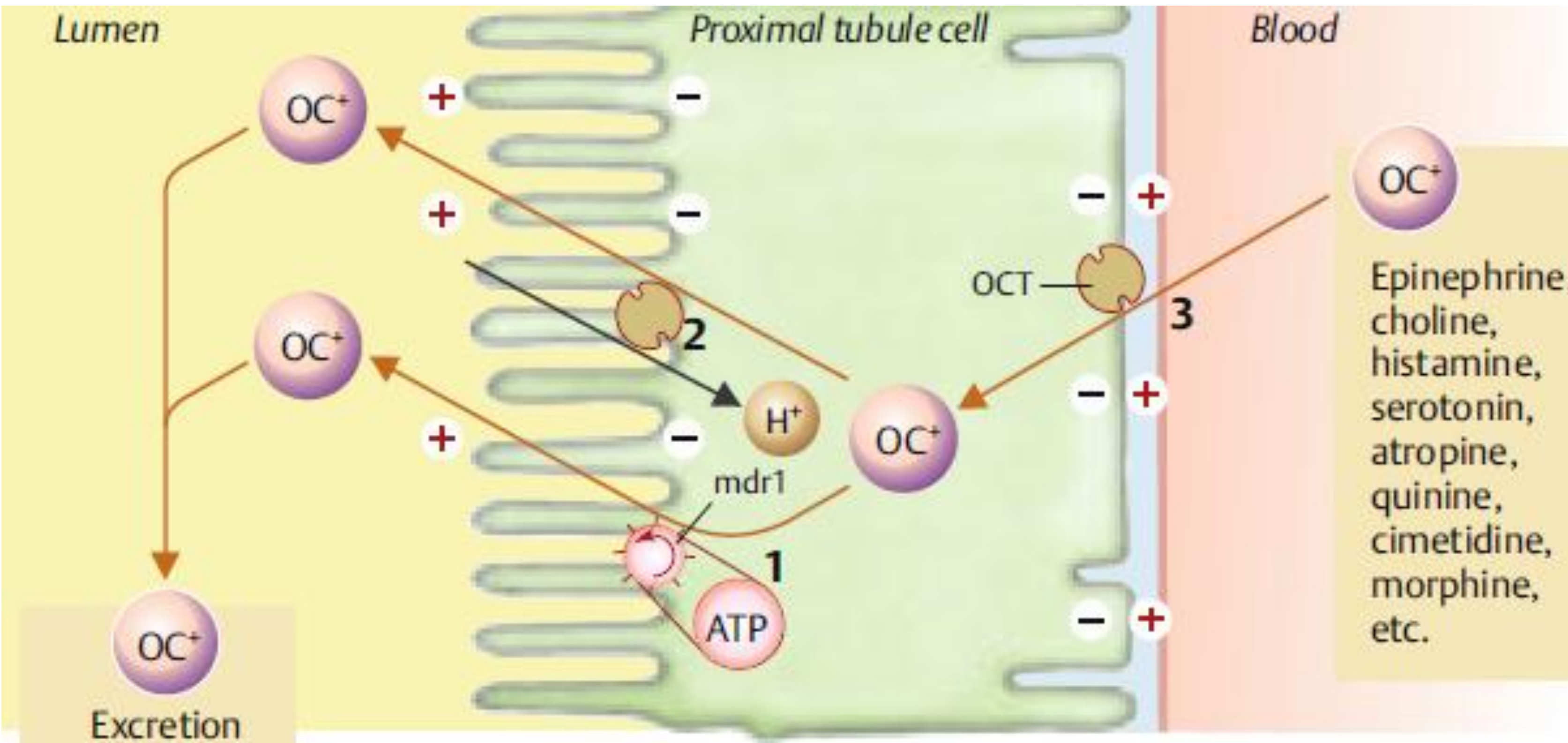
Hydrogen ion secretion in type B intercalated tubular cells



Secretion of organic anions



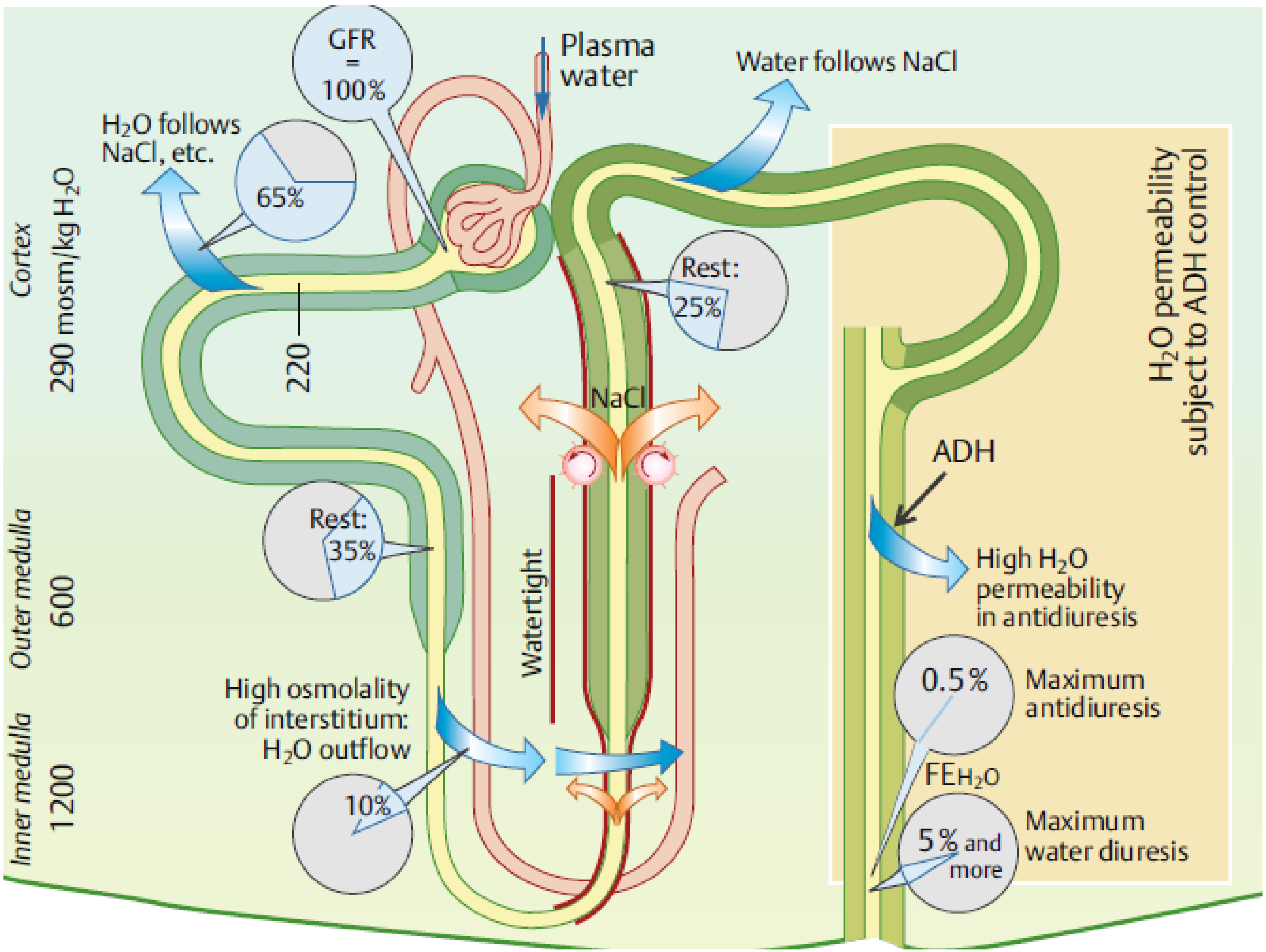
Secretion of organic cations



Ca, Mg, Phosphate Transport

Urine Excretion

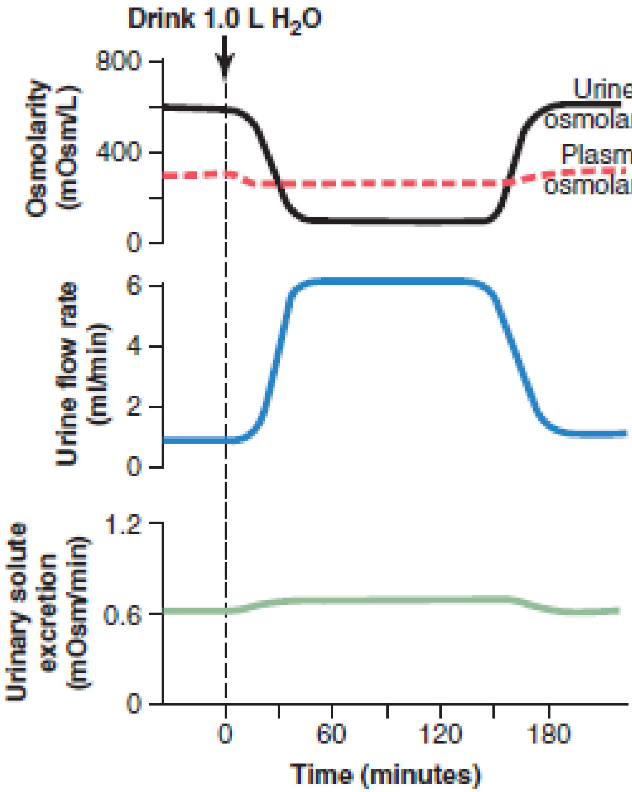
Water Reabsorption and Excretion



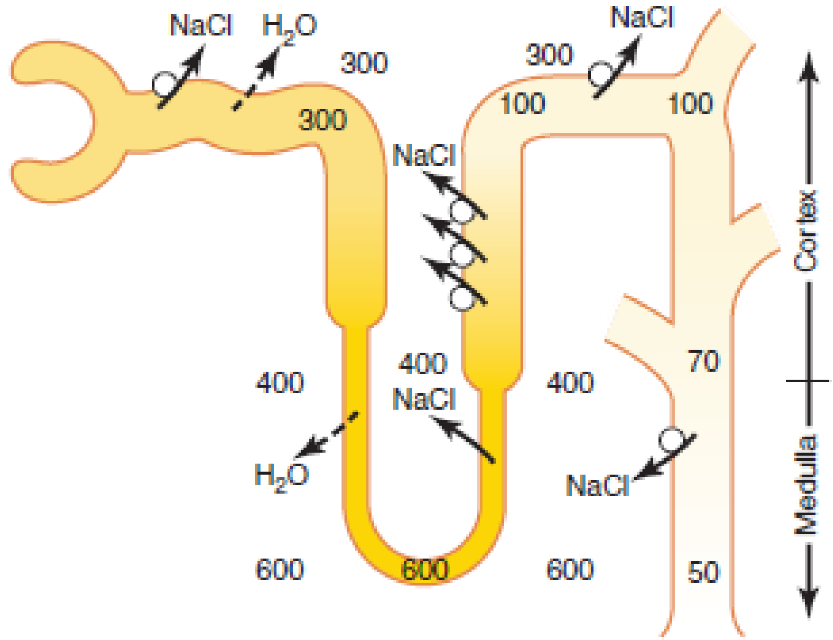
KIDNEYS EXCRETE EXCESS WATER BY FORMING DILUTE URINE

- Variation in renal excretion rate of water
- Urine osmolarity varies between 50-1200 mOsm/liter
- Regulation of water excretion independent of solute loss in urine

- **ROLE OF ANTIDIURETIC HORMONE IN CONTROLLING URINE CONCENTRATION**



Drink 1.0 L H_2O
800
400
0
Osmolarity (mOsm/L)
Urine osmolarity
Plasma osmolarity
6
4
2
0
Urine flow rate (ml/min)
1.2
0.6
0
Urinary solute excretion (mOsm/min)
0
60
120
180
Time (minutes)

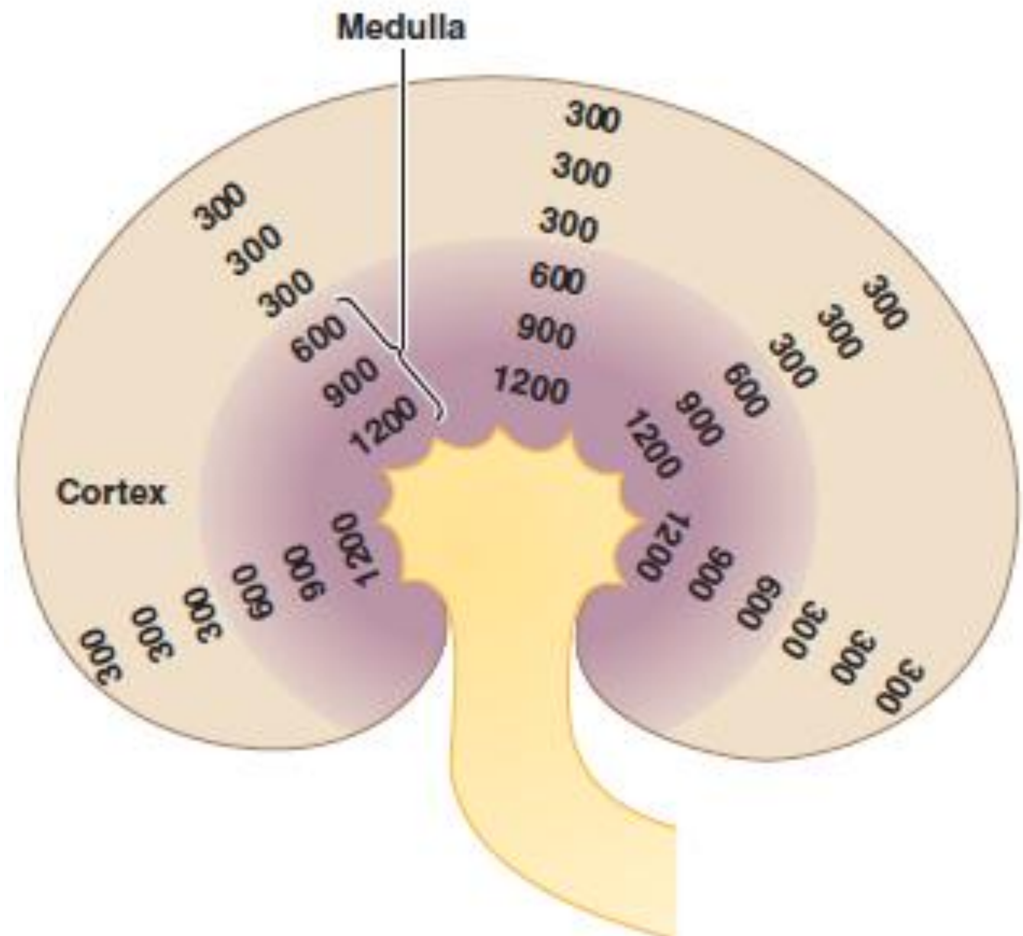


NaCl
H_2O
300
300
NaCl
300
100
100
NaCl
400
400
400
NaCl
70
H_2O
NaCl
600
600
600
50
Cortex
Medulla

Formation of concentrated urine

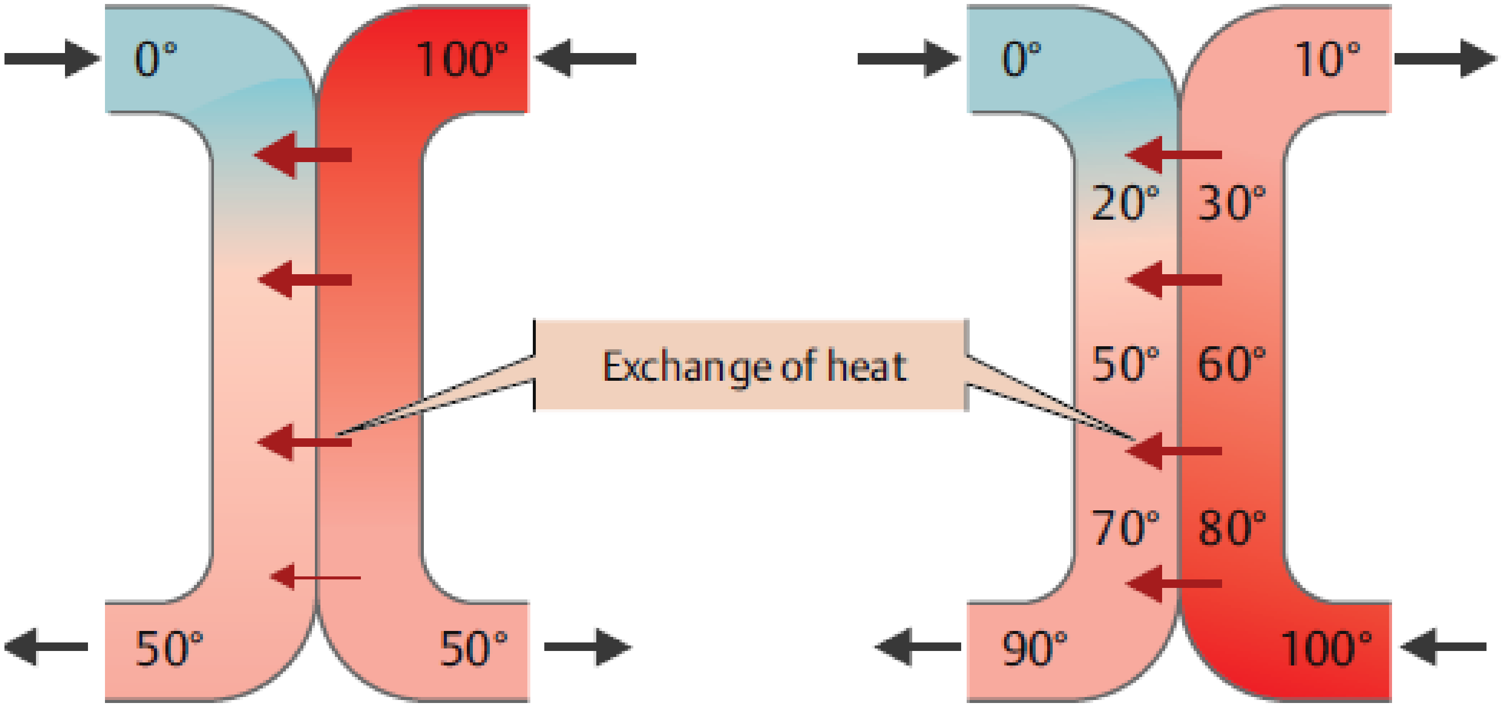
- Two Basic requirements:
  - High ADH Levels &
  - High osmolarity of renal medullary interstitium
- COUNTER CURRENT MECHANISM
  - Counter Current Multiplier
  - Counter Current Exchanger
- ROLE OF VASA RECTA

Vertical osmotic gradient in medulla



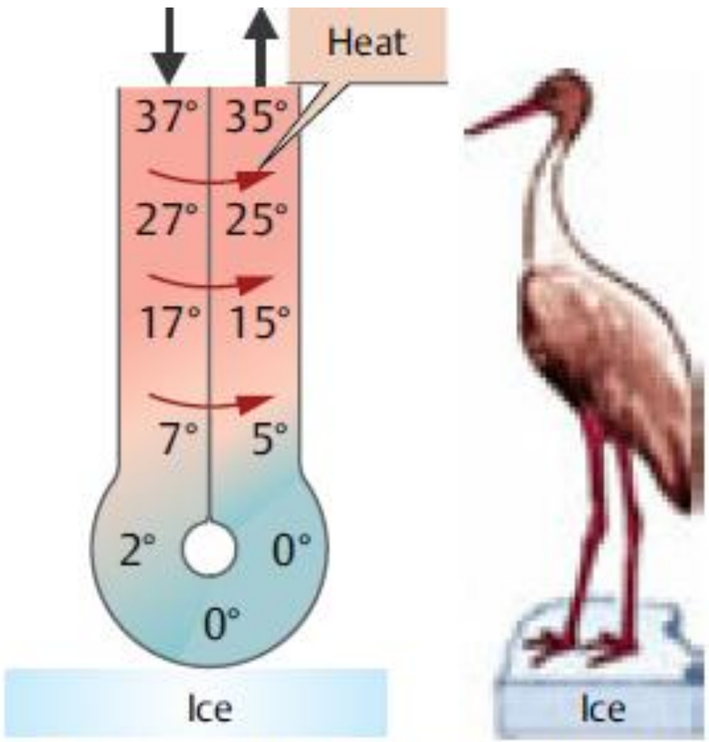
COUNTERCURRENT MECHANISM

- Osmolarity of interstitial fluid
- Osmolarity of renal medullary interstitium is very high --- 1200-1400 mOsm/L
- Factors responsible:
  - Active transport of Na & co-transport of other ions from ascending thick segment of LOH
  - Active transport of ions from CD
  - Facilitated diffusion of urea from inner MCD
  - Diffusion of small amount of water from MT

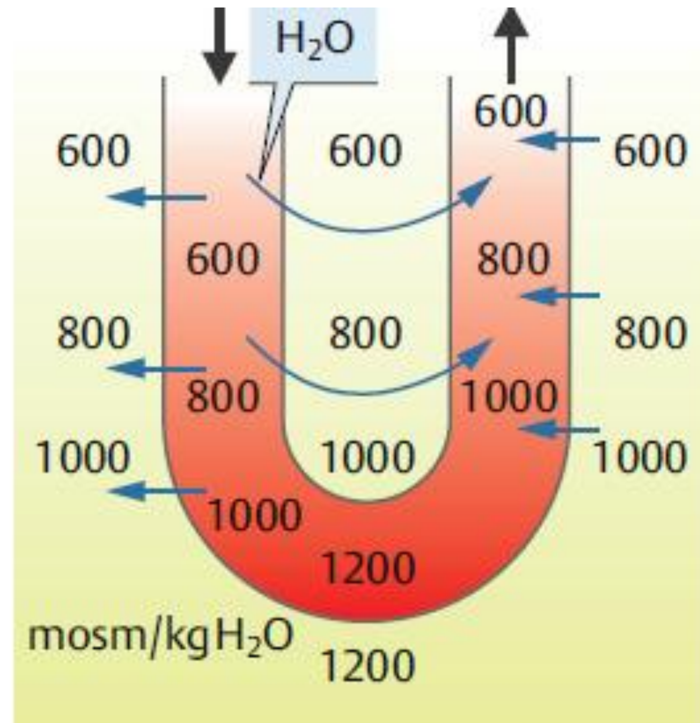


1 Simple exchange system

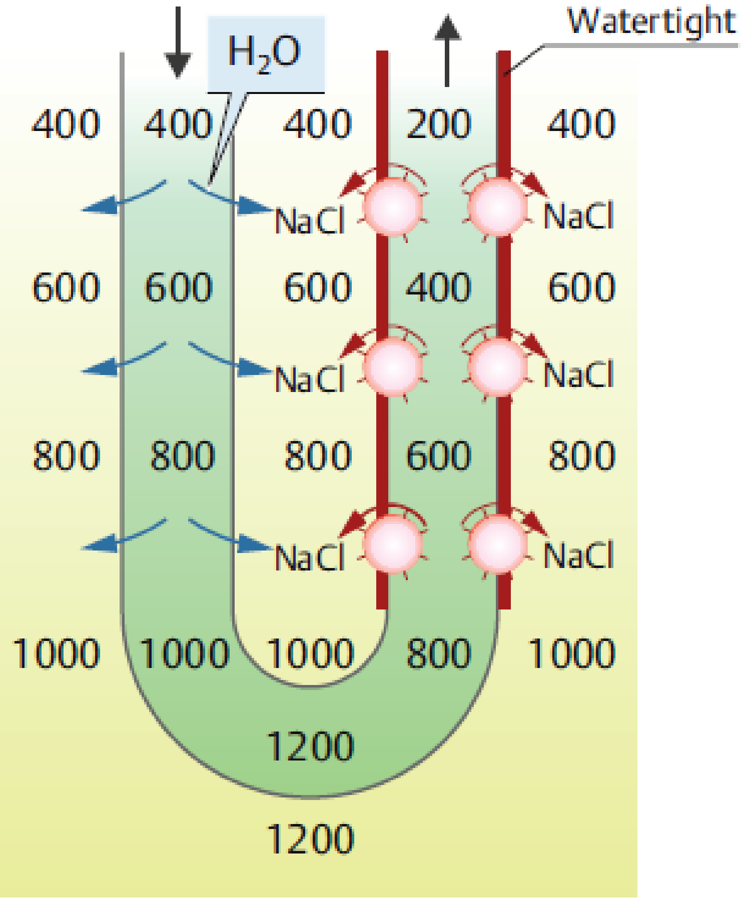
2 Countercurrent exchange



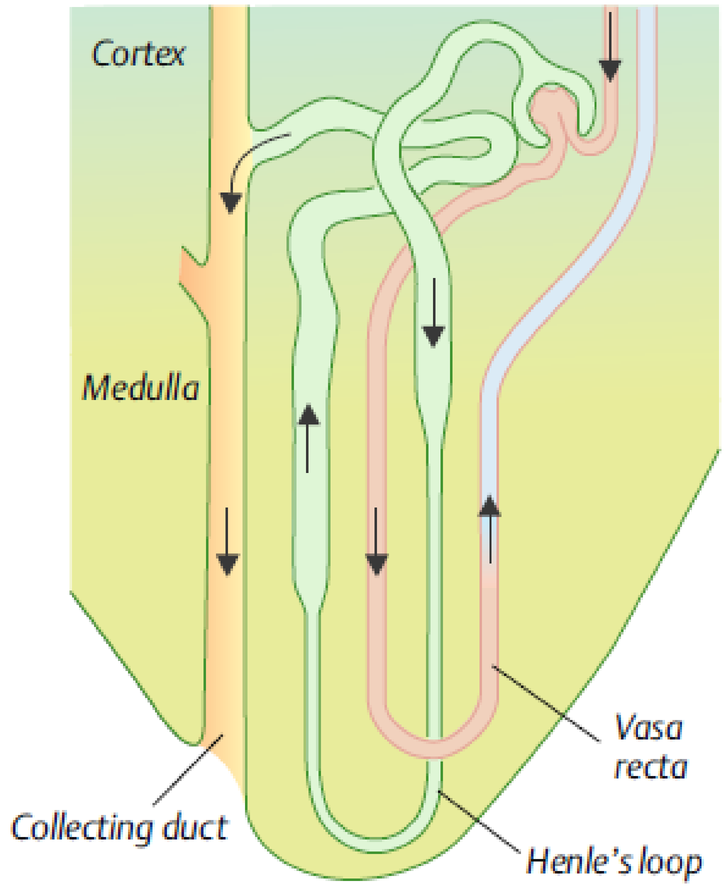
3 Countercurrent exchange (heat) in loop



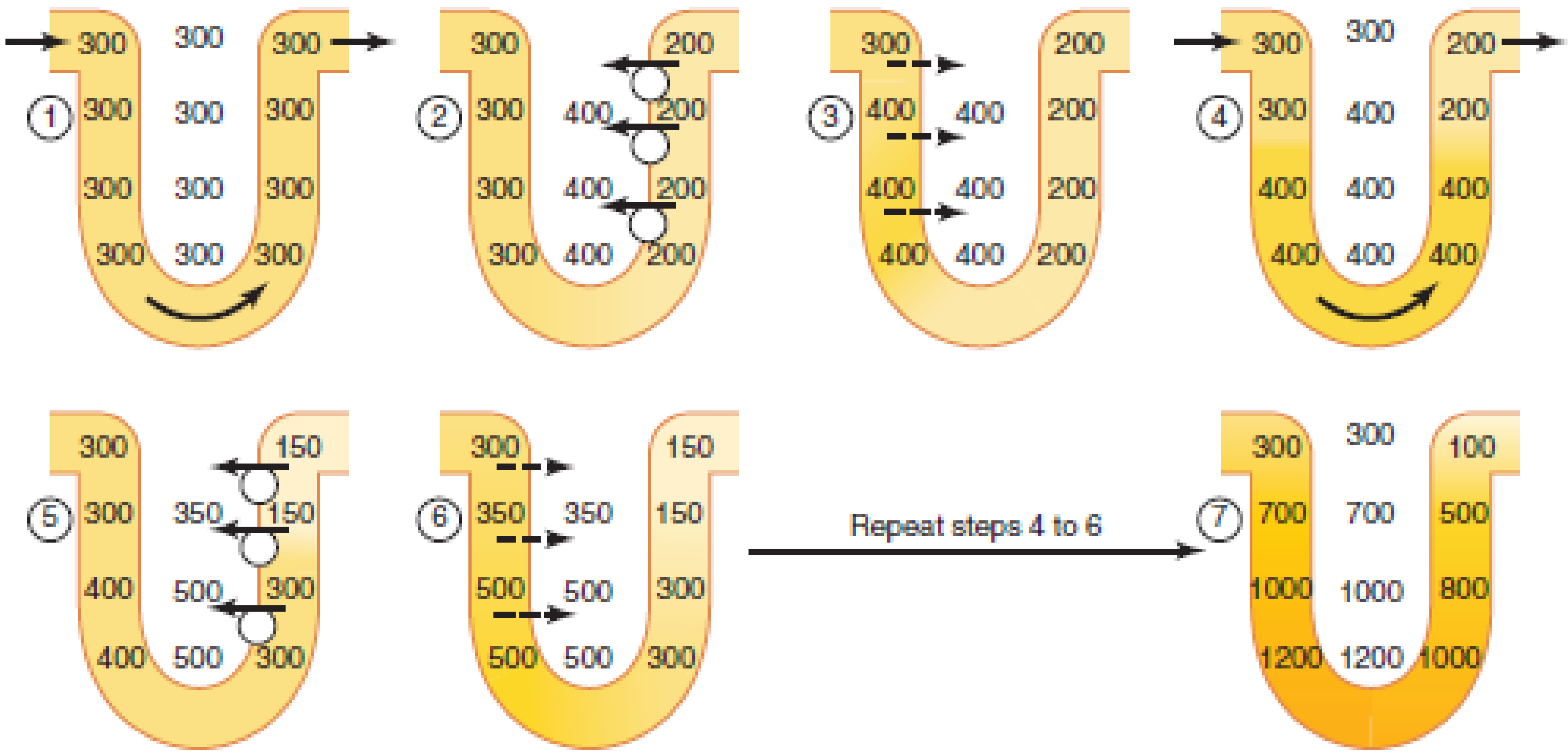
4 Countercurrent exchange (water) in loop (e.g. vasa recta)



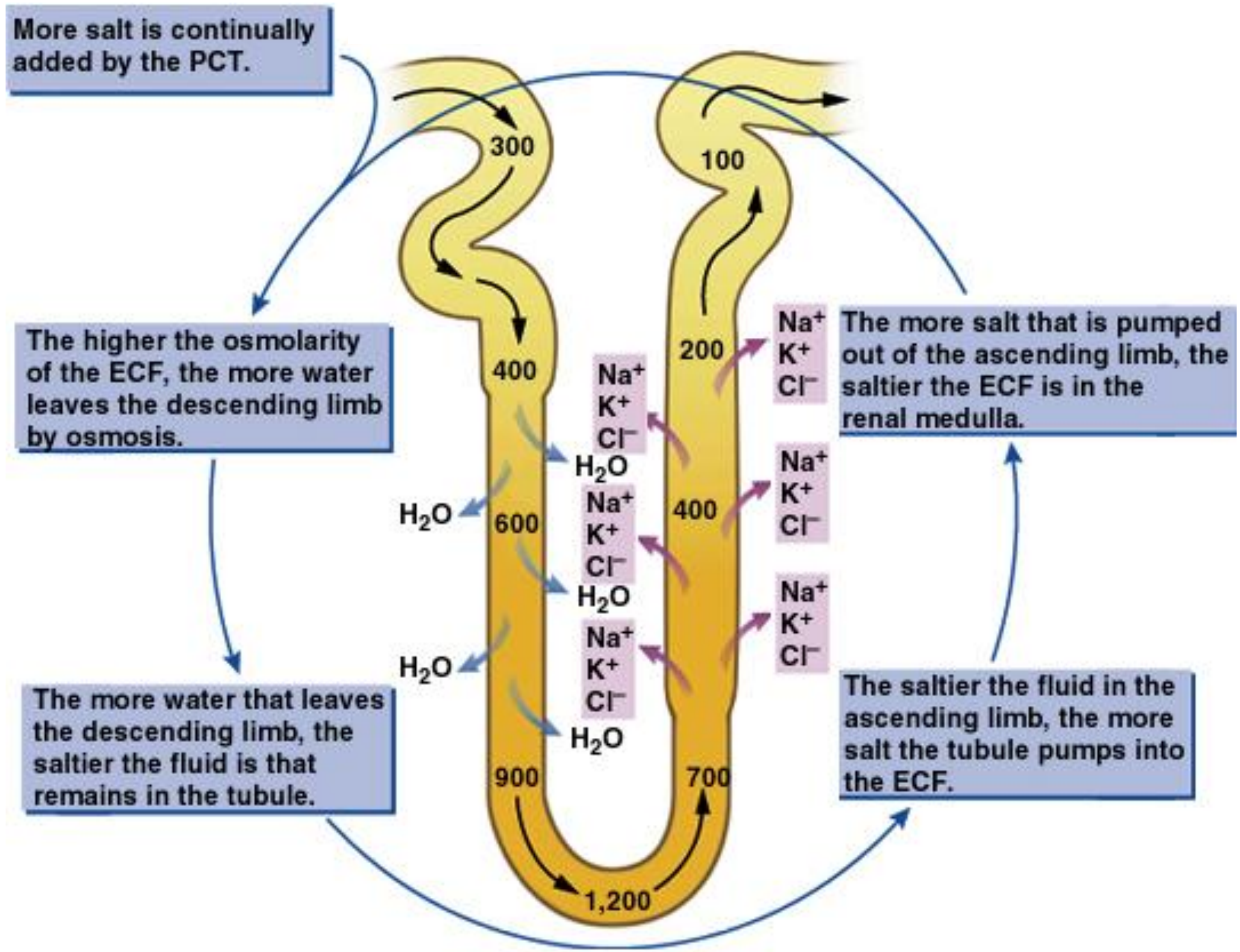
5 Countercurrent multiplier (Henle's loop)



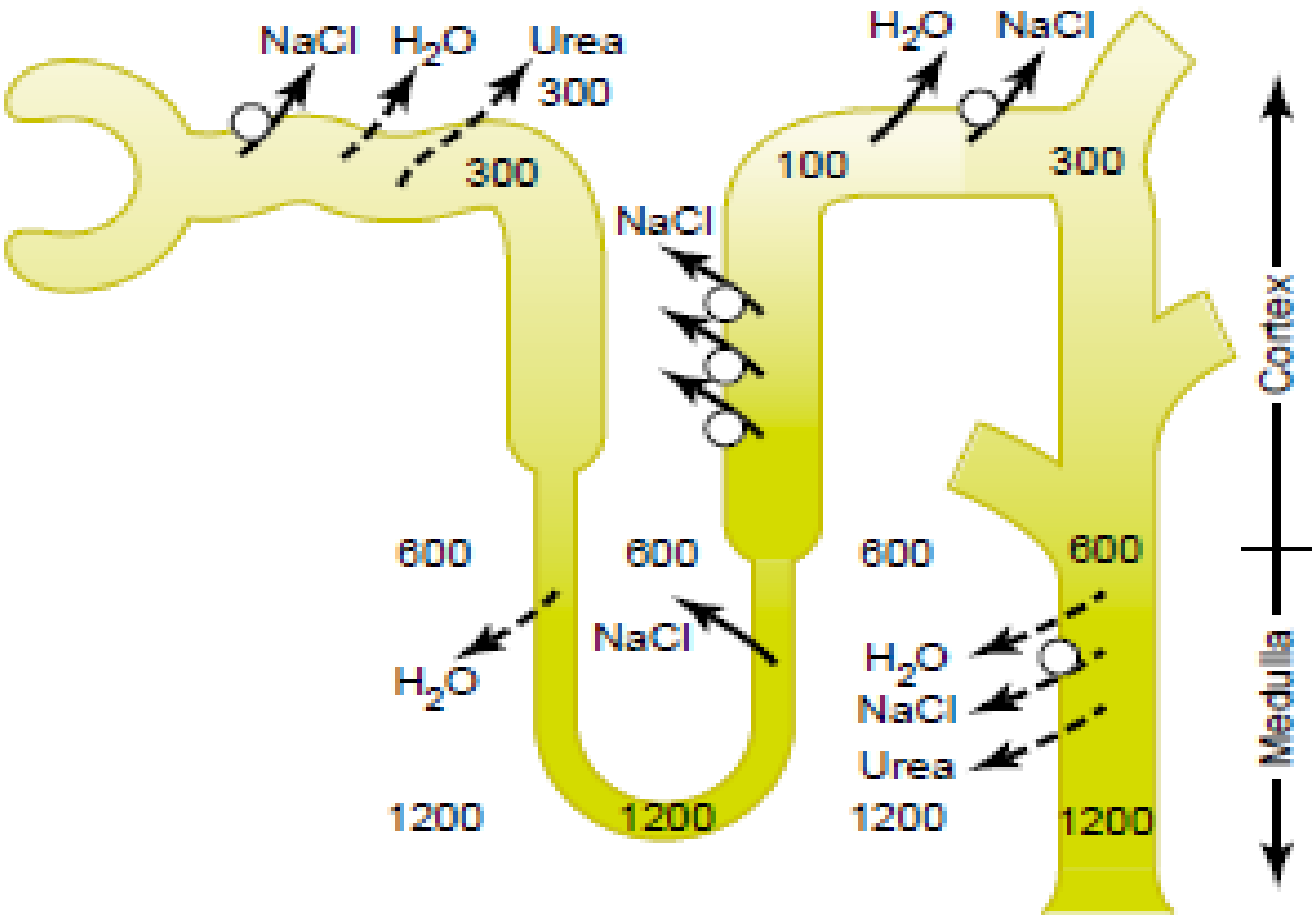
6 Countercurrent systems in renal medulla


1
300 300 300
300 300 300
300 300 300
300 300 300
2
300 200
300 400 200
300 400 200
300 400 200
3
300 200
400 400 200
400 400 200
400 400 200
4
300 300 200
300 400 200
400 400 400
400 400 400
5
300 150
300 350 150
400 500 300
400 500 300
6
300 150
350 350 150
500 500 300
500 500 300
Repeat steps 4 to 6
7
300 300 100
700 700 500
1000 1000 800
1200 1200 1000

COUNTERCURRENT MULTIPLIER



ROLE OF DT & CD



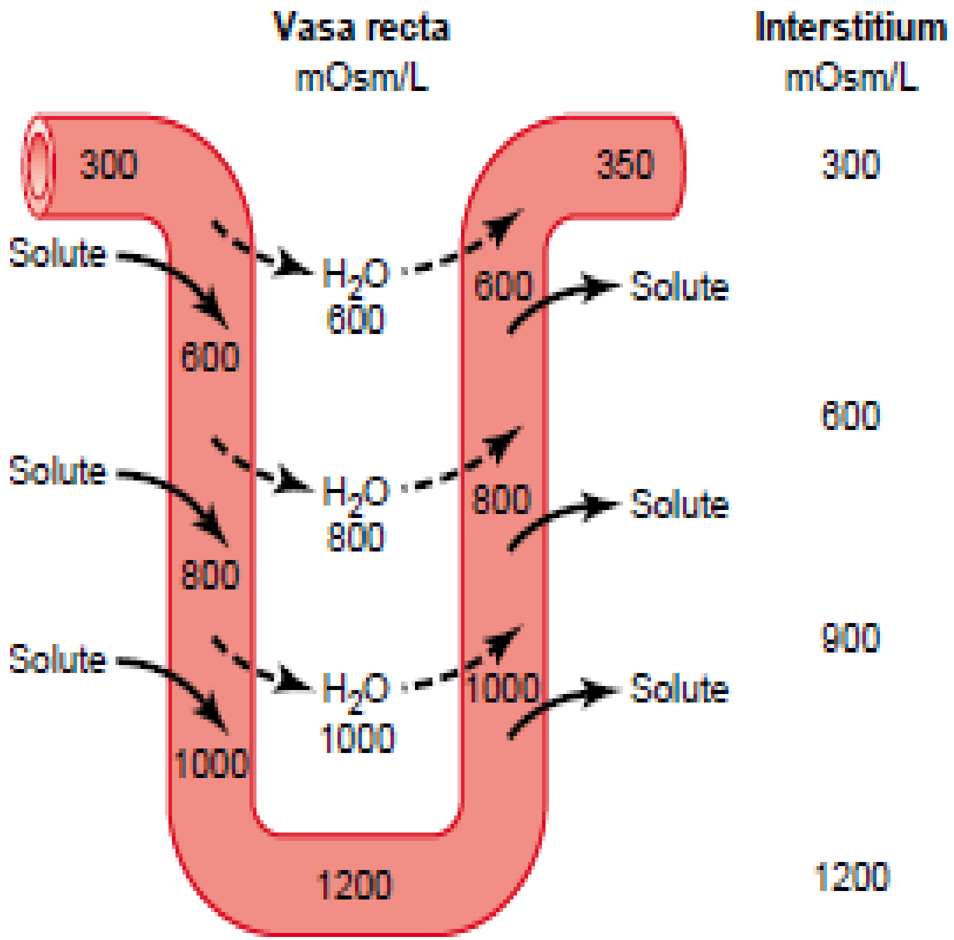
NaCl
H_2O
Urea
300
300
H_2O
NaCl
100
300
NaCl
Cortex
600
600
600
600
NaCl
H_2O
H_2O
NaCl
Urea
Medulla
1200
1200
1200
1200

COUNTERCURRENT EXCHANGE SYSTEM

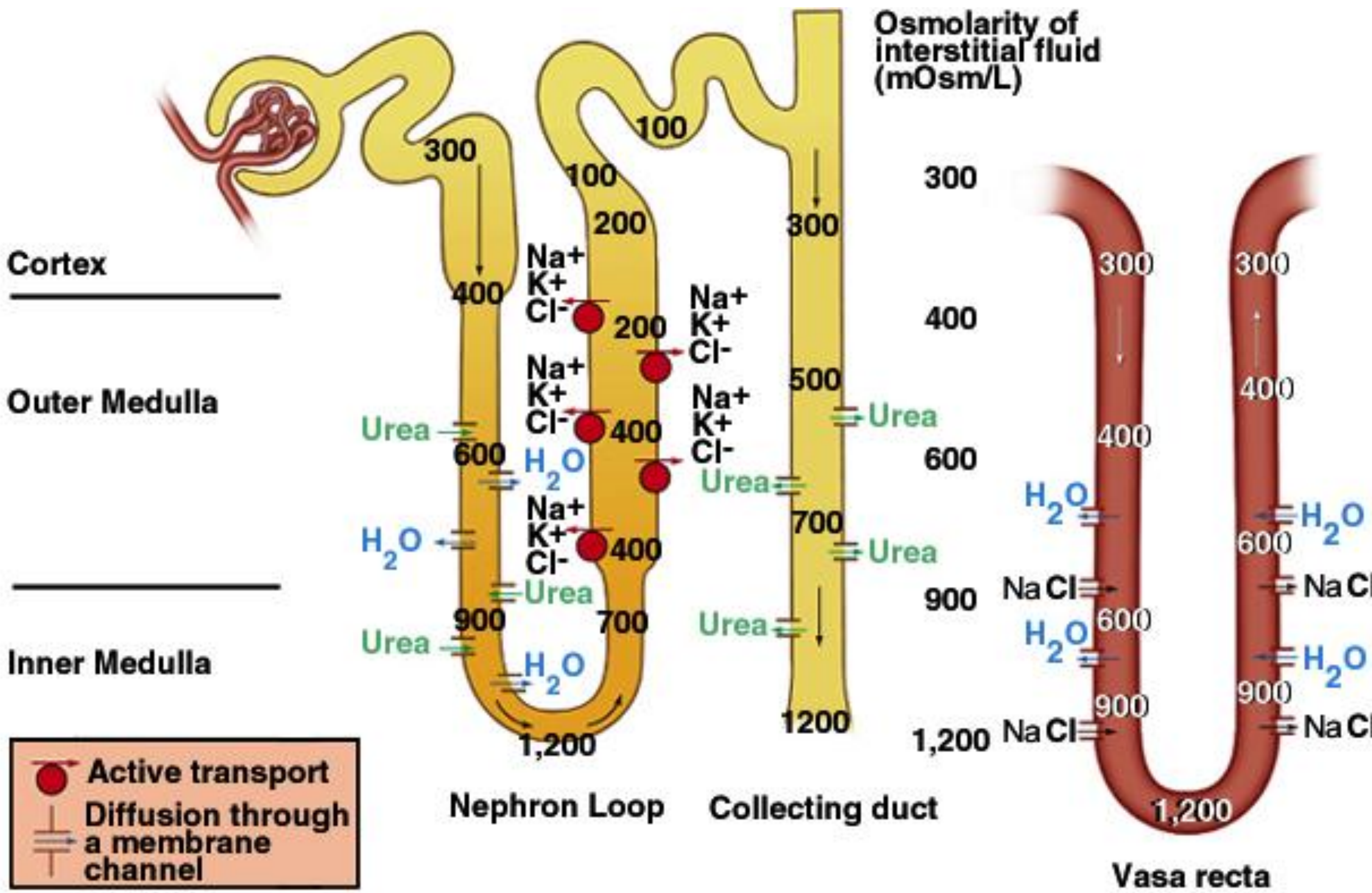
- Formed by vasa recta
  - provide blood supply to medulla
  - do not remove NaCl from medulla
- Descending capillaries
  - water diffuses out of blood
  - NaCl diffuses into blood
- Ascending capillaries
  - water diffuses into blood
  - NaCl diffuses out of blood

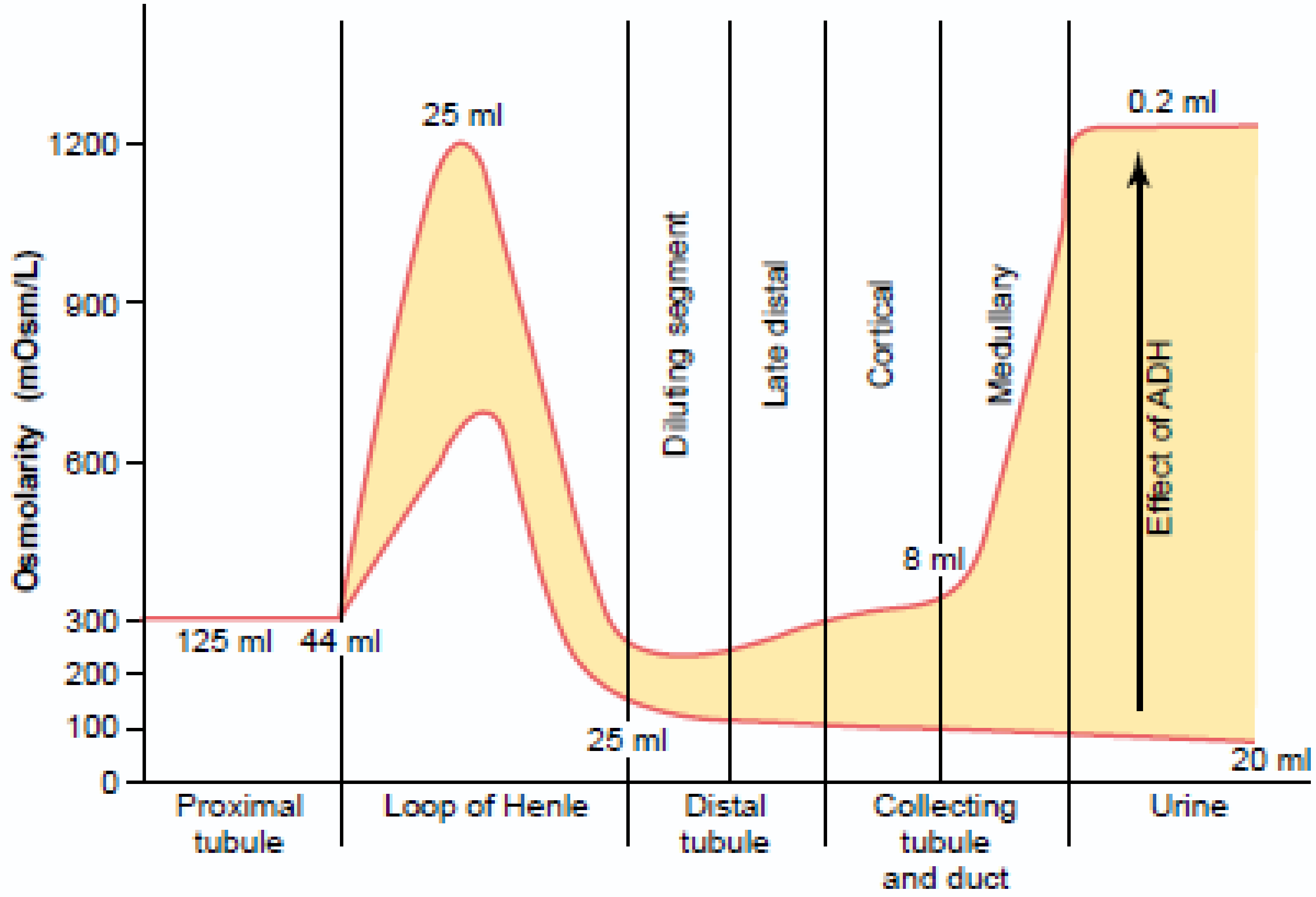
VASA RECTA

- Help preserve the hyperosmolarity
- Two special features of medullary blood flow:
  1. Low blood flow --- less than 5%
  2. Vasa recta serve as countercurrent exchanger



MAINTENANCE OF OSMOLARITY IN RENAL MEDULLA



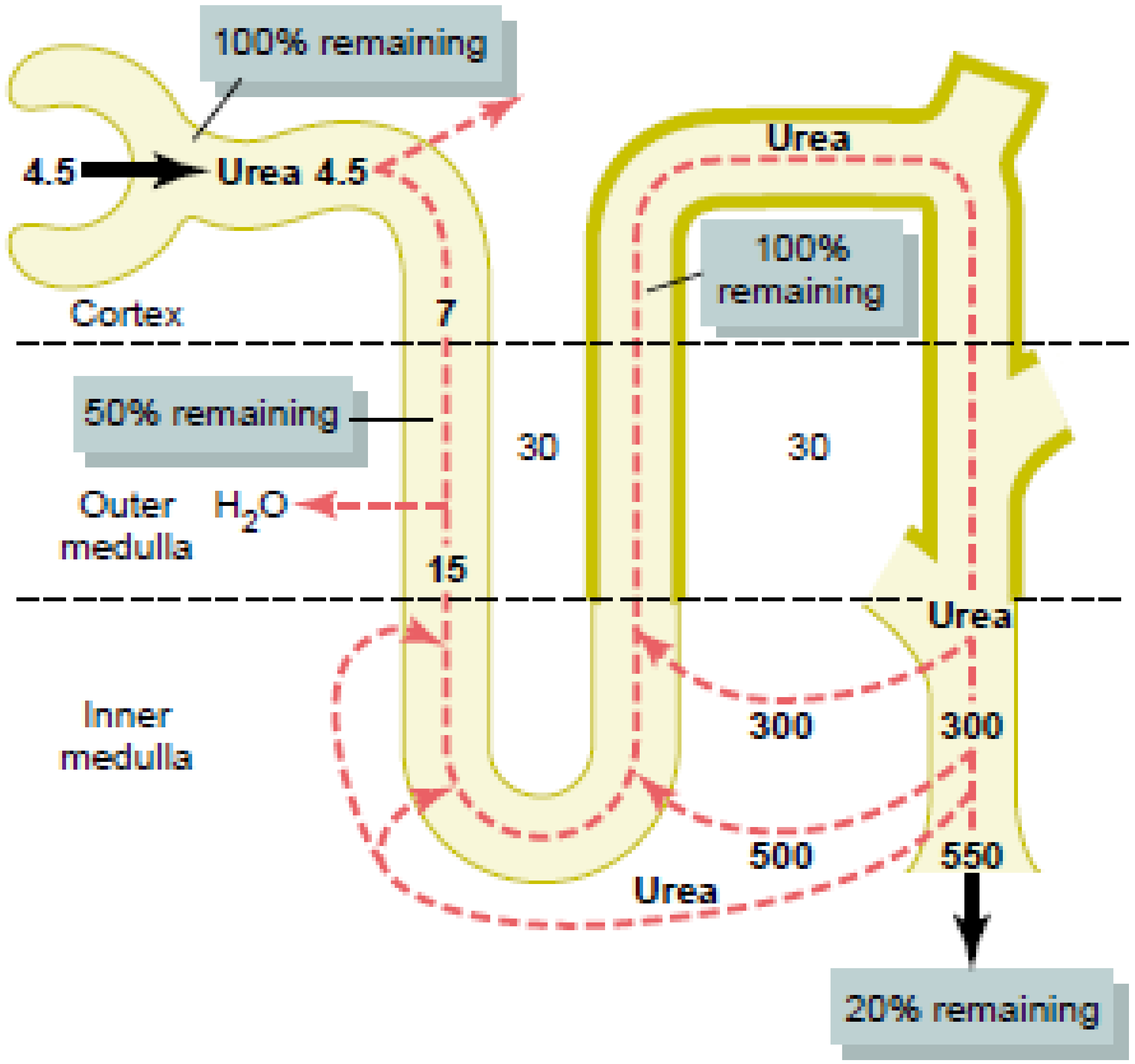

Osmolarity (mOsm/L)
1200
900
600
300
200
100
0
25 ml
125 ml
44 ml
25 ml
Diluting segment
Late distal
Cortical
Medullary
8 ml
0.2 ml
Effect of ADH
20 ml
Proximal tubule
Loop of Henle
Distal tubule
Collecting tubule and duct
Urine

ROLE OF UREA IN CONCENTRATING URINE

- Urea very useful in concentrating urine.
- High protein diet = more urea = more concentrated urine.
- Kidneys filter, reabsorb and secrete urea.
- Urea excretion rises with increasing urinary flow.

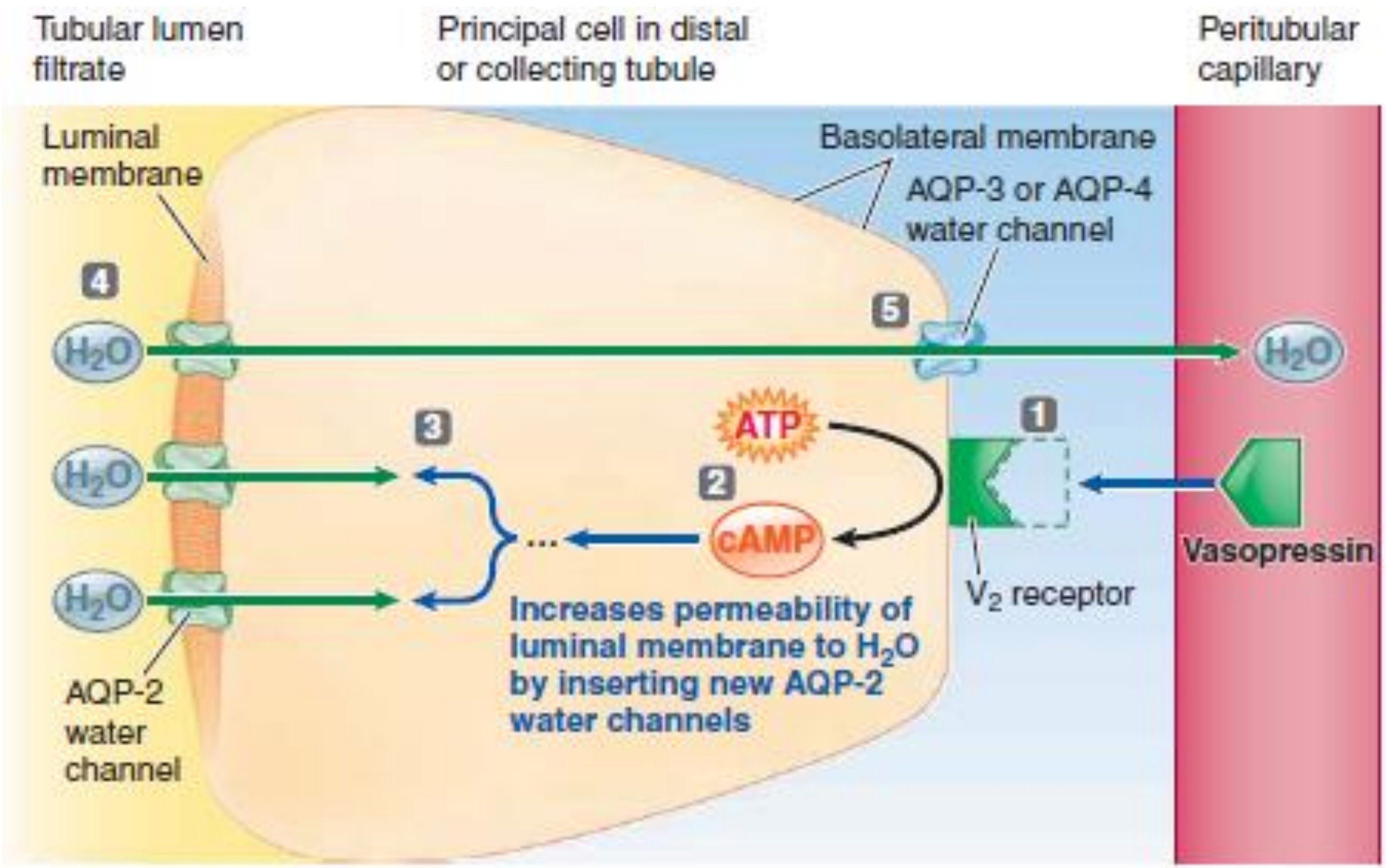
CONTRIBUTION OF UREA (Urea Recycling)

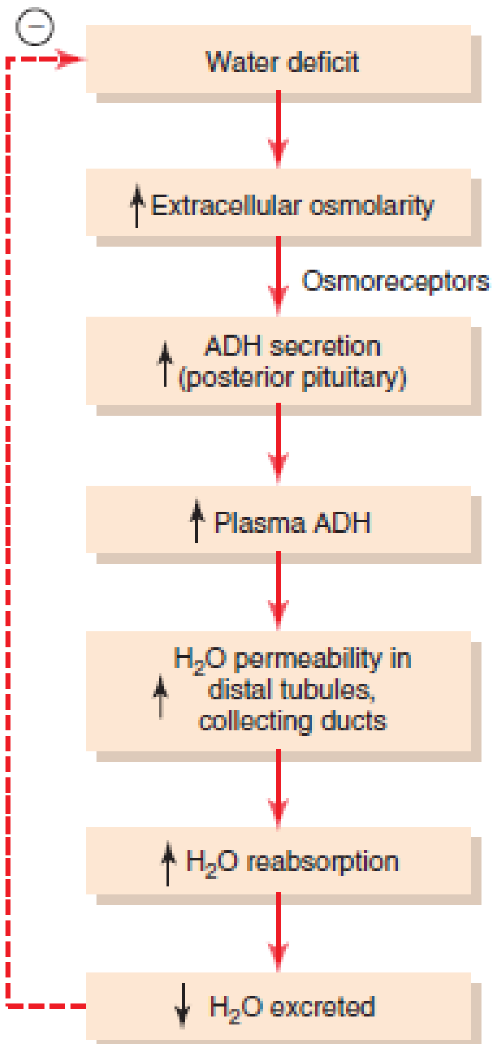
- Urea contriutes about 40-50% in forming hyperosmolar interstitium
- Passively reabsorbed from tubules
- Dependant on ADH
- main site: Medullary ducts
- Urea transporters: UT-A I & AIII
- Activated by ADH
- Dietary protein intake important in forming concentrated urine
- High urea levels in impaired renal function

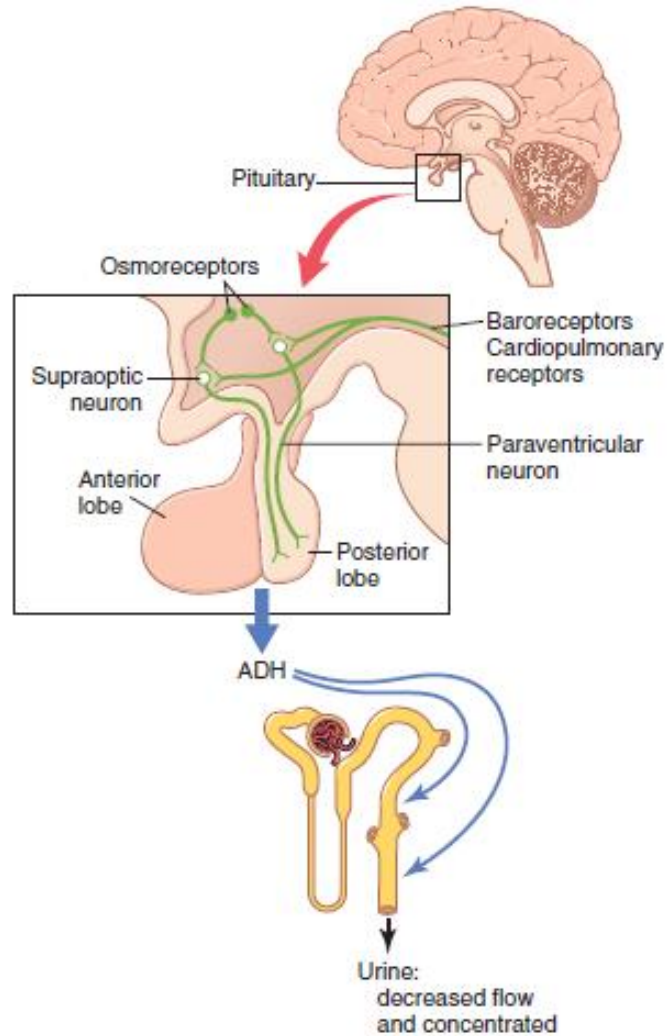


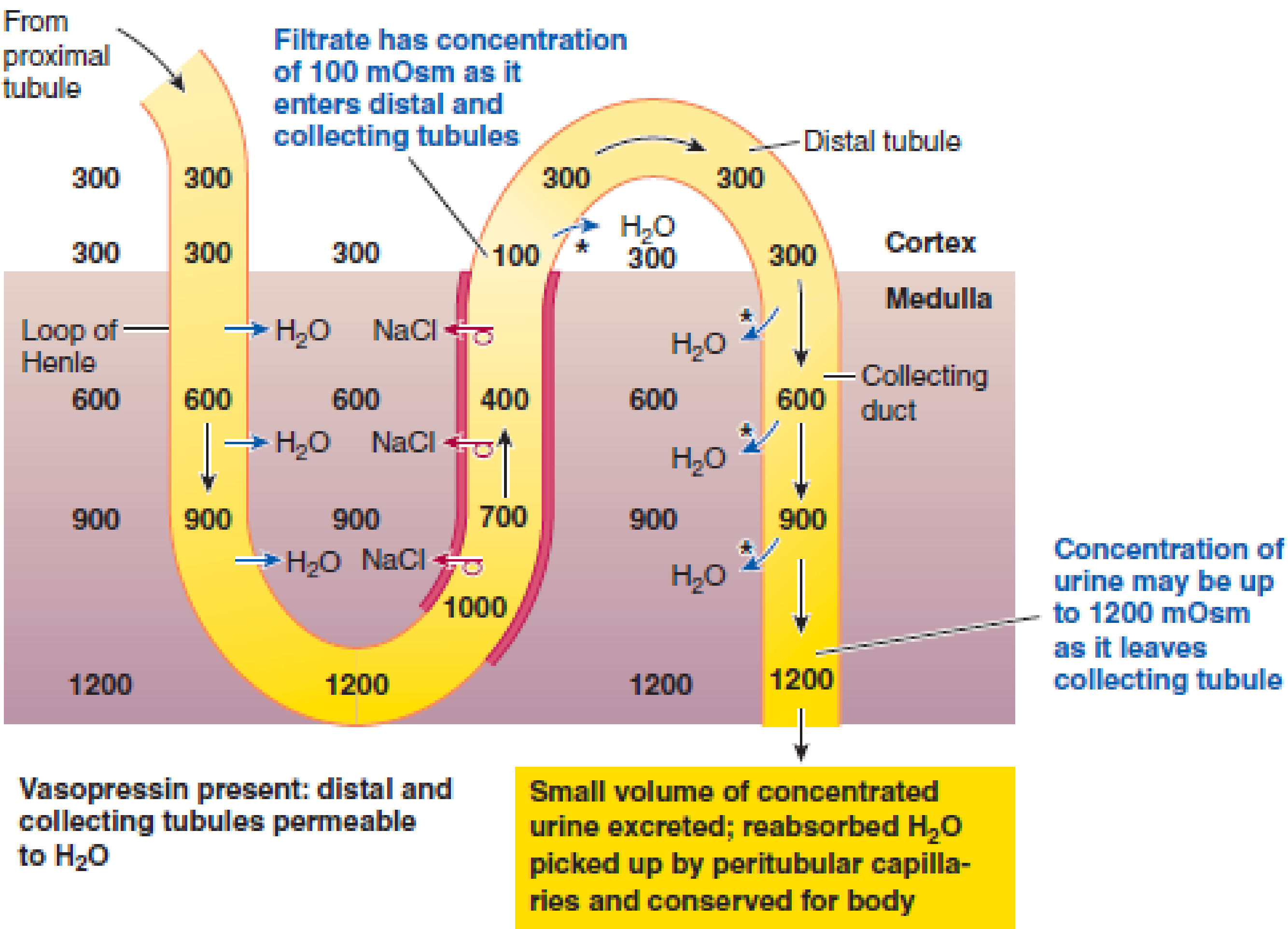
100% remaining
4.5
Urea 4.5
Urea
100% remaining
Cortex
7
50% remaining
30
30
Outer medulla
H2O
15
Urea
Inner medulla
300
300
500
550
Urea
20% remaining

Role of Vassopressin

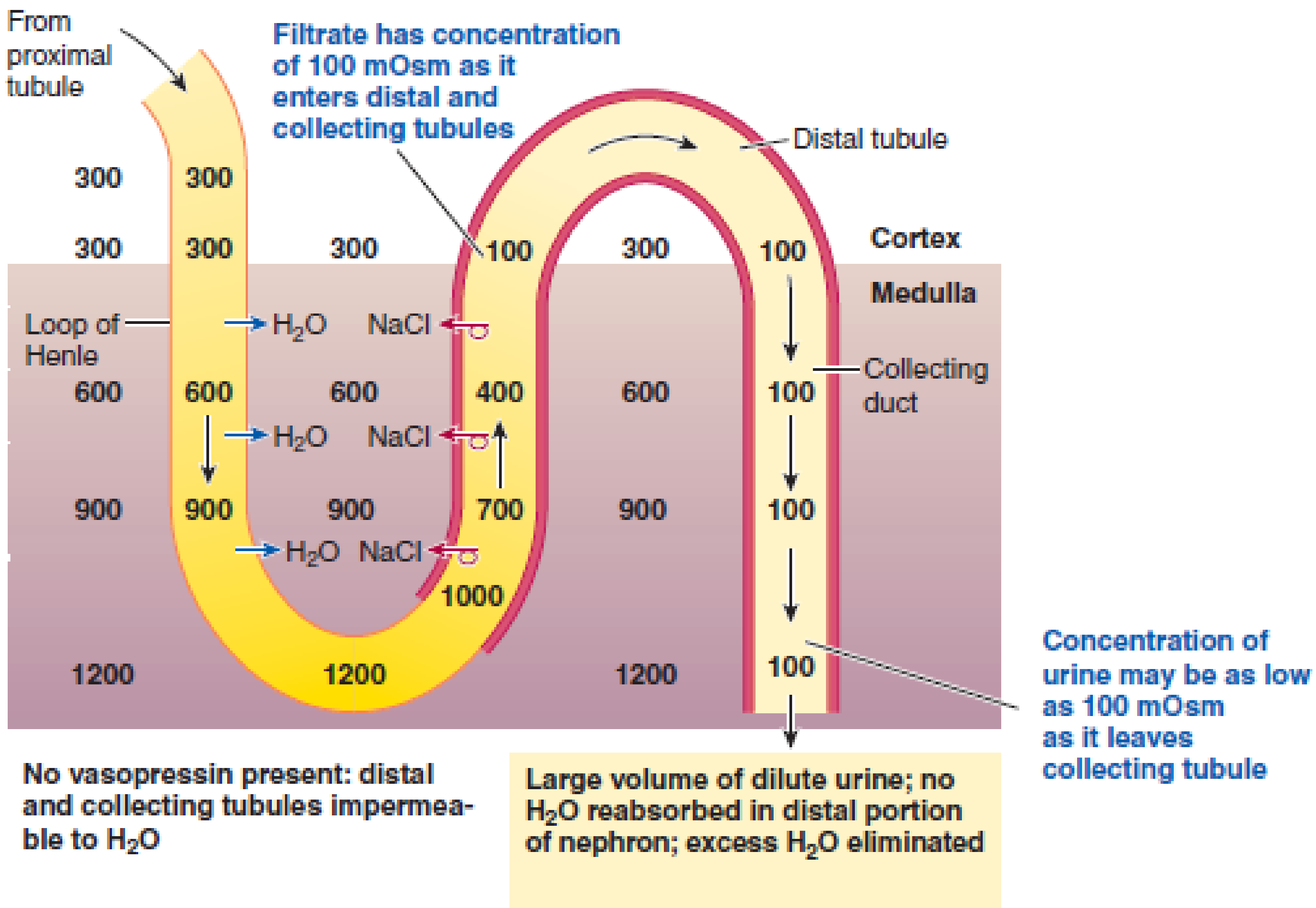



Water deficit
↑ Extracellular osmolarity
Osmoreceptors
↑ ADH secretion (posterior pituitary)
↑ Plasma ADH
↑ H_2O permeability in distal tubules, collecting ducts
↑ H_2O reabsorption
↓ H_2O excreted


Pituitary
Osmoreceptors
Baroreceptors
Cardiopulmonary receptors
Supraoptic neuron
Paraventricular neuron
Anterior lobe
Posterior lobe
ADH
Urine:
decreased flow and concentrated



(a) In the face of a water deficit



(b) In the face of a water excess

Control of ADH secretion

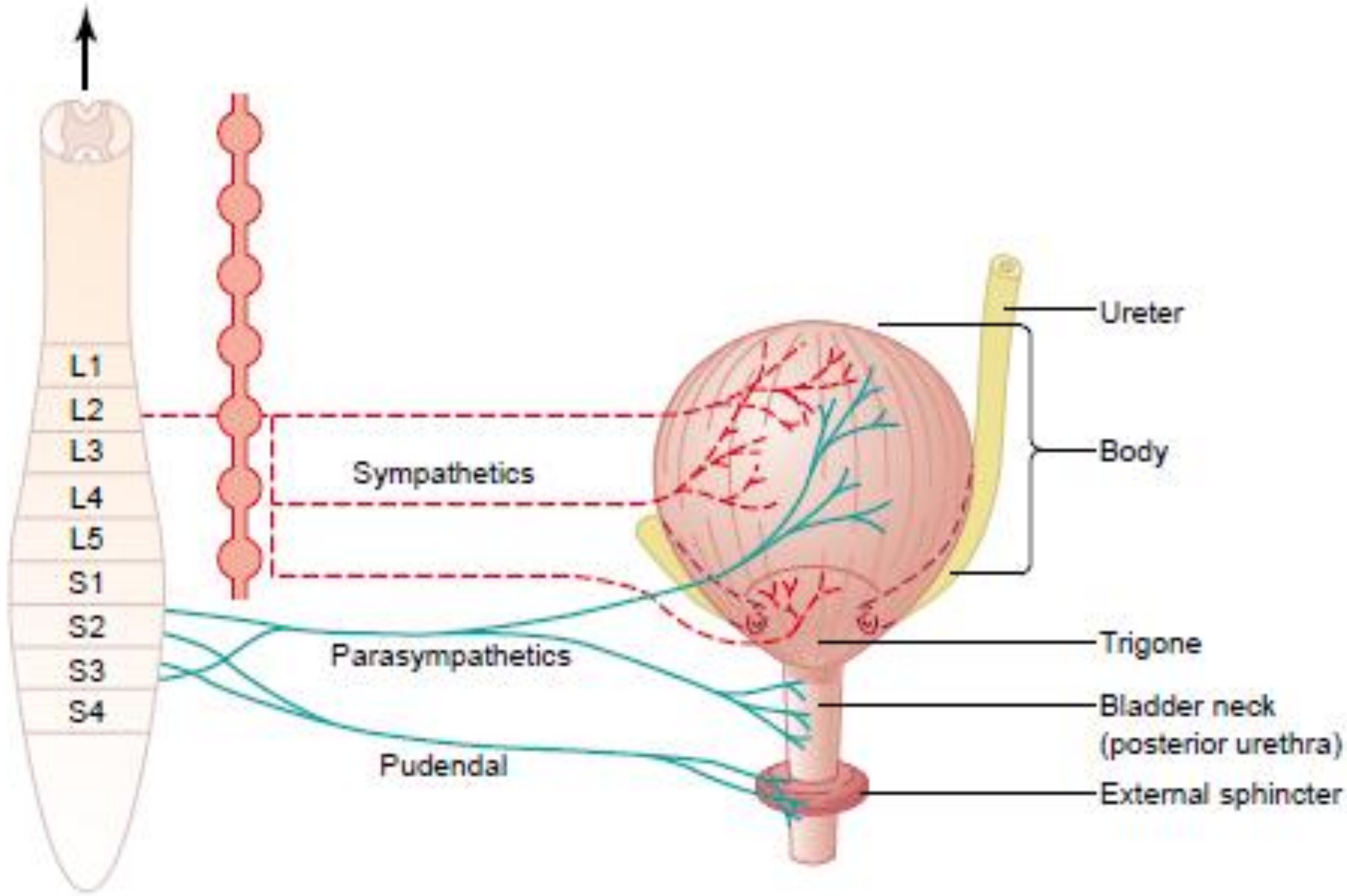
Increase ADH	Decrease ADH
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
Nausea	
Hypoxia	
Drugs: Morphine Nicotine Cyclophosphamide	Drugs: Alcohol Clonidine (antihypertensive) Haloperidol (dopamine blocker)

Mictuirition

Micturition is the process by which the urinary bladder empties when it becomes filled

- Progressive filling of bladder
- Mictuirition Reflex (Emptying of reflex)
- Autonomic Reflex
- Can be controlled by higher centres

Physiologic Anatomy of Urinary Bladder



Physiologic Anatomy of Urinary Bladder

- Composed of Smooth muscles
  - Body
  - Neck (posterior urethra)
- Detrusor muscle --- Smooth muscles of U.B.
- Low resistance pathways b/w muscle cells
  - Trigone
  - Rugae
  - Ureters enter through trigone
- Internal Sphincter (Lies in bladder neck)
- External sphincter (lies in urogenital Diaphragm)

Nerve supply of Urinary Bladder

- **Pelvic nerves** from sacral plexus
  - **S-2--- S-3**
  - Sensory & Motor fibers
  - Motor nerves --- Parasympathetic (Long Preganglionic part)
- **Skeletal motor fiber**
  - Pudendal Nerve (External sphincter)
- **Sympathetic Supply**
  - L-2
  - Supply blood vessels
  - Sensory- pain, fullness sensation

- Transport of urine from kidneys to bladder through ureter
- Collecting Ducts > Calyces > Renal Pelvis > Ureter
- **Ureters**
  - Smooth muscles
  - Sympathetic & parasympatheic nerve supply
  - Intramural nerve supply
- Ureters enter bladder through **TRIGONE**
- **VESICOURETERAL REFLEX**
- **URETERORENAL REFLEX**

CYSTOMETROGRAM

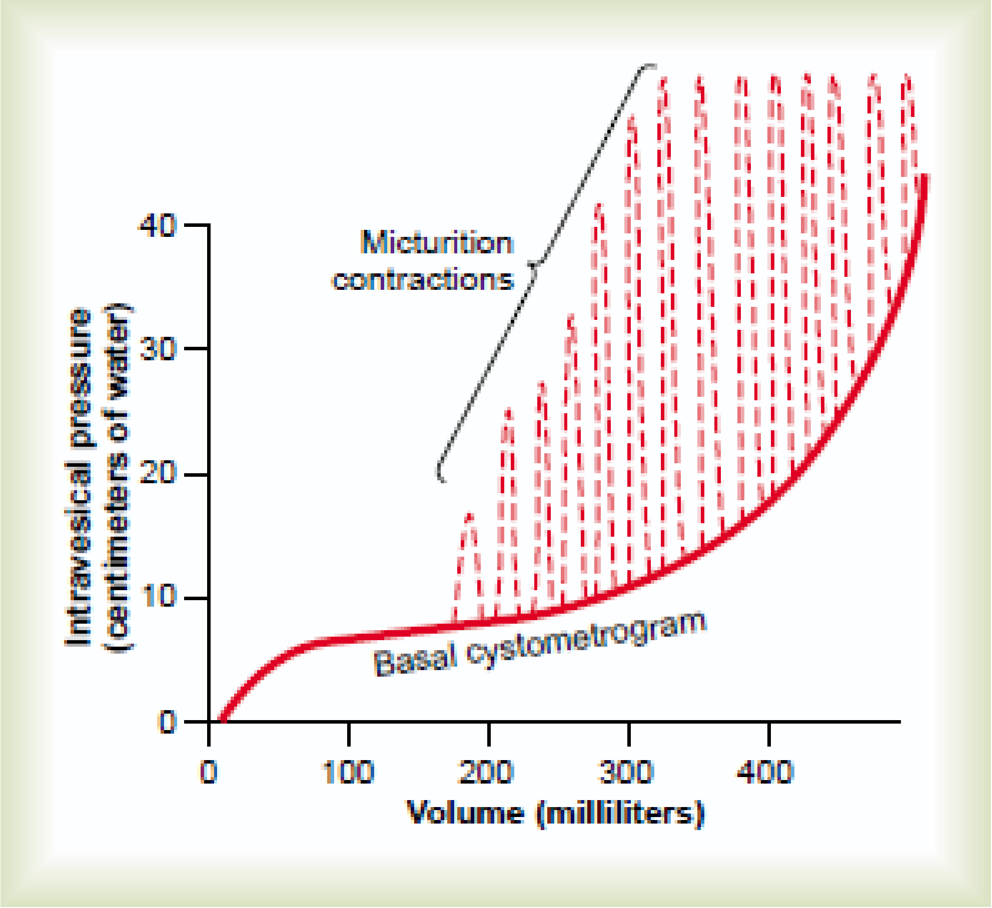


Figure 26–7

Normal cystometrogram, showing also acute pressure waves (*dashed spikes*) caused by micturition reflexes.

Mictuirition Reflex

- Mictuirition Reflex is a single complete cycle of:
  - Progressive & rapid increase of pressure
  - Period of sustained pressure
  - Return of pressure to basal level
- Basal tone of detrusor muscle
- **Mictuirition Contractions**
  - Superimposed contractions of detrusor muscle initiated by sensory strech receptors
- Mictuirition reflex is self generative

Control of Mictuirition by Brain

- Facilitative & inhibitory center in brain stem (Pons)
- Cerebral cortex
- Higher centers keep:
  - mictuirition reflex partially inhibited
  - Can prevent mictuirition
  - Can initiate mictuirition
- **Voluntary Mictuirition**

Abnormalities of Mictuirition

ATONIC BLADDER

- Destruction of sensory nerve fibers from bladder to spinal cord
- **Causes**
    - Injury to spinal cord at sacral level
    - Syphilis (Tabes Dorsalis) Tabetic Bladder
- Overflow Incontinence

Automatic Bladder

- Spinal cord injury above sacral segments
- Sacral segments intact
- Mictuirition reflexes suppressed during early days after injury because of spinal shock
- Return of mictuirition after few days is bladder is empties properly
- Unannounced periodic emptying of bladder
- Some patients can control urination by stimulation of skin in genital area

Uninhibited Neurogenic Bladder

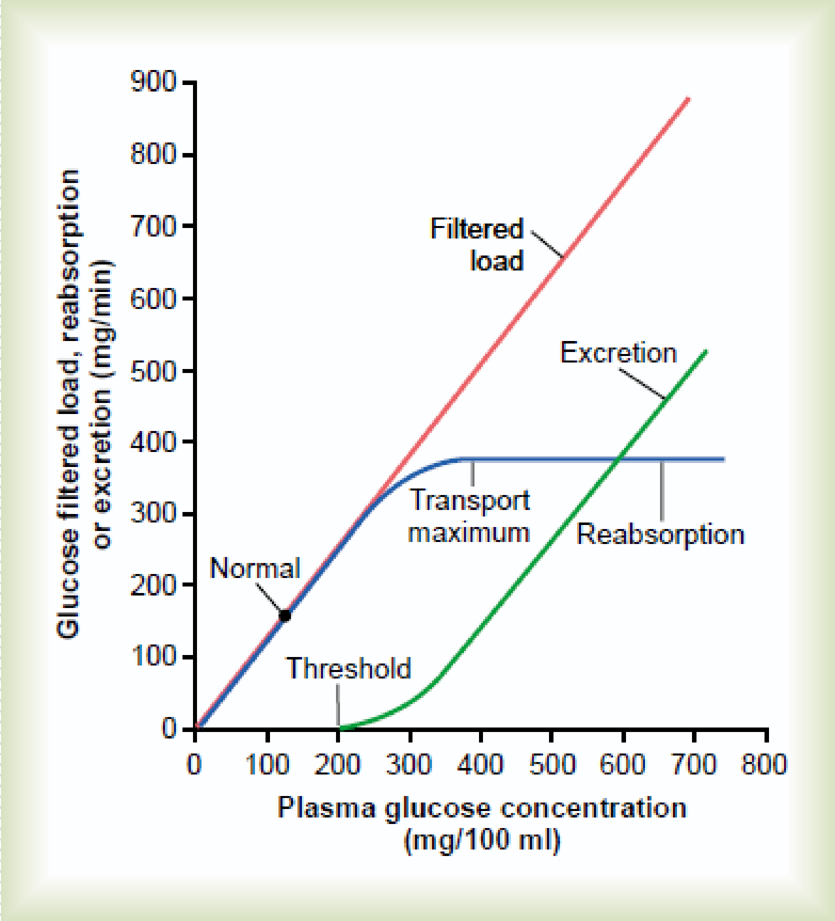
- Frequent & uncontrolled emptying of urinary bladder
- Cause: Loss of inhibitory signals from higher centers
- Spinal cord or brain stem damage

RENAL PHYSIOLOGY

CLEARANCE METHODS & TUBULAR MAXIMUM

Transport Maximum

- Most substances that are actively reabsorbed or secreted, there is a limit to the rate at which the solute can be transported known as the *transport maximum* or TMax
- Saturation of specific transport systems involved when tubular load exceeds the carrier protein or enzyme capacity
- Glucose reabsorption in proximal tubules exhibits Tmax.
- Tmax for Glucose is 365mg/min



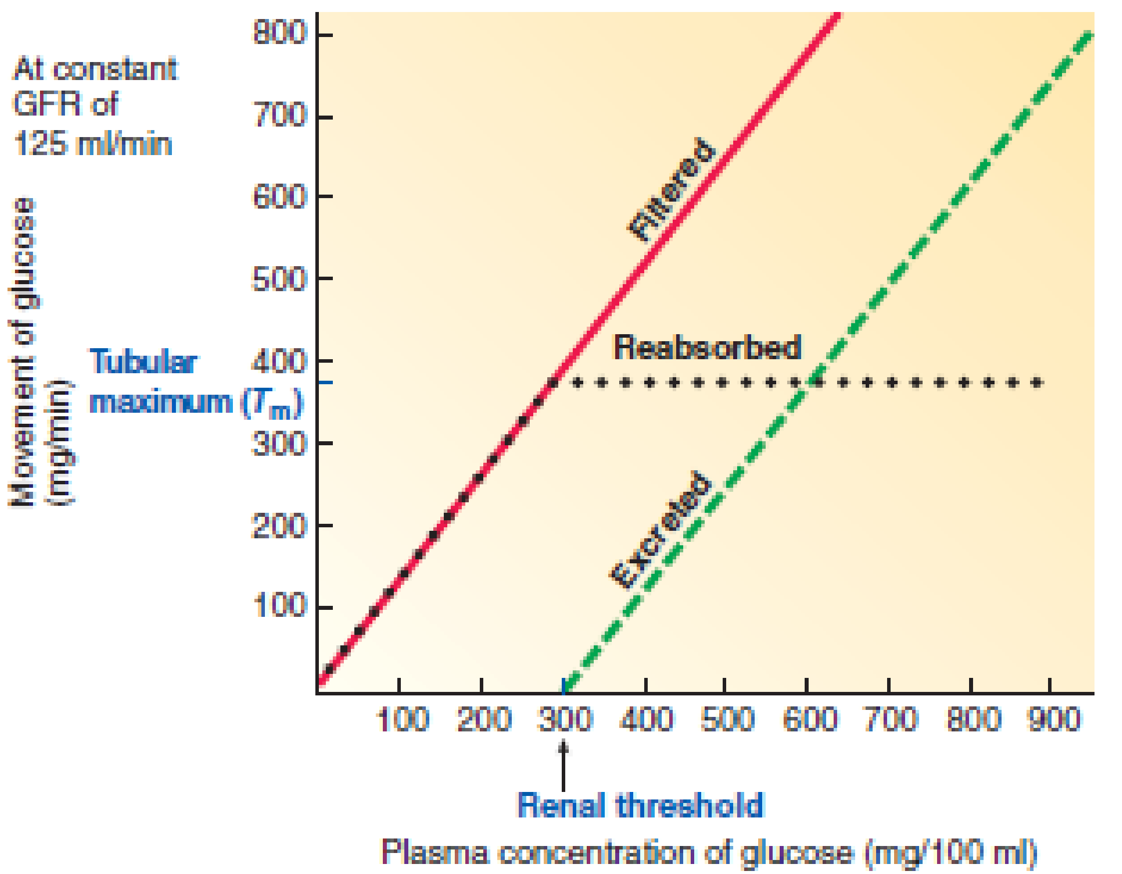
Passively reabsorbed substances do not demonstrate a transport maximum as their rates of transport is determined by:

1. Electrochemical gradient for diffusion across the membrane
2. The permeability of the membrane for the substance
3. The time that the fluid containing the substance remains within the tubule. (Gradient-time transport)

Some actively transported substances also exhibit Gradient-time transport. E.g. Sodium

- Increased Na concentration gradient or
- Reduced blood flow in PTC
- T_{max} of Na can be increased by ALDOSTERONE

Renal threshold for glucose



Renal Clearance

Volume of plasma that is completely cleared of the substance per unit time by the kidneys

- Clearance rate(ml/min) =urine concentration (quantity/ml urine) × urine flow rate (ml/min)/plasma concentration of the substance (quantity/ml plasma)

- Used to assess the excretory functions of kidneys.
- GFR, Tubular Reabsorption & Secretion can also be estimated.

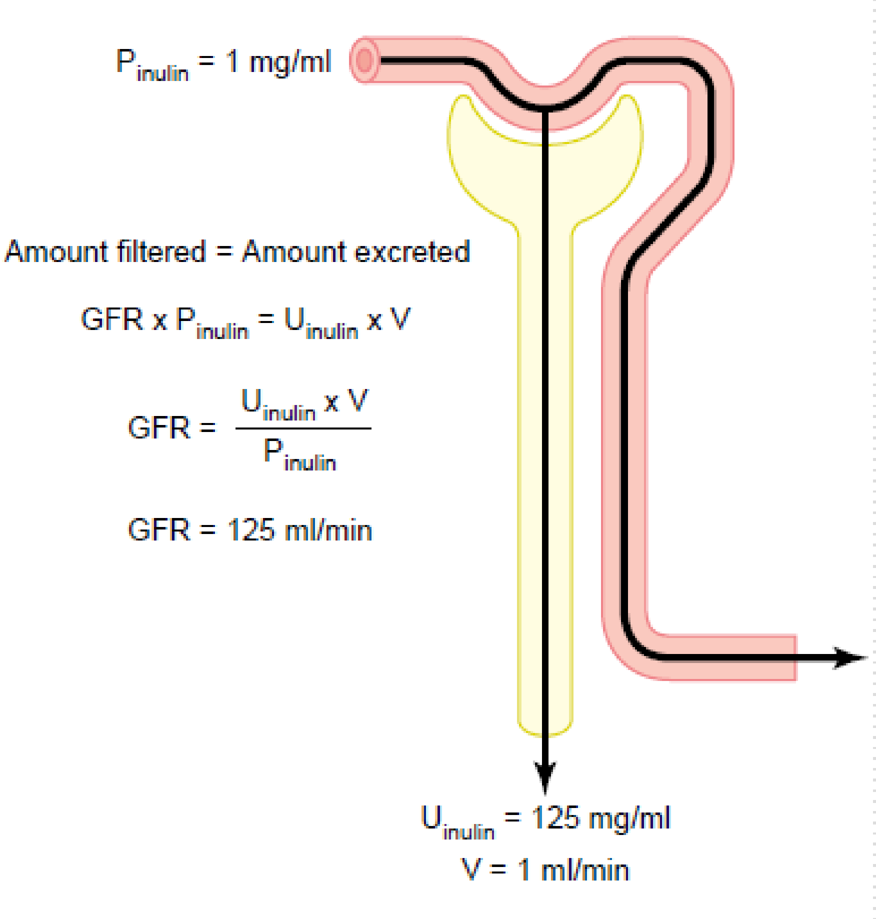
$$\text{Clearance Rate} = \frac{\text{Excretion Rate}}{\text{Plasma Conc.}}$$

$$C_s = \frac{U_s \times V}{P_s}$$

- GFR = Clearance of a substance that is freely filtered, neither reabsorbed nor secreted
- RBF = Clearance of a substance that is completely cleared from the plasma

Inulin Clearance CAN BE USED TO ESTIMATE GFR

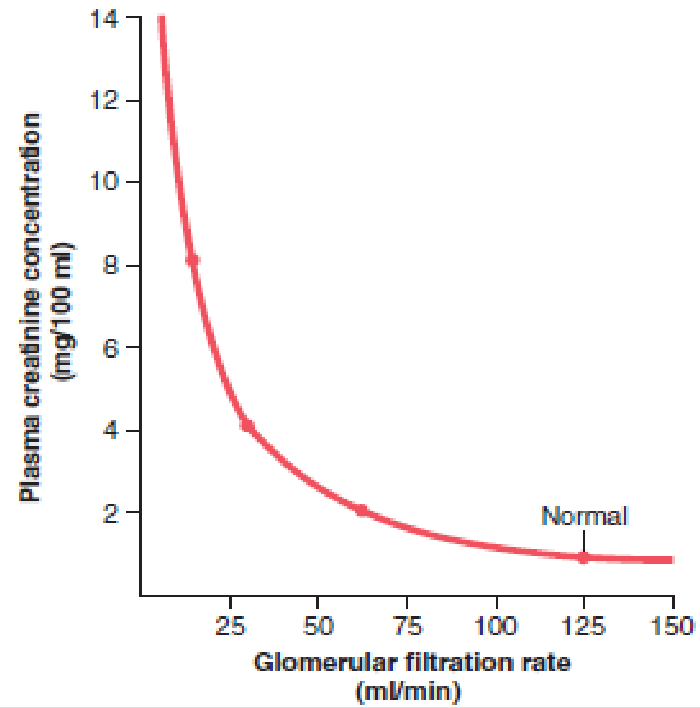
- Polysaccharide molecule
- Molecular weight = 5200
- Not produced in the body
- Freely filtered
- No reabsorption or secretion
- Its clearance rate = GFR



Creatinine Clearance CAN BE USED TO ESTIMATE GFR

- By product of muscle metabolism
- Cleared thru GF mainly
- Can be used to assess the GFR
- Partly secreted
- Error in plasma conc. calculation

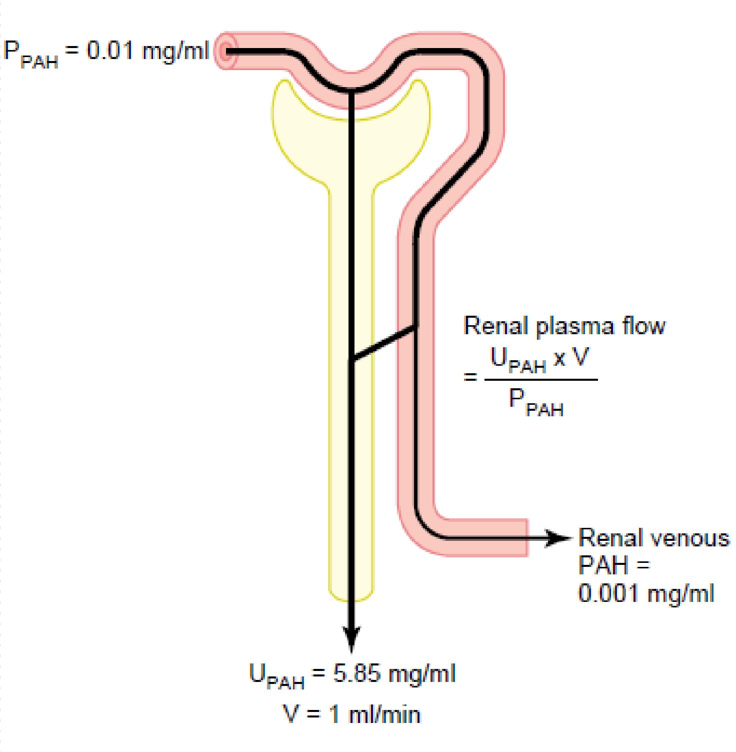
$$GFR \approx C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$$



PAH Clearance CAN BE USED TO ESTIMATE RPF

- About 90% is cleared from the plasma by the kidneys
- Can be used to assess the RBF
- PAH Clearance is also known as Extraction Ratio

Total renal plasma flow =
Clearance of PAH/Extraction ratio of PAH



Filtration Fraction

FF = GFR (inulin clearance)/RPF (PAH clearance = 125/650 = 0.19=20%

Tubular Reabsorption & Secretion

Urine flow rate = 1 ml/min

Urine concentration of sodium (U_{Na}) = 70 mEq/L

= 70 µEq/ml

Plasma sodium concentration = 140 mEq/L

= 140 µEq/ml

GFR (inulin clearance) = 100 ml/min

Clearance of different substances

Substance	Clearance Rate (ml/min)
Glucose	0
Sodium	0.9
Chloride	1.3
Potassium	12.0
Phosphate	25.0
Inulin	125.0
Creatinine	140.0

RENAL PHYSIOLOGY

By
Dr. Shahid Javed
MBBS, PhD.

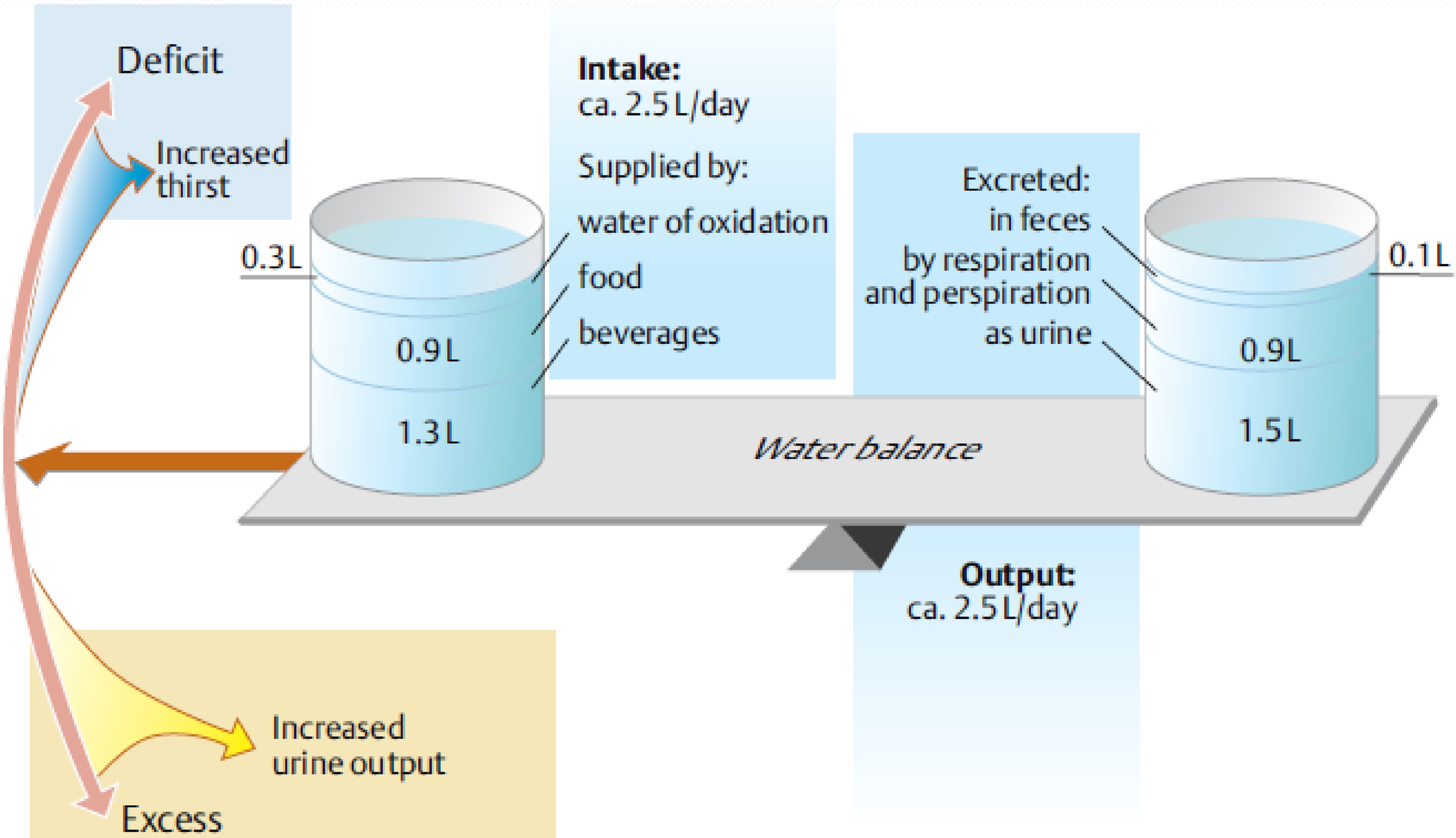
BODY FLUID COMPARTMENTS
ECF & ICF FLUIDS

- **HARMONY IN BODY FLUID CONCENTRATION IS VERY VITAL FOR HOMEOSTASIS**

- **Maintenance of nearly constant conditions in the internal environment.**

- FLUID INTAKE AND OUTPUT ARE BALANCED DURING STEADY STATE CONDITIONS

INTAKE = OUTPUT


Deficit
Increased thirst
0.3L
0.9 L
1.3 L
Intake:
ca. 2.5 L/day
Supplied by:
water of oxidation
food
beverages
Excreted:
in feces
by respiration and perspiration
as urine
0.1L
0.9L
1.5L
Water balance
Output:
ca. 2.5 L/day
Increased urine output
Excess

DAILY WATER INTAKE

- Two Sources
  1. Ingested Food & water = 2100ml/ day
  2. Synthesized in the body = 200ml/ day

  Total Intake = 2300ml/ day
- Intake is highly variable
  - Climate
  - Habits
  - Level of physical activity

DAILY LOSS OF BODY WATER

- Insensible losses from:
  - Skin (350 ml/day)
  - Respiratory Tract (350 ml/day)
  - Total = 700 ml/day

- Insensible loss of water from skin is independent of sweating.
- Minimized by cholesterol filled cornified layer of epithelium.
- Increased loss in cases of burns

- Water loss through respiratory tract is utilized in humidification of inspired air
- Air is humidified to a vapor pressure of 47mmHg
- Vapor pressure of atmosphere reaches 0mmHg during winter

FLUID LOSS IN SWEAT

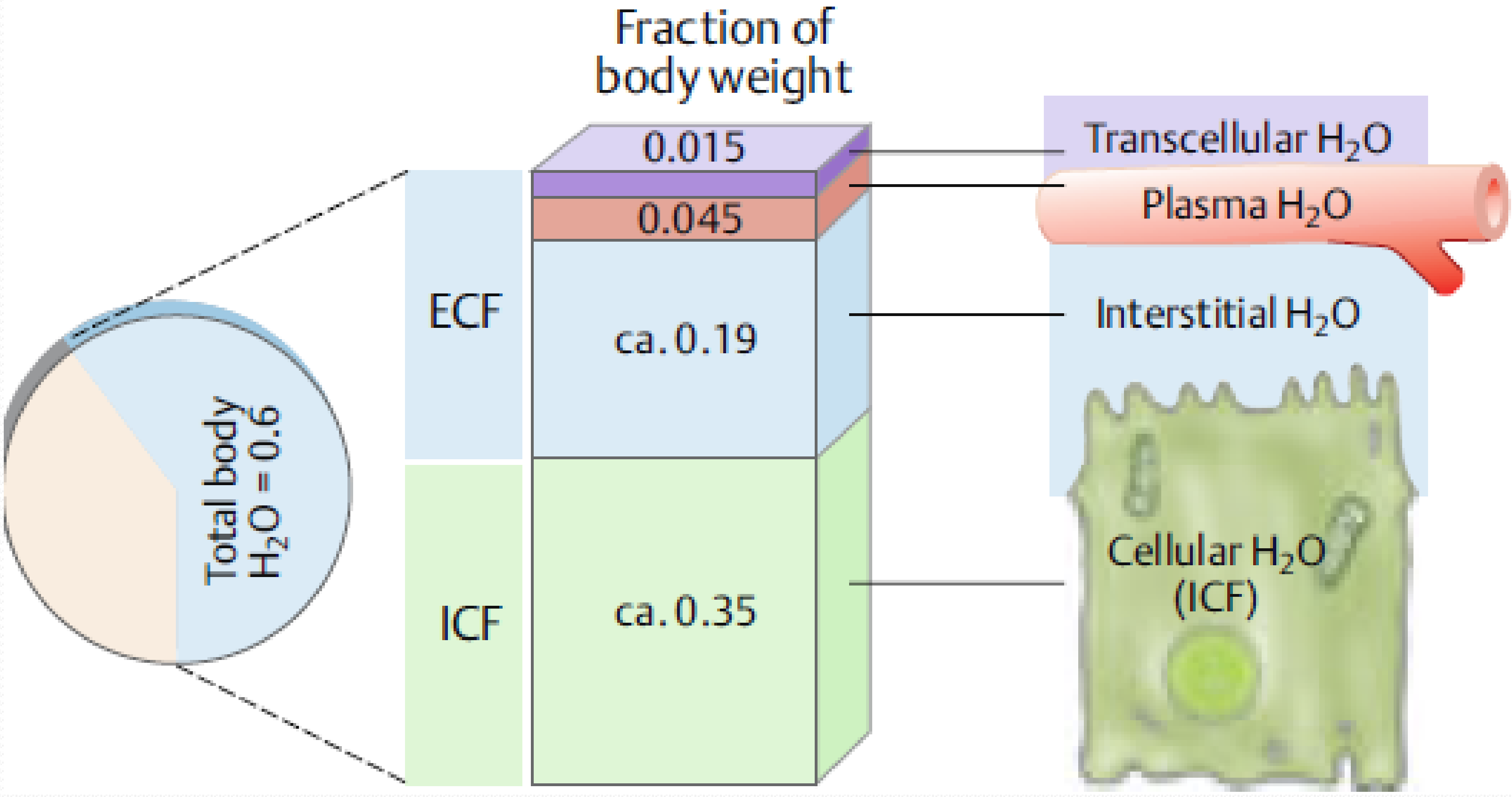
- Normal fluid loss in sweat is 100ml/day
- Increased up to liters in:
  - Exercise
  - Hot Weather

FLUID LOSS IN FECES

- Normal = 100ml/day
- Increased up to liters in patients of severe diarrhea

FLUD LOSS BY KIDNEYS

- Most important in regulation of water and electrolyte balance
- Is highly variable.
- Urine volume is variable ---0.5L/day to 20L/day.
- Salt intake highly variable ---Na intake 20mEq/day to 500mEq/day.



Fraction of body weight
0.015
0.045
ca. 0.19
ca. 0.35
ECF
ICF
Total body H_2O = 0.6
Transcellular H_2O
Plasma H_2O
Interstitial H_2O
Cellular H_2O (ICF)

Daily Intake and Output of Water (ml/day)

	Normal	Prolonged, Heavy Exercise
Intake		
Fluids ingested	2100	?
From metabolism	200	200
Total intake	2300	?
Output		
Insensible—skin	350	350
Insensible—lungs	350	650
Sweat	100	5000
Feces	100	100
Urine	1400	500
Total output	2300	6600

Body Fluid Compartments

Two main compartments:

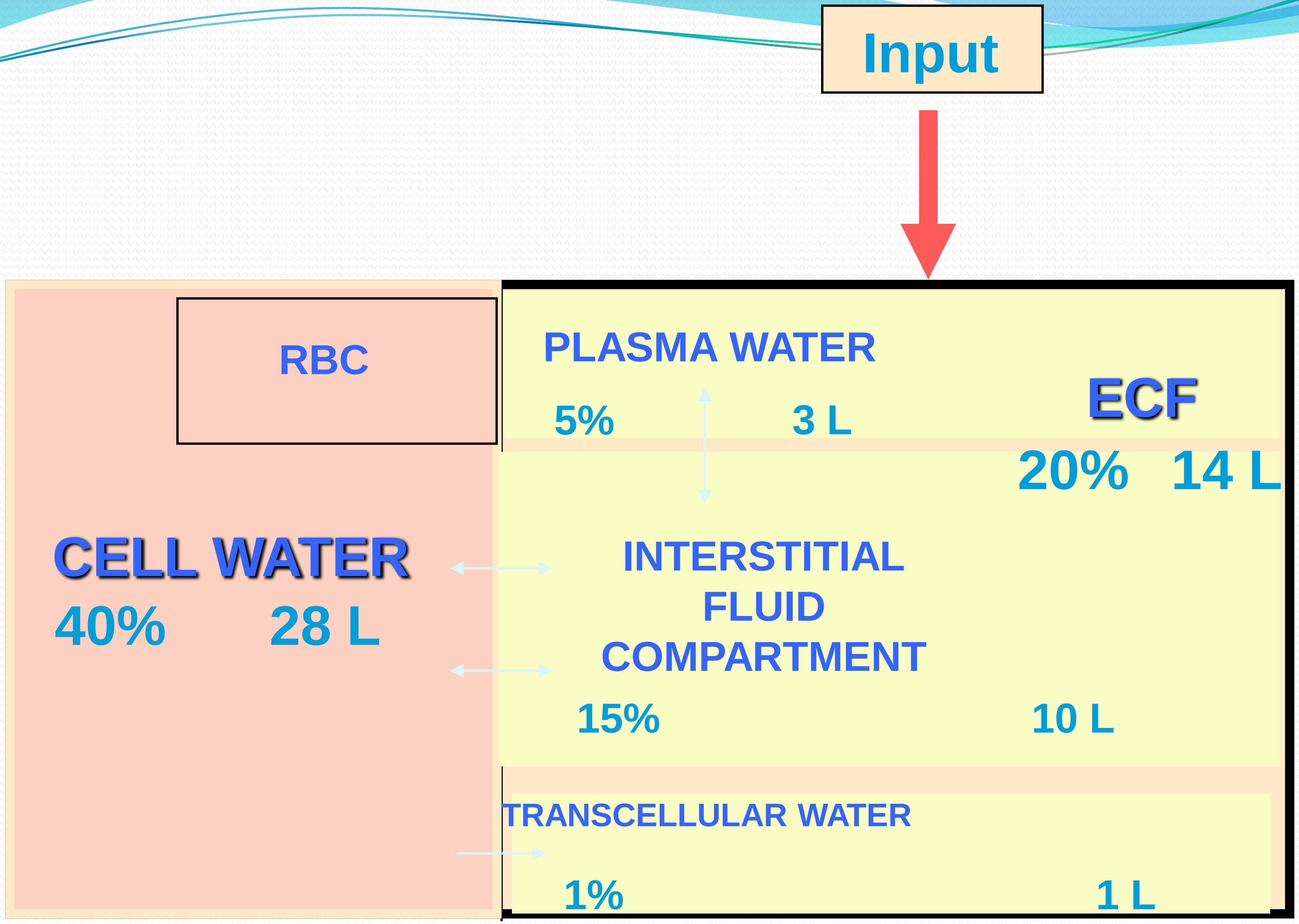
- Extracellular compartment
- Intracellular compartment
- Transcellular fluid (1-2 liters)
  - Synovial fluid
  - Peritoneal fluid
  - Pericardial fluid
  - CSF
  - aqueous humor
  - Specialized type of ECF (1.5% of B.Wt.)
- In a 70kg adult TBW is 60% of B.Wt. i.e. 42liters
  - Percentage changes with age, gender, degree of obesity

Intracellular Fluid Compartment

- 2/3 of body water (40% body weight) is present in the 75 trillion cells.
- Fluid in each cell is a mixture of several constituents but concentration of these is almost same in all cells.

Extracellular Fluid Compartment

- 1/3 of body water (20% body weight)
- 14 liters in a 70kg adult
- Two compartments
  - 1/4th the blood plasma (water=4.5% body weight)
  - 3/4th interstitial fluid and lymph (water=15% body weight)
- Plasma
  - Non-cellular part of blood
  - Continuous exchange of fluids b/w plasma and interstitial fluid
  - Same composition as interstitial fluid except proteins


Input
RBC
PLASMA WATER
5%
3 L
ECF
20%
14 L
CELL WATER
40%
28 L
INTERSTITIAL
FLUID
COMPARTMENT
15%
10 L
TRANSCELLULAR WATER
1%
1 L

Blood Volume

- Blood is a part of ECF as well as ICF
- 7% of B.Wt.
- 5 liters
- 60% of blood --- plasma
- 40% of blood --- RBC
- These %ages vary with age, gender, weight.

Hematocrit (Packed Cell Volume)

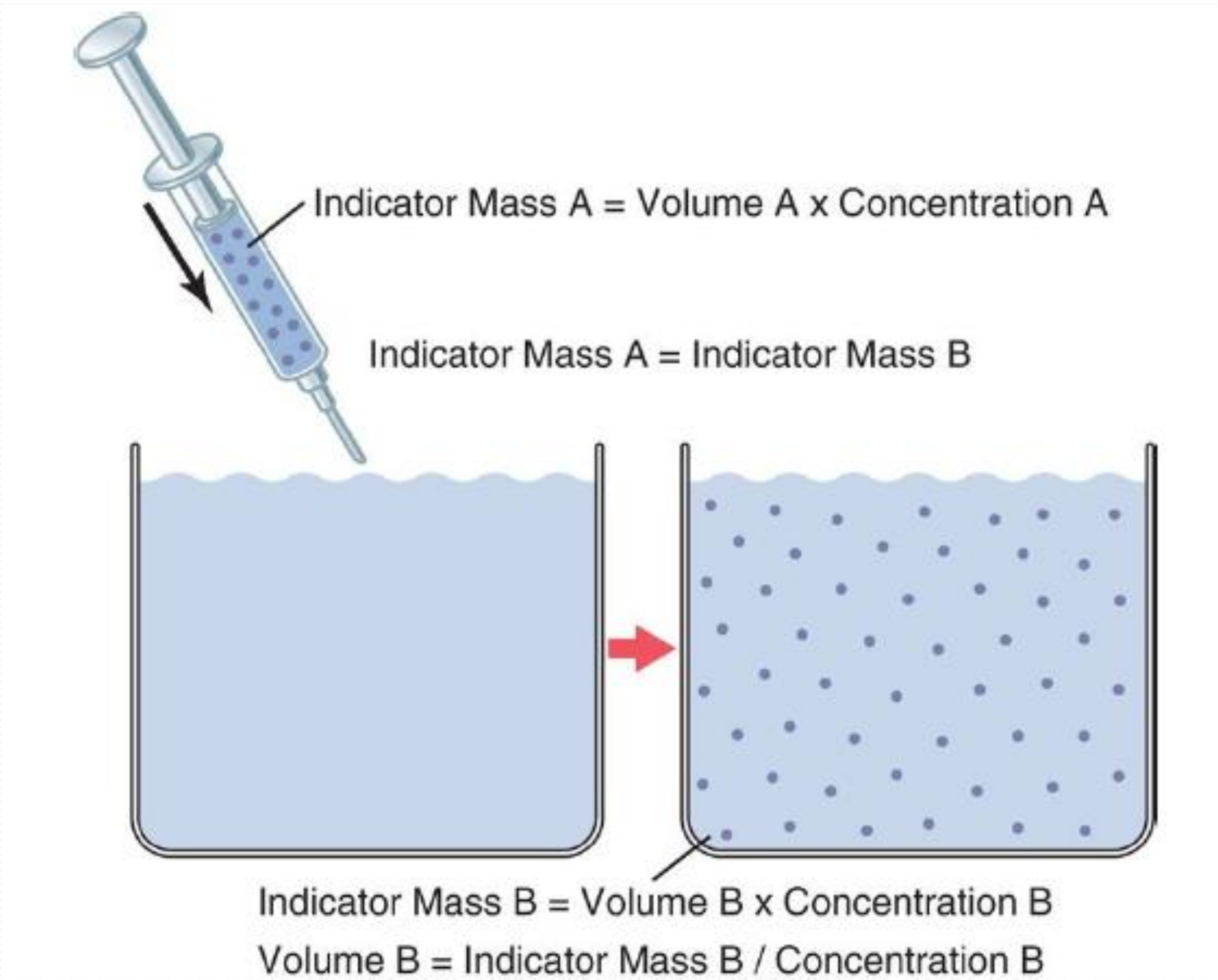
- Fraction of blood composed of RBCs
- Determined by centrifugation of blood
- Actual PCV is 3-4% less than actual
  - Normal Values
    - Males 0.40
    - Females 0.36
      - Decrease in ----- anemias
      - Increased in ----- polycythemias

Measurements of fluids in different body compartments

- **Indicator-Dilution Method**
  - **Principle**

    An indicator is placed in the compartment & allowed to disperse evenly and then analyzed extent of dilution.

  - **Can be used to measure volume of all body compartments as long as:**
    - **Indicator disperses evenly throughout the compartment**
    - **Indicator disperses only in that compartment**
    - **Indicator is not metabolized or excreted**


Indicator Mass A = Volume A x Concentration A
Indicator Mass A = Indicator Mass B
Indicator Mass B = Volume B x Concentration B
Volume B = Indicator Mass B / Concentration B

DETERMINATION OF VOLUMES OF SPECIFIC COMPARTMENTS OF BODY

- Measurement of Total Body Water
  - Radioactive water
    - Tritium or
    - Heavy water
  - Antipyrine
    - Highly lipid soluble

MEASUREMENT OF ECF

- Can be measured by injecting a substance that does not permeate the cell membrane
  - Radioactive sodium
  - Radioactive chloride
  - Radioactive iothalamate
  - Thiosulfate ion
  - Inulin

CALCULATION OF ICF

- No method of direct measurement
- Can be calculated

$$ICF = TBW - ECF$$

MEASUREMENT OF PLASMA VOLUME

- Can be measured by substance that does not permeate the capillary membrane & remains in vascular system
  - Radioactive Albumin
  - Evans blue dye (Binds to Plasma proteins)

Calculation of Interstitial Fluid

Interstitial fluid volume = ECF volume – Plasma volume

MEASUREMENT OF BLOOD VOLUME

- Radioactive labelled RBCs
- Can also be calaculated

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$

Table 25-3. Measurement of Body Fluid Volumes

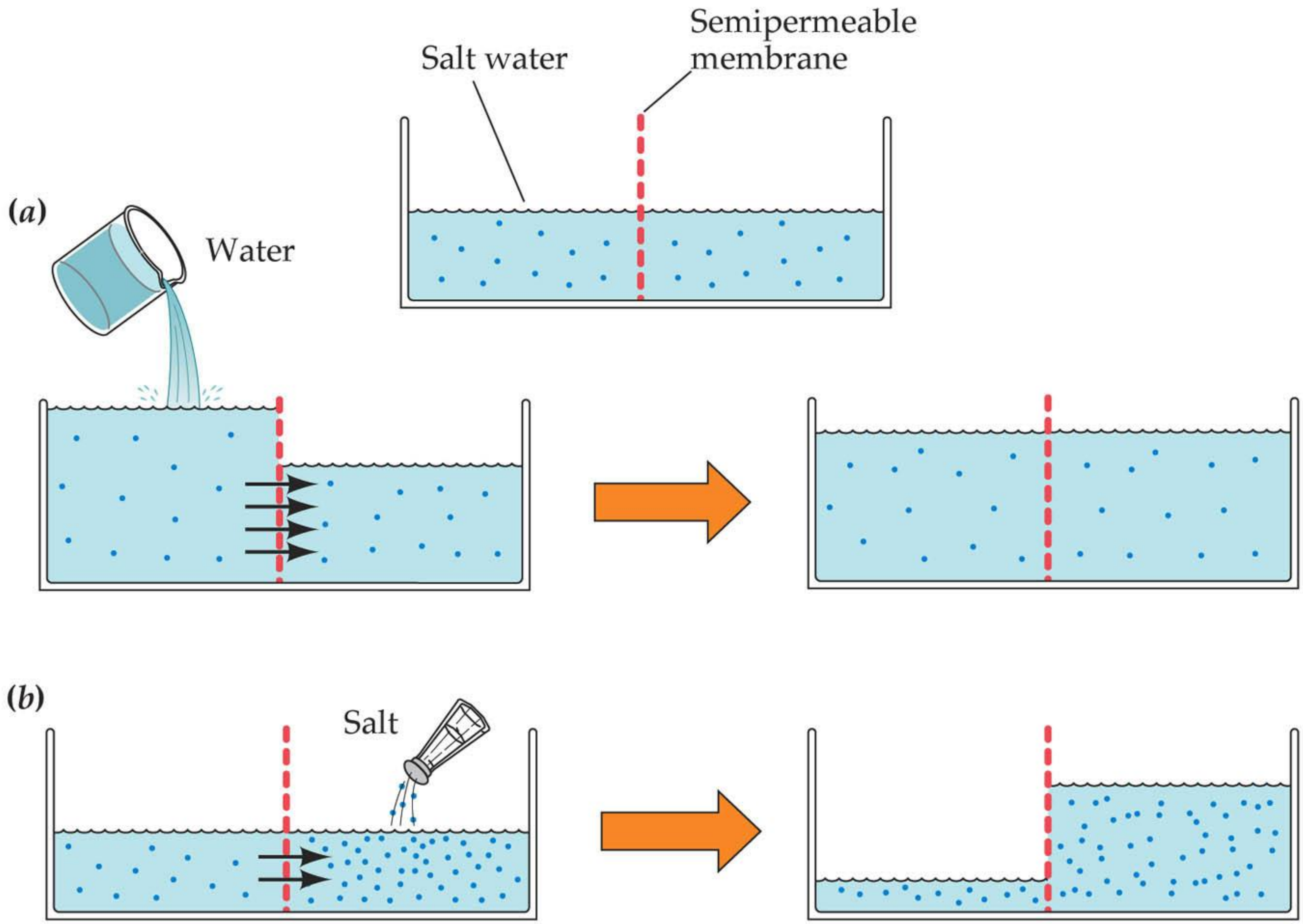
Volume	Indicators
Total body water	$^{3}H_2O$, $^{2}H_2O$, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as total body water - Extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled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

- Maintenance of adequate fluids in ECF & ICF ------ Important Clinical problem
- **Hydrostatic** forces & **Colloid osmotic** forces across capillary membrane responsible for this equilibrium within ECF
- **Osmotic effect of solutes** responsible for equilibrium b/w ICF & ECF
- Important role of Cell membrane

Osmosis

Net diffusion of water across a selectively permeable membrane from a region of high water concentration to one that has a lower water concentration.

OSMOSIS



BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 13.11 © 2004 Sinauer Associates, Inc.

CELL MEMBRANE

- Semipermeable membrane
- Highly water soluble
- Almost impermeable to solutes
- Addition or removal of solutes from one side results in osmosis
- Rate of diffusion of water molecules is called **Rate of Osmosis**

MOLES & OSMOLES

- Total no. of osmotically active particles in a solution is measured in **Osmoles**
- 1 osm = 1 mole **(If substance does not dissociate)**
- A solution containing 1 mole of glucose in a liter has a conc. of 1 osm/liter
- 1 mole of NaCl = 2 osm/liter
- 1 mole of Na2SO4 = 3 osm/liter
- 1 milliosmole (mOsm) = 1/1000 Osm

OSMOLALITY & OSMOLARITY

- No. of osmoles per kg of water—OSMOLALITY
- No. of osmoles per liter of water is OSMOLARITY
- In dil. solutions like body fluids both are same

OSMOTIC PRESSURE

- The amount of pressure required to oppose the movement of water molecules, and to stop osmosis --- Osmotic Pressure
- It is the indirect measurement of solutes & water.
- Higher the osmotic pressure, lower the water content.

OSMOTIC PRESSURE & OSMOLARITY

- Osmotic pressure directly proportional to no. of osmotically active particles
- Independent of molecular wt
- Albumin & Glucose exert same osmotic pressure
- NaCl has double osmotic effect

- Each mOsm/Liter of a solute exerts an osmotic pressure of 19.3 mmHg
- Calculating the osmolarity & osmotic pressure of a solution
- 1 liter 0.9% NaCl solution
- 308 mosm/liter
- Osmotic pressure of 5944 mm Hg
- Correction factor(Osmotic Coefficient) 0.93
- Corrected osmolarity = 286mosm/liter

- Osmolarity of body fluids
- Na & Cl --- maintain osmolarity of ECF (80%)
- K --- maintains osmolarity of ICF
- Plasma osmolarity slightly higher than Interstitial fluid
- Corrected osmolarity --- 282 mosm/liter

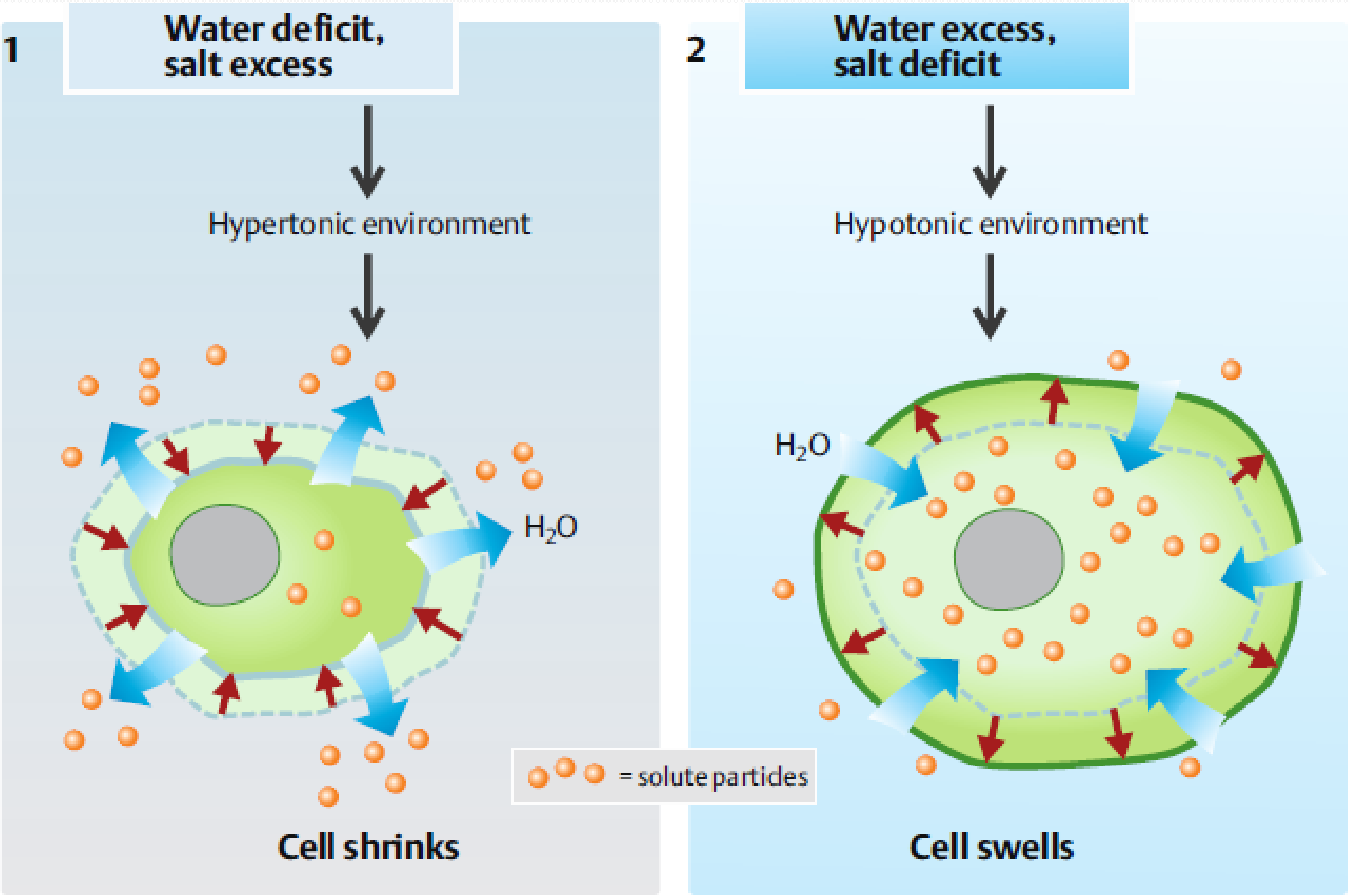
COMPARISON OF ECF & ICF

Osmolar Substances in Extracellular and Intracellular Fluids

	Plasma (mOsm/L H_2O)	Interstitial (mOsm/L H_2O)	Intracellular (mOsm/L H_2O)
Na^+	142	139	14
K^+	4.2	4.0	140
Ca^{++}	1.3	1.2	0
Mg^+	0.8	0.7	20
Cl^-	108	108	4
HCO_3^-	24	28.3	10
HPO_4^-, $H_2PO_4^-$	2	2	11
SO_4^-	0.5	0.5	1
Phosphocreatine			45
Carnosine			14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate			5
Hexose monophosphate			3.7
Glucose	5.6	5.6	
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/L	301.8	300.8	301.2
Corrected osmolar activity (mOsm/L)	282.0	281.0	281.0
Total osmotic pressure at 37°C (mm Hg)	5443	5423	5423

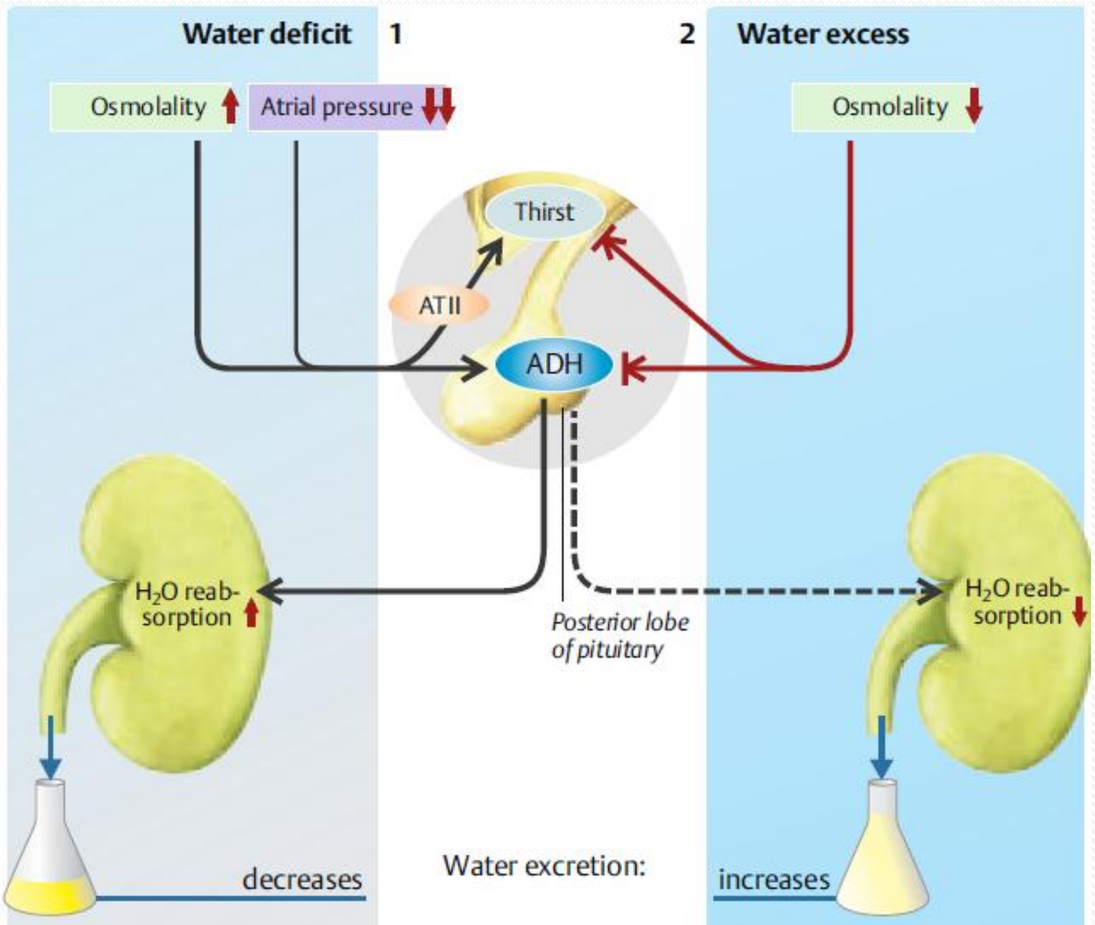
MAINTAINANCE OF OSMOTIC EQUILIBRIUM B/W ECF & ICF

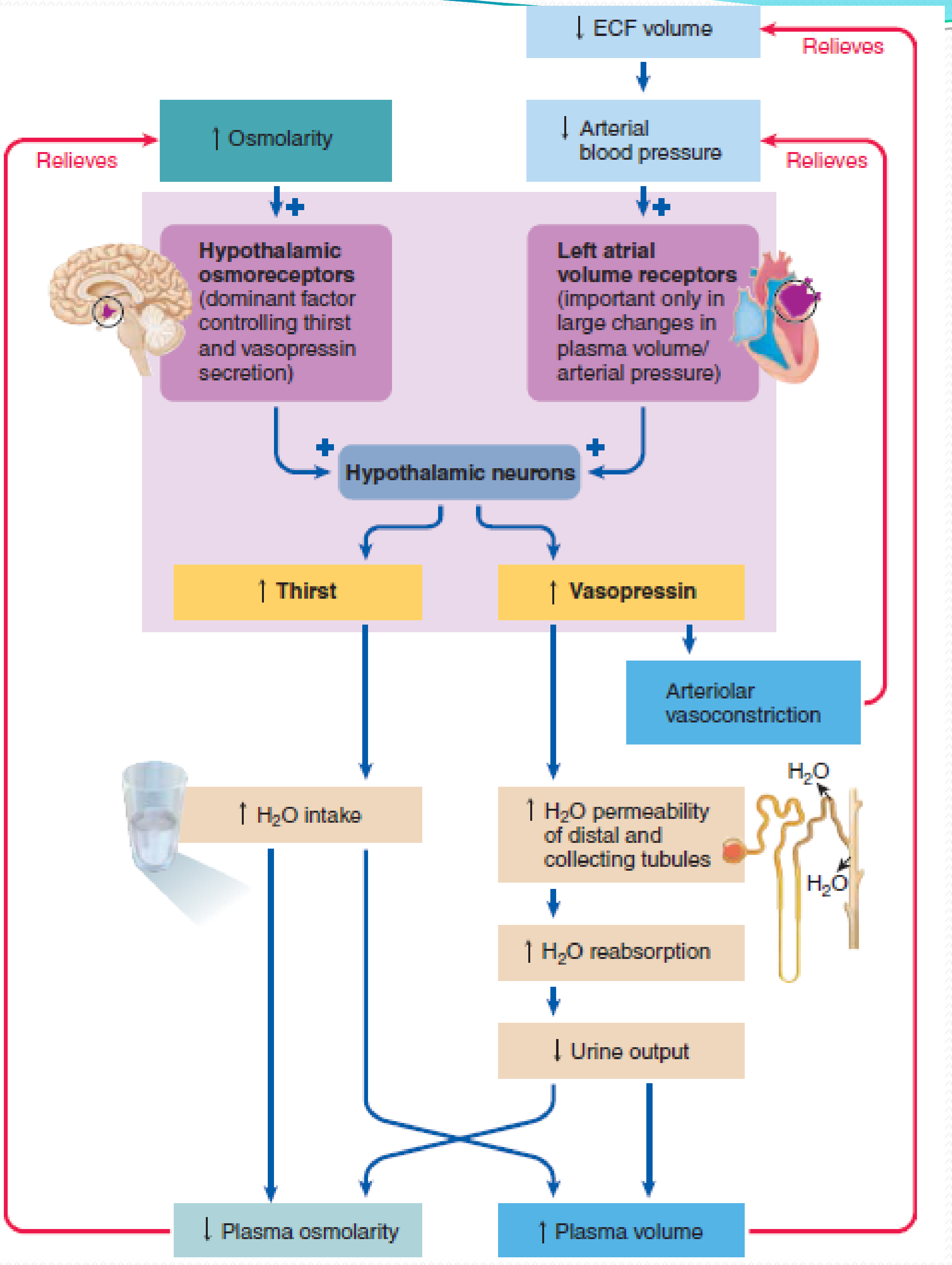
- Minute changes in solute conc. lead to large increase or decrease in osmotic pressure
- Hypertonic
- Isotonic
- Hypotonic
- 0.9% NaCl solution
- 5% Glucose solution


1
Water deficit,
salt excess
Hypertonic environment
H_2O
Cell shrinks
2
Water excess,
salt deficit
Hypotonic environment
H_2O
= solute particles
Cell swells

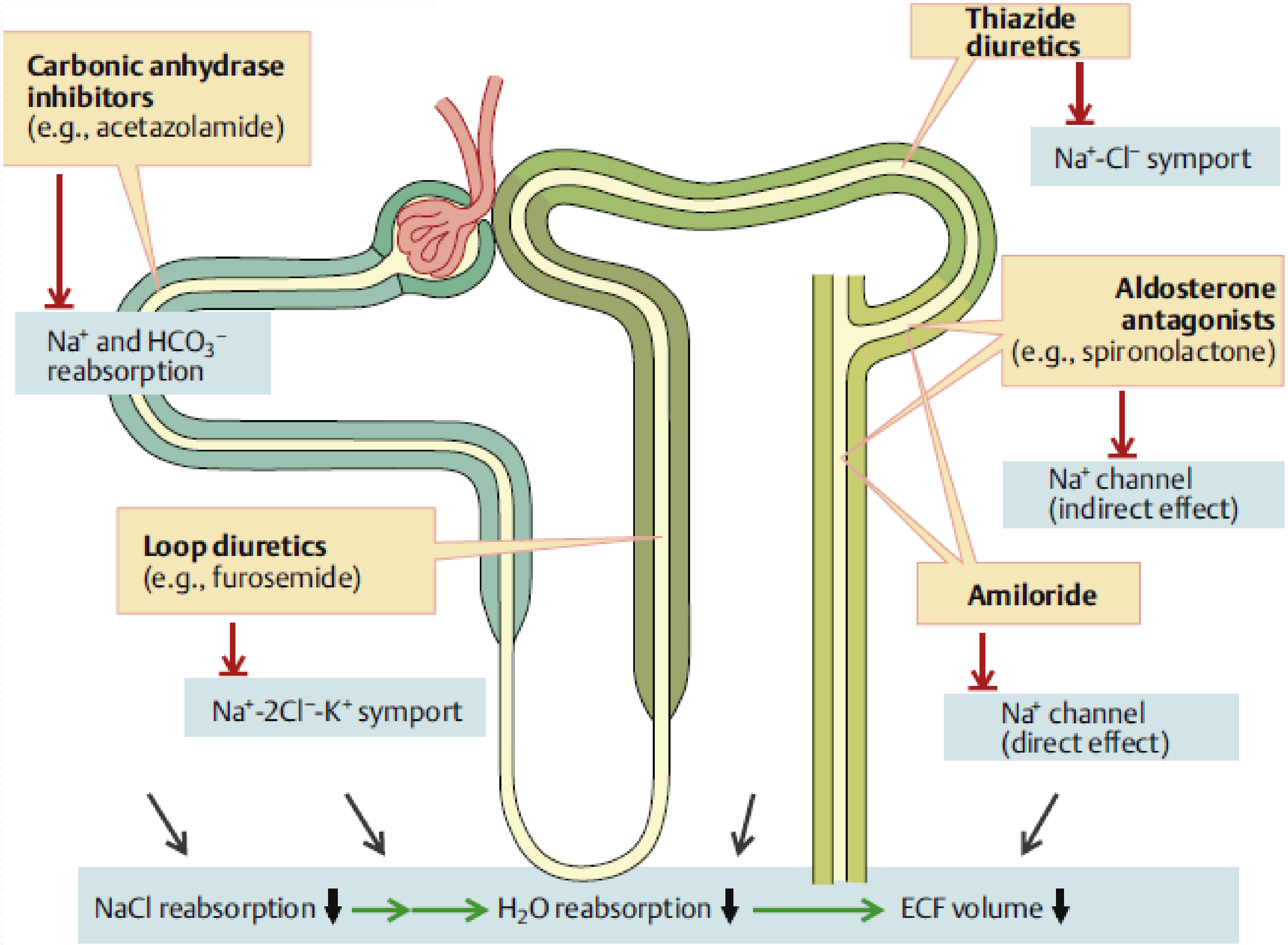
- Isosmotic
- Hyposmotic
- Hyperosmotic
- Permeating and non-permeating solutes
- NaCl
- Urea
- Osmotic equilibrium is maintained within minutes

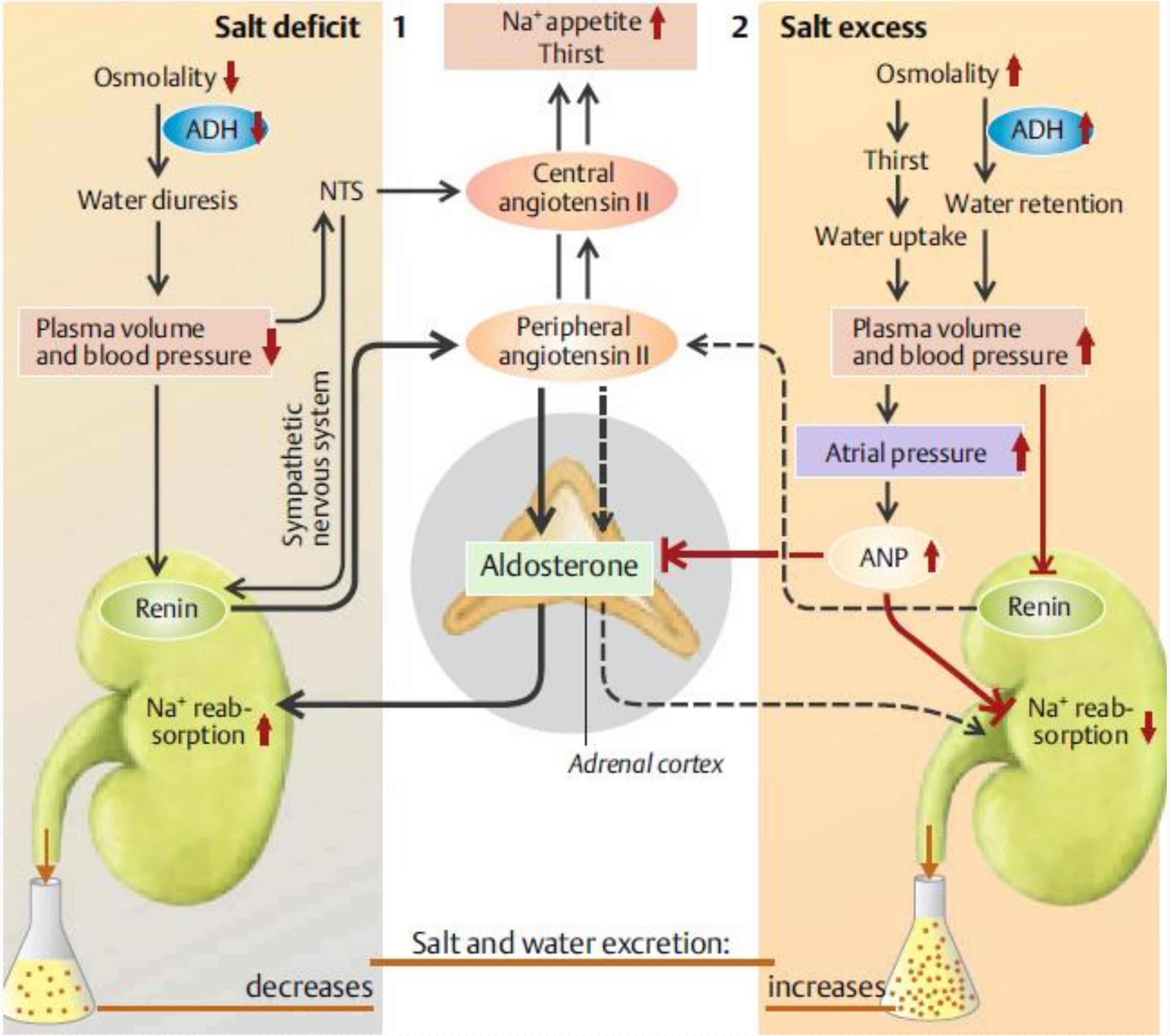
Regulation of water and salt balance

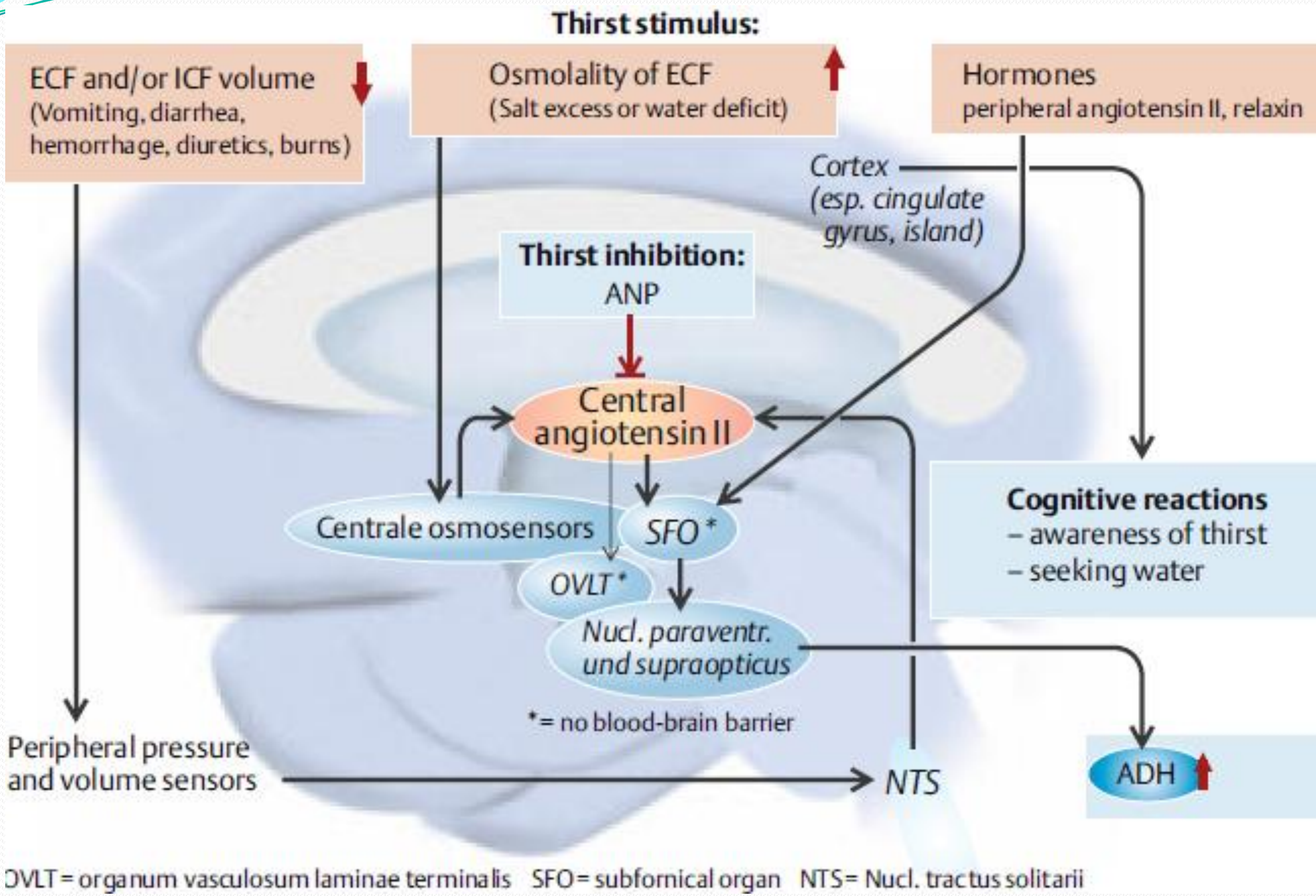




↓ ECF volume
Relieves
↑ Osmolarity
↓ Arterial blood pressure
Relieves
Relieves
Hypothalamic osmoreceptors (dominant factor controlling thirst and vasopressin secretion)
Left atrial volume receptors (important only in large changes in plasma volume/ arterial pressure)
Hypothalamic neurons
↑ Thirst
↑ Vasopressin
Arteriolar vasoconstriction
↑ H_2O intake
↑ H_2O permeability of distal and collecting tubules
H_2O
H_2O
↑ H_2O reabsorption
↓ Urine output
↓ Plasma osmolarity
↑ Plasma volume


Carbonic anhydrase inhibitors (e.g., acetazolamide)
Na+ and HCO_3^- reabsorption
Thiazide diuretics
Na+-Cl− symport
Aldosterone antagonists (e.g., spironolactone)
Na+ channel (indirect effect)
Loop diuretics (e.g., furosemide)
Na+-2Cl−-K+ symport
Amiloride
Na+ channel (direct effect)
NaCl reabsorption ↓ → H_2O reabsorption ↓ → ECF volume ↓


Salt deficit
1
Na⁺ appetite
Thirst
2
Salt excess
Osmolality
ADH
Water diuresis
NTS
Central angiotensin II
Thirst
Water retention
Water uptake
Plasma volume and blood pressure
Peripheral angiotensin II
Plasma volume and blood pressure
Sympathetic nervous system
Atrial pressure
Aldosterone
ANP
Renin
Renin
Na⁺ reab-sorption
Na⁺ reab-sorption
Adrenal cortex
Salt and water excretion:
decreases
increases


Thirst stimulus:
ECF and/or ICF volume
(Vomiting, diarrhea, hemorrhage, diuretics, burns)
Osmolality of ECF
(Salt excess or water deficit)
Hormones
peripheral angiotensin II, relaxin
Cortex
(esp. cingulate gyrus, island)
Thirst inhibition:
ANP
Central angiotensin II
Centrale osmosensors
SFO *
OVLT *
Nucl. paraventr. und supraopticus
*= no blood-brain barrier
Cognitive reactions
– awareness of thirst
– seeking water
Peripheral pressure and volume sensors
NTS
ADH
OVLT = organum vasculosum laminae terminalis SFO = subfornical organ NTS = Nucl. tractus solitarii

VOLUME & OSMOLARITY OF ECF & ICF IN ABNORMAL STATES

- WATER INGESTION
- DEHYDRATION
- I/V INFUSION
- GIT LOSSES
- PROFUSE SWEATING
  - WATER MOVES RAPIDLY ACROSS THE MEMB.
  - CELL MEMB. IMPERMEABLE TO SOLUTES

Effect of addition of 2 Liters of 3% NaCl to ECF

Step 1. Initial Conditions

	Volume (Liters)	Concentration (mOsm/L)	Total (mOsm)
Extracellular fluid	14	280	3,920
Intracellular fluid	28	280	7,840
Total body fluid	42	280	11,760

SOLUTIONS USED FOR NUTRITIVE PURPOSES

- .
- Glucose
- Amino acids
- Homogenized fat solution

CLINICAL ABNORMALITIES OF FLUID VOLUME REGULATION

- **Hyponatremia**
- **Hypernatremia**

Hyponatremia Defined

- Definition: Serum Na+ <135 meq/L
  - Generally associated with decreased osmolality to <275
  - Most common electrolyte abnormality in the US
  - Occurs in 3% of hospitalized patients

- Caused by retention of water
  - Usually a drop in osmolality will suppress ADH to allow excretion of the excess water via dilute urine
  - Most forms of hyponatremia are associated with elevated ADH (whether appropriate or inappropriate), which concentrates urine

Signs & Symptoms

- More profound when the decrease in sodium is **very large** or occurs **rapidly** (i.e. over hours)
- Generally asymptomatic if Na+ level >125
- Symptoms include:
  - Headache
  - Nausea, vomiting
  - Muscle cramps
  - Disorientation, depressed reflexes, lethargy, restlessness
  - Seizure, coma, permanent brain damage, respiratory arrest, brainstem herniation & death
    - Serious complications are more commonly seen in primary polydipsia, after surgery, and in menstruating women

Causes of hyponatremia

Decreased total body water	GI losses (diarrhea, emesis), diuretics, Addisons Disease
Increased total body water	CHF, acute renal failure, SIADH, water intoxication (dilute formula feeding), Bronchogenic CA
Normal total body water	Hyperglycemia
Pseudohyponatremia	Severe hyperlipidemia or hypoproteinemia

•Hyperglycemia leads to hyperosmolarity with translocation of fluids from intracellular to extracellular space

•Pseudohyponatremia: displacement of plasma water resulting in falsely low serum by laboratory measurement

Clinical manifestations of hyponatremia

- Neurologic symptoms related to edema caused by hypo-osmolarity
  - Children at higher risk due to higher brain-to-skull ratio
- Symptoms include headache, nausea, emesis, weakness, disorientation
- Severity worsens as edema increases leading to signs of cerebral herniation
  - Respiratory changes, posturing, pupillary changes, seizure

Fluid management goals

- Hyponatremia with neurologic symptoms is a **medical emergency**

Clinical picture	Fluid	Rate
Seizure	3% hypertonic saline	raise serum sodium by 4-8 mEq/L/hour until seizure activity stops
No seizure activity but not at neurologic baseline	3% hypertonic saline	raise serum sodium by 1mEq/L/hour until: -patient at baseline -plasma sodium increases by 20-25mEq/L OR -serum sodium increases to 125-130mEq/L
Asymptomatic	0.9% normal saline	raise sodium no faster than 0.5 mEq/L/hour

Hypernatremia

- Defined as serum sodium >/= 145mEq/L
- Causes:

Excess sodium intake	Concentrated formula, salt ingestion (seawater, accidental), hypertonic IV fluids, sodium bicarbonate, blood products
Increased free water losses	1) Renal: diabetes insipidus, tubular disorder 2) GI: diarrhea, vomiting, colostomy/ileostomy output, malabsorption 3) Insensible: fever, tachypnea, burns
Decreased free water intake	Ineffective breastfeeding, poor access to water, blunted thirst mechanisms, fluid restriction

Clinical Manifestations and Evaluation of Hypernatremia

- Early neurologic signs include agitation and irritability→can progress to seizure and coma
- Neurologic exam can reveal increased tone, brisk reflexes and rigidity
- Lab evaluation can include:
  - Serum osmolarity
  - Serum glucose
  - Urine osmolarity and specific gravity

Neurologic Sequelae

- In acute phase:
  - Intracellular fluid moves to extracellular space-volume loss in brain → separation from meninges
- If hypernatremia has existed for >2-3 days:
  - Neurons protect themselves by making osmolytes to maintain gradient
  - With rapid correction, neurons can swell leading to cerebral edema
- Mortality estimated at 10-16% despite correct rate of rehydration

What is this ????

EDEMA

- Abnormal accumulation of fluid in the body tissues
  - Intracellular Edema
  - Extracellular Edema

Intracellular Edema

- Three main causes
  - Hyponatremia
  - Depression of Metabolic systems
  - Lack of adequate nutrients
    - Lack or decrease in tissue blood supply
    - Inflammatory conditions lead to edema

Extracellular Edema

- Two general causes
  - Abnormal leakage of fluid from plasma into interstitial spaces across the capillaries
  - Failure of lymphatics to return fluid back to plasma (**Lymphedema**)
- Increased capillary fluid filtration is the most common cause

Organ specific:

- Brain: Cerebral edema
- Lung: Intra-alveolar=pulmonary edema, intra-pleural=pleural effusion
- Peritoneum=ascites
- Severe generalized edema=anasarca

Factors increasing Capillary filtration

- Increased capillary filtration coefficient.
- Increased capillary hydrostatic pressure.
- Decreased plasma colloid osmotic pressure

Lymphatic Blockage

- Failure of lymphatics to return plasma proteins back to plasma.
- Causes
  - Infections of lymph nodes. e.g., **Filaria Nematode**
  - Cancers
  - Surgical removal of lymph nodes. e.g., Radical Mastectomy

SUMMARY OF CAUSES OF EXTRACELLULAR EDEMA

I. **Increased capillary pressure**

A. **Excessive kidney retention of salt and water**

1. Acute or chronic kidney failure
2. Mineralocorticoid excess

B. **High venous pressure and venous constriction**

1. Heart failure
2. Venous obstruction
3. Failure of venous pumps
    - (a) Paralysis of muscles
    - (b) Immobilization of parts of the body
    - (c) Failure of venous valves

C. Decreased arteriolar resistance

1. Excessive body heat
2. Insufficiency of sympathetic nervous system
3. Vasodilator drugs

II. Decreased plasma proteins

A. Loss of proteins in urine (nephrotic syndrome)

B. Loss of protein from denuded skin areas

1. Burns
2. Wounds

C. Failure to produce proteins

1. Liver disease (e.g., cirrhosis)
2. Serious protein or caloric malnutrition

III. Increased capillary permeability

A. Immune reactions that cause release of histamine and other immune products

B. Toxins

C. Bacterial infections

D. Vitamin deficiency, especially vitamin C

E. Prolonged ischemia

F. Burns

IV. BLOCKAGE OF LYMPH RETURN

A. Cancer

B. Infections (e.g., filaria nematodes)

C. Surgery

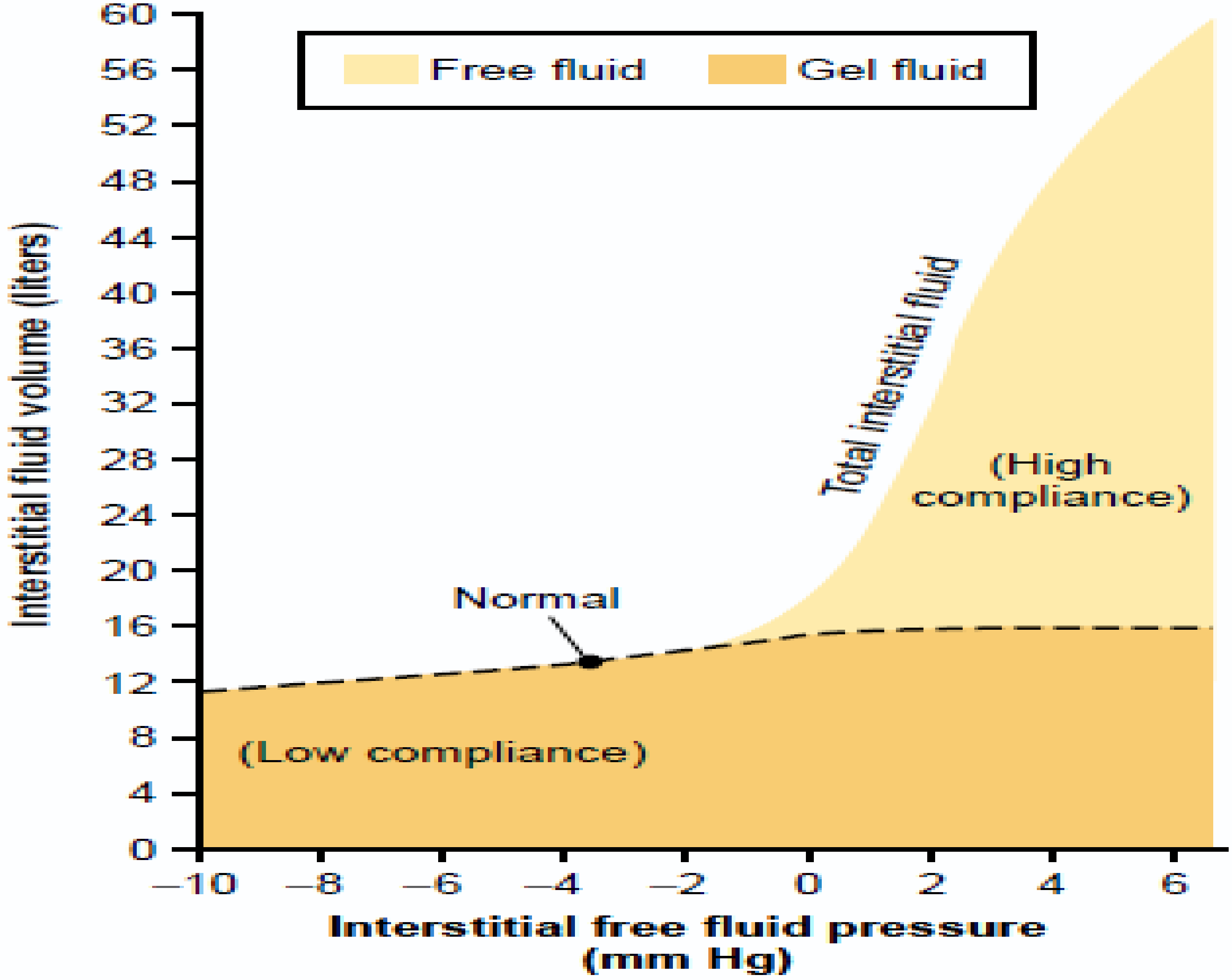
D. Congenital absence or abnormality of lymphatic vessels

Safety Factors Preventing Edema

- Low compliance of interstitium when I.F. pressure is in negative range
- 10-50 fold increase in lymph flow
- Wash down of interstitial fluid protein concentration

Low Compliance of Interstitium

- Normal I.F. pressure = -3mmHg
- Slight suction pressure
- Low compliance when pressure is in negative range



Free fluid
Gel fluid
Interstitial fluid volume (liters)
60
56
52
48
44
40
36
32
28
24
20
16
12
8
4
0
–10
–8
–6
–4
–2
0
2
4
6
Total interstitial fluid
(High compliance)
Normal
(Low compliance)
Interstitial free fluid pressure (mm Hg)

Importance of Interstitial Gel

- Interstitium is in the form of gel supported by proteoglycan filaments
- Accumulation of free fluid in +ve range
- Pitting Edema
- Non-Pitting Edema

Increased Lymph Flow

- 10-50 fold increase in lymph flow
- Removal of fluids and proteins from interstitium
- 7mm Hg

Washdown of I.F. proteins

- Increased I.F. volume --- Increased I.F. pressure
- Increased lymph flow
- Increased removal of proteins
- 7mm Hg

Summary of safety factors

- Low compliance=3 mmHg
- Increased lymph flow=7 mmHg
- Washdown of Plasma Proteins=7mmHg
- Total safety factor = 17mmHg

Fluids in potential spaces

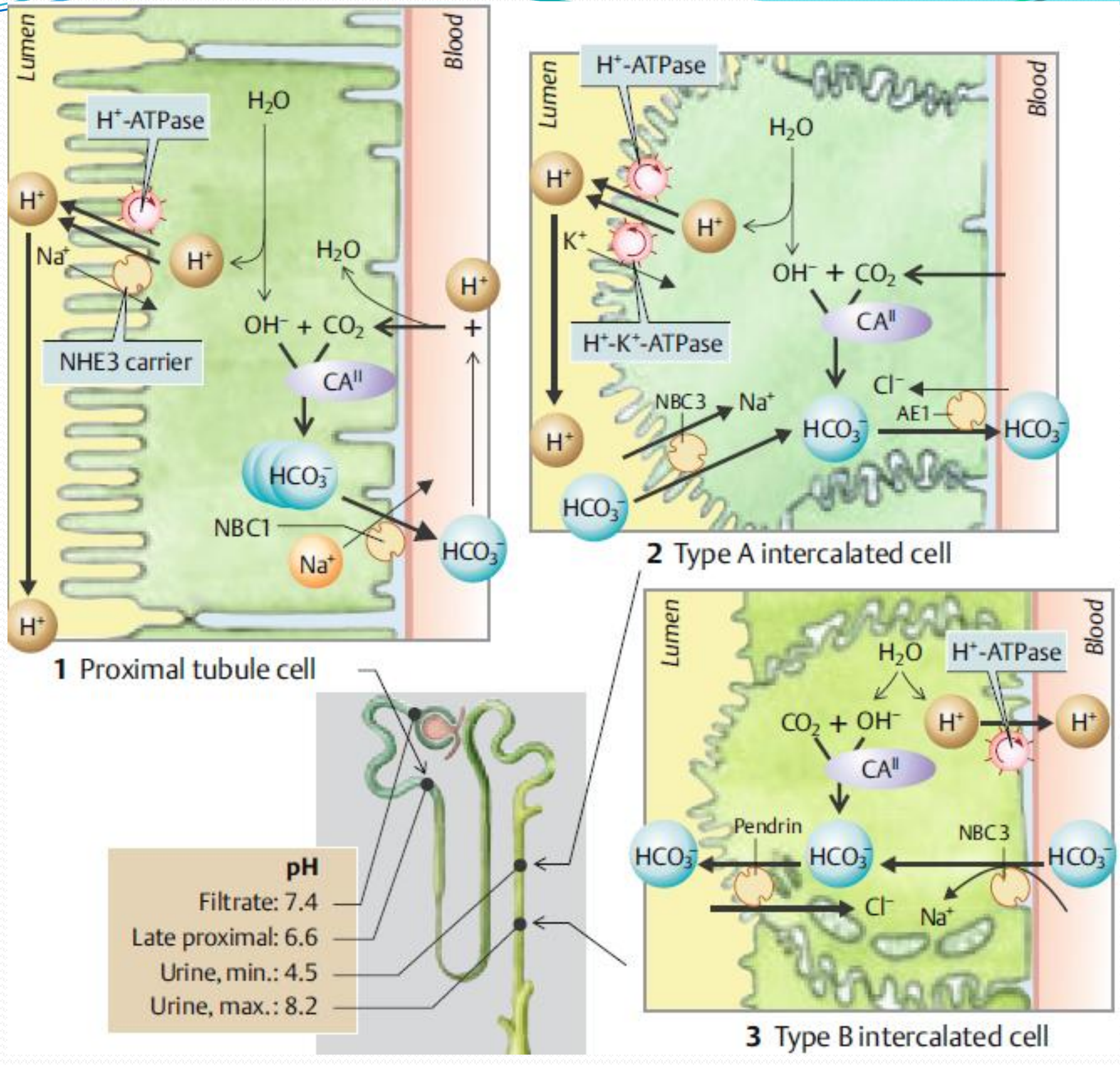
- Pleural cavity
- Pericardial cavity
- Peritoneal cavity
- Synovial cavity

Effusion

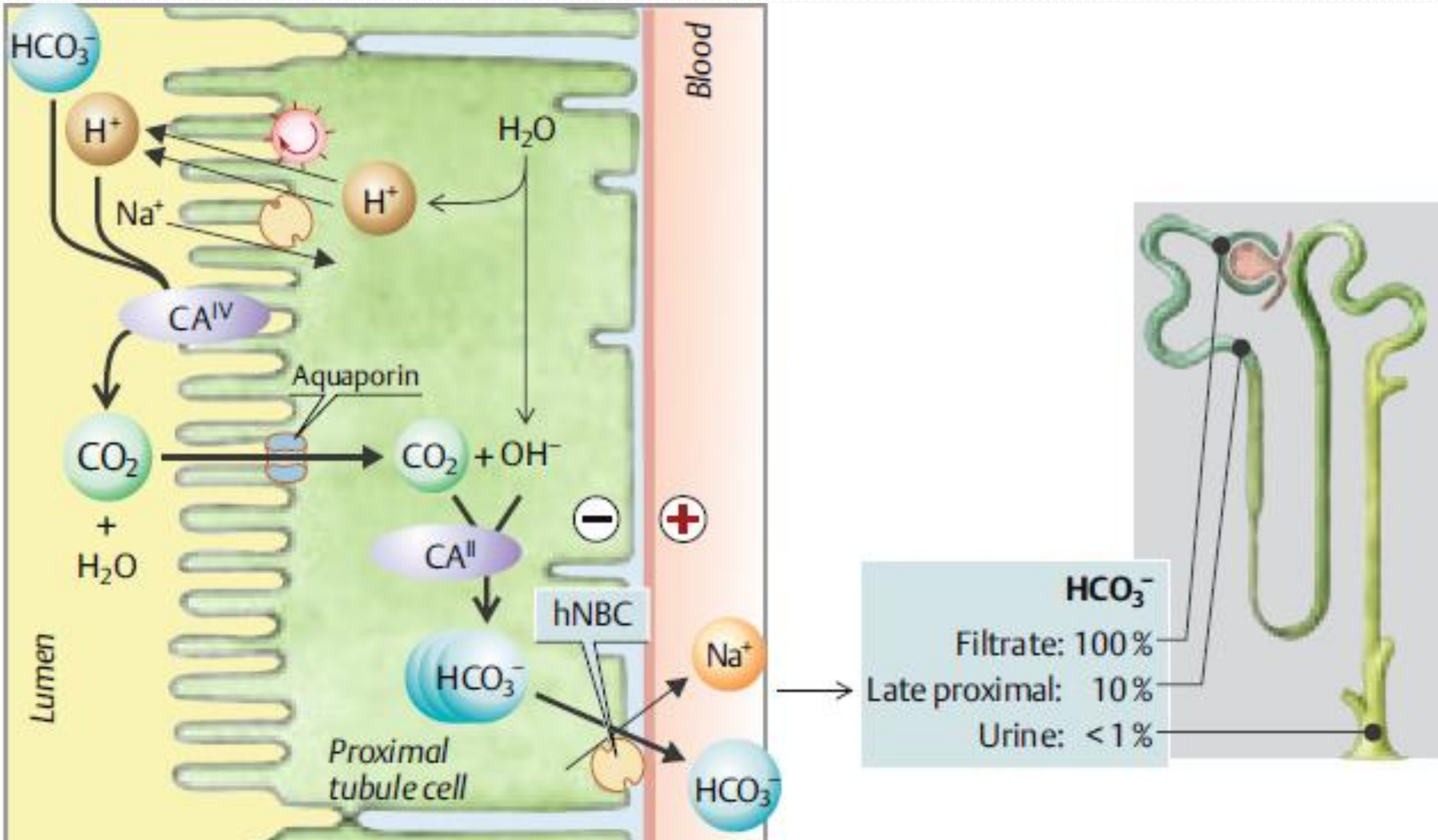
- Collection of fluid in potential spaces
- Pleural effusion, pericardial effusion
- Ascites--- collection of fluid in peritoneal cavity. (May be upto 20 liters)
- Cause of effusion--- Infection, Injury, lymphatic blockage

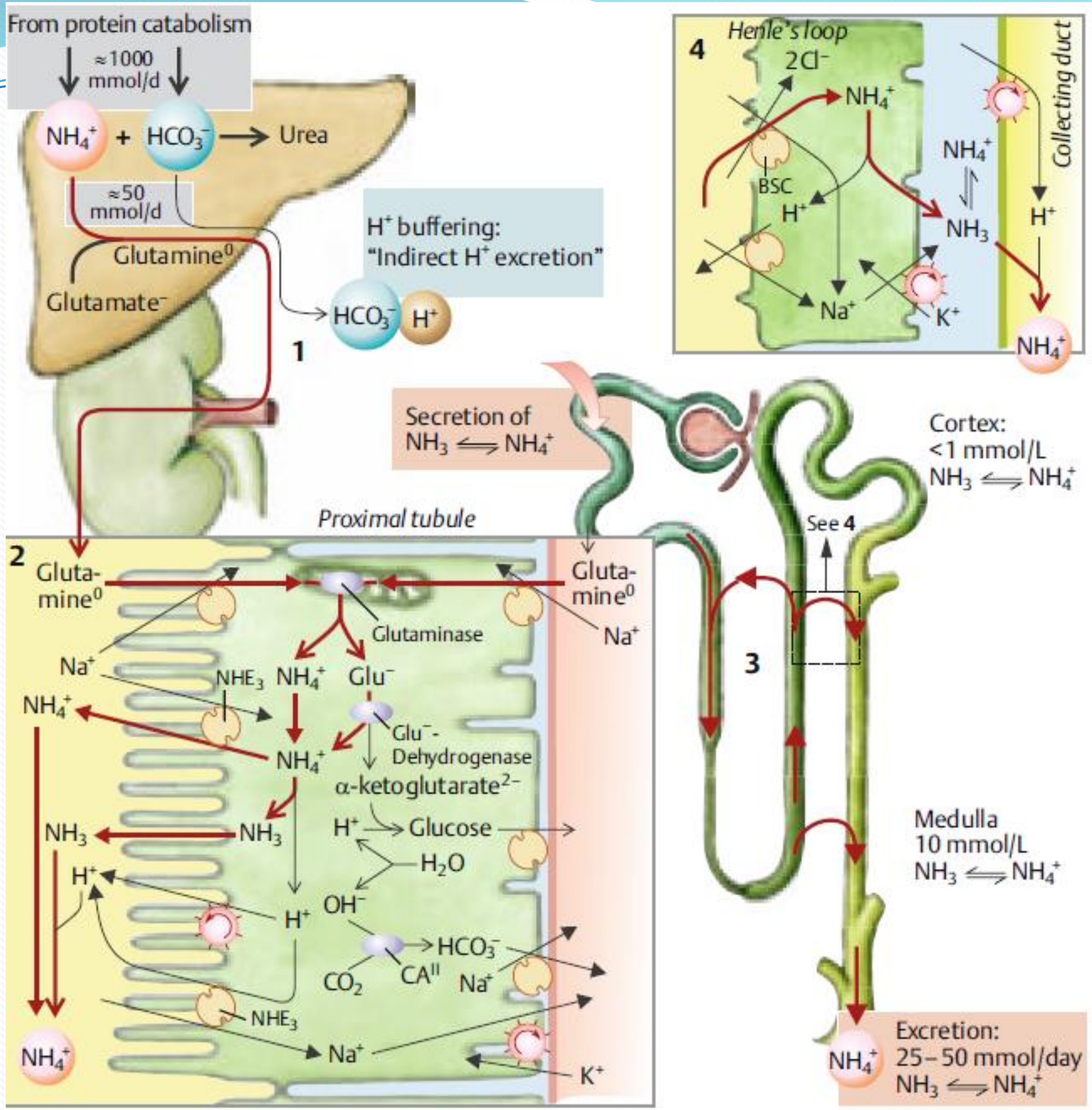
Kidney and Acid Base Balance

- Kidneys adjust their rate of hydrogen ion excretion by varying the extent of hydrogen ion secretion
- Kidneys conserve or excrete bicarbonate ions depending on the plasma hydrogen ion concentration
- Kidneys secrete ammonia during acidosis to buffer secreted hydrogen ions
- The phosphate buffer system is an important urinary buffer



Lumen
Blood
H+-ATPase
H2O
H+
Na+
NHE3 carrier
H2O
OH− + CO2
CAII
HCO3−
NBC1
Na+
HCO3−
1 Proximal tubule cell
H+-ATPase
Lumen
Blood
H2O
H+
K+
OH− + CO2
H+-K+-ATPase
CAII
Cl−
NBC3
Na+
HCO3−
AE1
HCO3−
HCO3−
2 Type A intercalated cell
pH
Filtrate: 7.4
Late proximal: 6.6
Urine, min.: 4.5
Urine, max.: 8.2
Lumen
Blood
H2O
H+-ATPase
CO2 + OH−
H+
CAII
Pendrin
NBC3
HCO3−
HCO3−
HCO3−
Cl−
Na+
3 Type B intercalated cell


HCO3−
H+
H2O
H+
Na+
CAIV
Aquaporin
CO2
CO2 + OH−
+
H2O
CAII
hNBC
HCO3−
Na+
HCO3−
Lumen
Proximal tubule cell
Blood
HCO3−
Filtrate: 100 %
Late proximal: 10 %
Urine: < 1 %



From protein catabolism
≈1000 mmol/d
NH4+ + HCO3- → Urea
≈50 mmol/d
Glutamine0
Glutamate-
H+ buffering: "Indirect H+ excretion"
HCO3- H+
1
Henle's loop
4
2Cl-
NH4+
BSC
H+
NH4+
NH3
H+
Na+
K+
Collecting duct
NH4+
Secretion of NH3 ⇌ NH4+
Cortex: <1 mmol/L NH3 ⇌ NH4+
Proximal tubule
See 4
2
Gluta-mine0
Glutaminase
Gluta-mine0
Na+
Na+
NHE3
NH4+
Glu-
NH4+
Glu--Dehydrogenase
NH4+
α-ketoglutarate2-
3
H+
Glucose
NH3
NH3
H2O
H+
OH-
H+
Medulla 10 mmol/L NH3 ⇌ NH4+
HCO3-
CO2
CAII
Na+
NHE3
Na+
NH4+
K+
Excretion: 25–50 mmol/day NH3 ⇌ NH4+
NH4+