THE UNIVERSITY OF MELBOURNE

Melbourne Veterinary School

# Structure and Function of the Kidney – Autoregulation, Glomerular Filtration and Urine Composition

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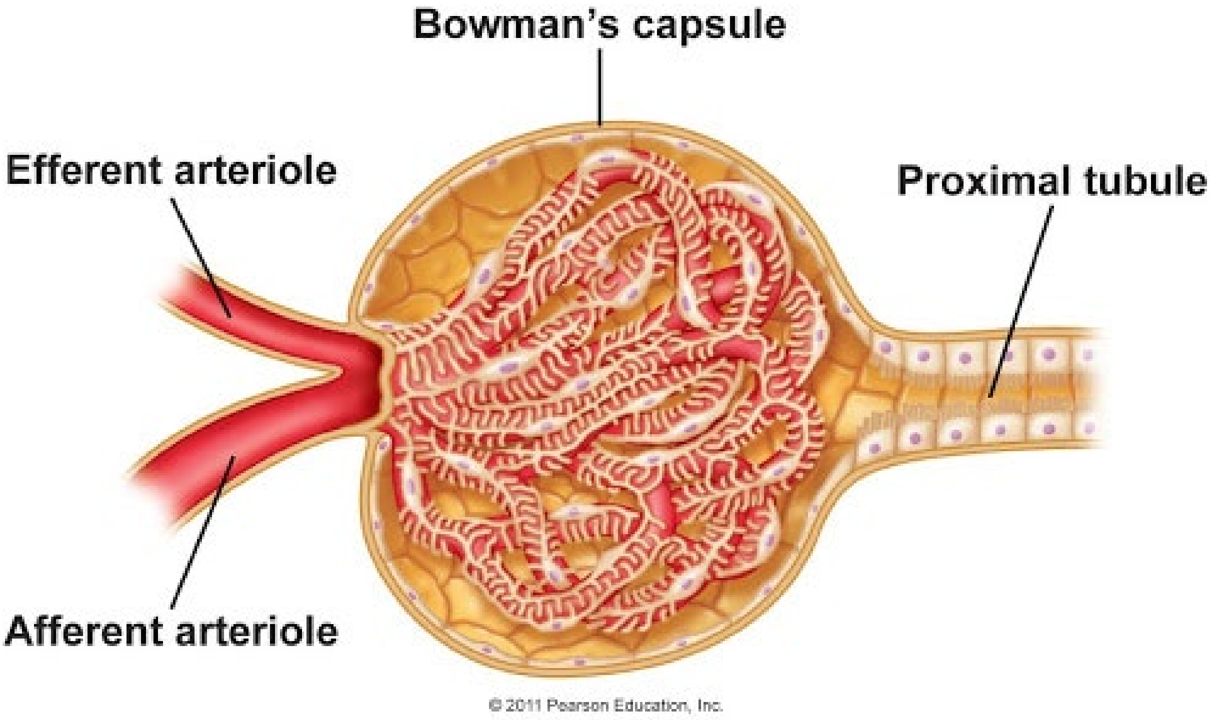
VETS30017 / VETS90125

# Intended Learning Outcomes

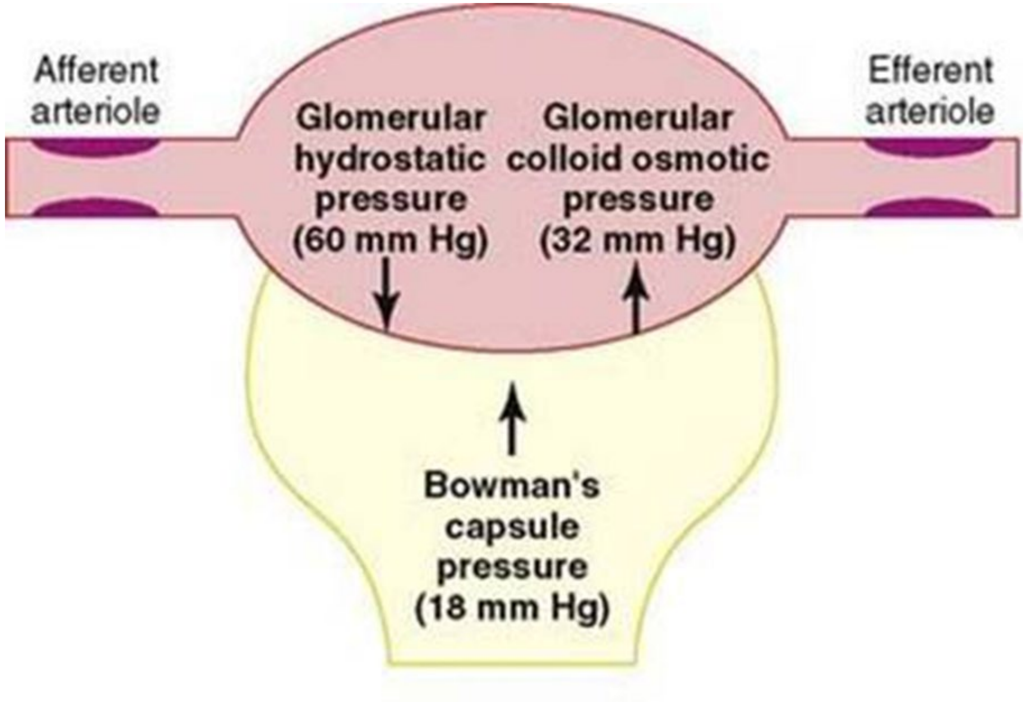
- Describe how glomerular filtration occurs, why it is important and the factors that regulate it
- Explain the processes of autoregulation and the factors and hormones that regulate it
- Explain how GFR can be measured and used as an assessment of renal function
- Describe how urine is formed and modified through glomerular filtration, tubular reabsorption and secretion
- Describe the composition of normal urine
- Describe transport mechanisms responsible for sodium reabsorption by the nephron
- Explain coupling of sodium and water reabsorption in the proximal tubule
- Describe how organic ions are secreted and why this is important

# Glomerular filtration

- High renal blood flow → large volumes filtered through glomeruli
- Most reabsorbed
- Filtrate/ultrafiltrate very similar composition to plasma
  - Minus protein and protein-bound substances
- Flow of fluid from plasma into Bowman's space over time = glomerular filtration rate



# Glomerular filtration rate

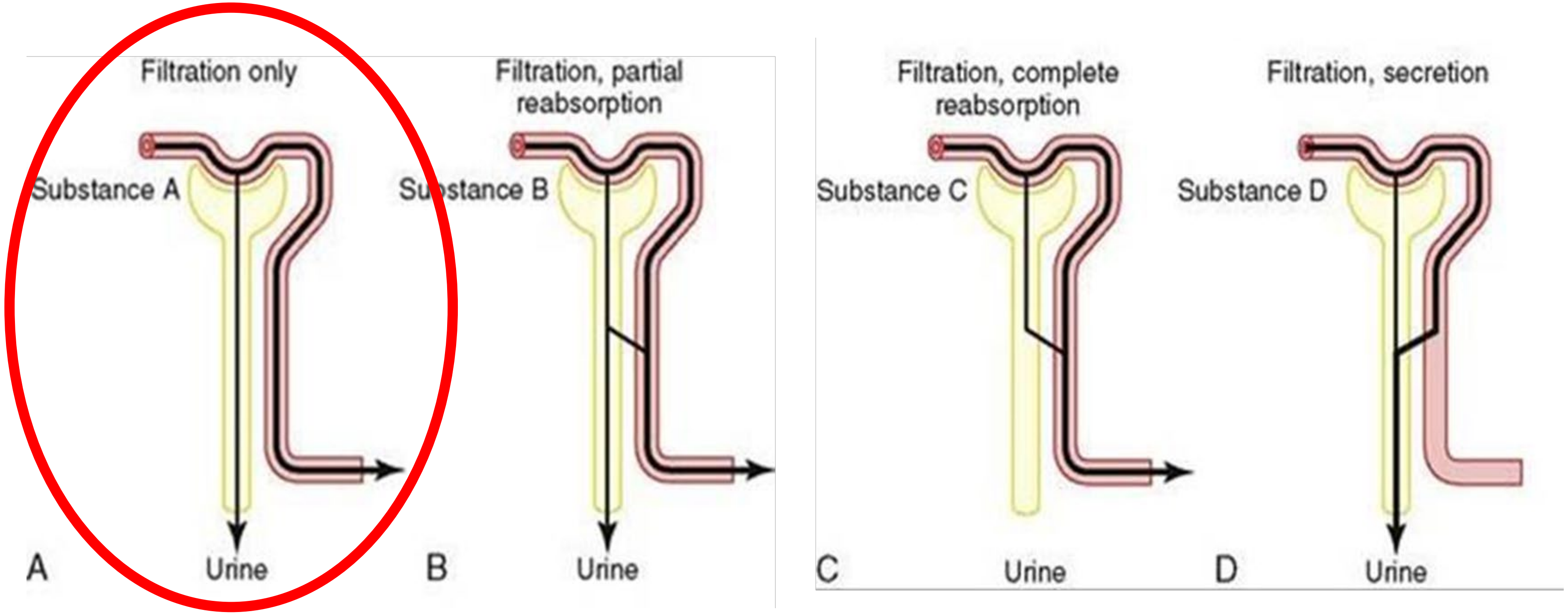



- Mainly determined by:
  - Hydrostatic and colloid osmotic forces across glomerular membrane
    = net filtration pressure
  - Capillary filtration coefficient ($K_f$)
    = permeability & surface area of glomerular capillaries

- GFR = $K_f$ x net filtration pressure

Guyton & Hall, 14th Ed. 2021

# Measuring GFR




- Can’t easily measure GFR, therefore we estimate it by measuring other things that are affected by GFR
- Typically these substances are filtered at the glomerulus but don’t undergo any reabsorption or secretion in the tubules

# Measuring/estimating GFR

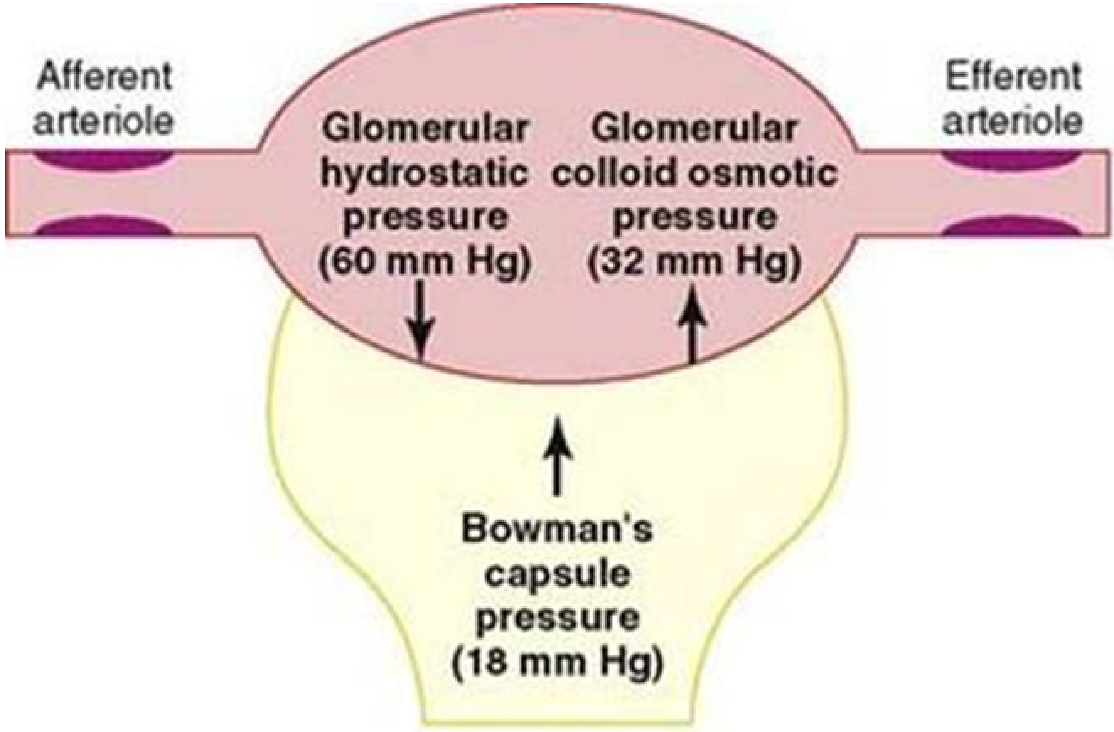
- Endogenous substances produced at a relatively constant rate
  - Creatinine
  - Blood urea nitrogen (dogs and cats)
- These are indirect estimations of GFR. Insensitive - ~75% of kidney function lost before they increase
- Creatinine measurement in plasma and urine to calculate eGFR
  - Creatinine clearance
- More complex testing involving administration of a substance that is not reabsorbed or secreted, measuring plasma and urine concentrations to calculate eGFR

# Glomerular filtration rate

- Kept relatively constant despite changes in BP, intravascular volume, etc.
- How?
  - Can’t change permeability and surface area of capillaries (in health)
  - PRESSURE

# Glomerular filtration rate

- Bowman's capsule pressure and glomerular colloid osmotic pressure **OPPOSE** filtration
- Glomerular hydrostatic pressure **DRIVES** filtration
  - This is the easiest factor to change
  - Controlled by:
    - Arterial pressure
    - Afferent arteriolar resistance
    - Efferent arteriolar resistance

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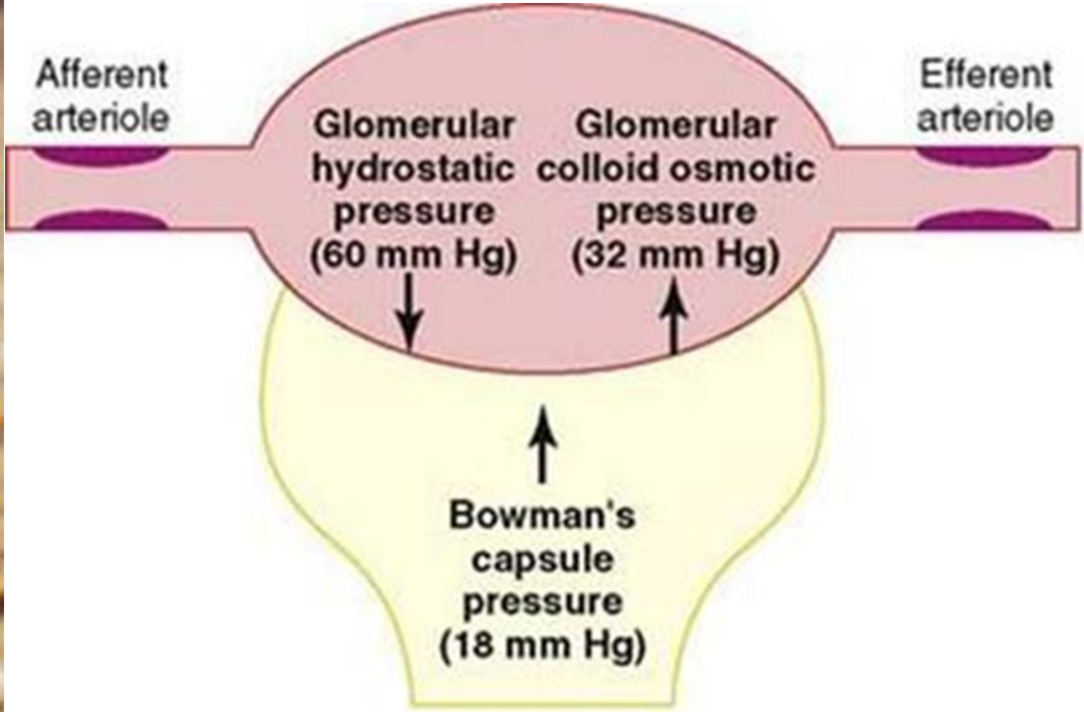
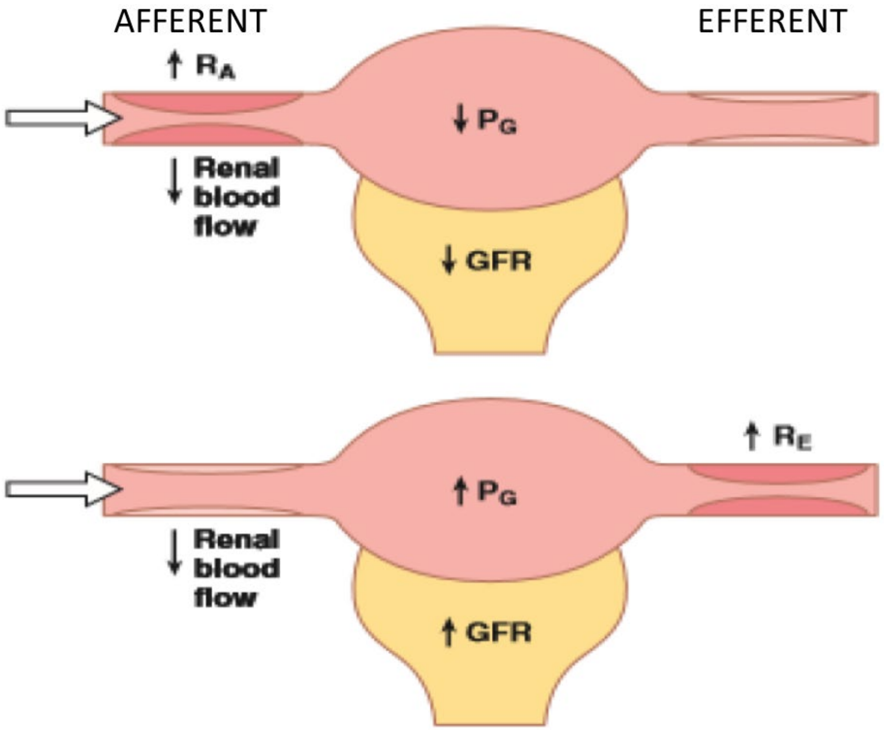
# What could possibly go wrong?




Plasma creatinine concentration = 926 µmol/L; reference range 40-80 µmol/L

# Physiological control of GFR

- Mostly changes hydrostatic pressure in the glomerular capillaries
  - Influenced by:
    - Arterial blood pressure
    - Afferent arteriolar resistance
    - Efferent arteriolar resistance
- Mechanisms:
  - Sympathetic nervous system
  - Autacoid/hormonal control
  - Tubuloglomerular feedback (autoregulation)

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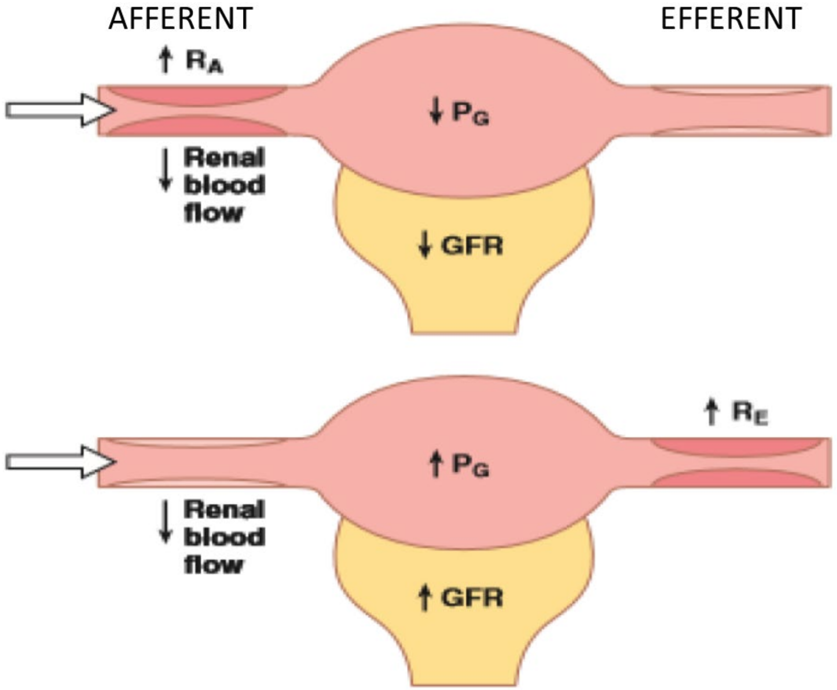
# How do the arterioles know what to do?

- ↑ BP → afferent arteriolar constriction → ↓ glomerular hydrostatic pressure and ↓ filtration at the glomerulus
- ↓ BP → efferent arteriolar constriction → ↑ glomerular hydrostatic pressure and ↑ filtration at the glomerulus
- However, if efferent arterioles are severely constricted, glomerular filtration actually decreases:
  - Glomerular colloid osmotic pressure increases
  - Overall renal blood flow decreases
- What makes either arteriole constrict?

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# Sympathetic nervous system

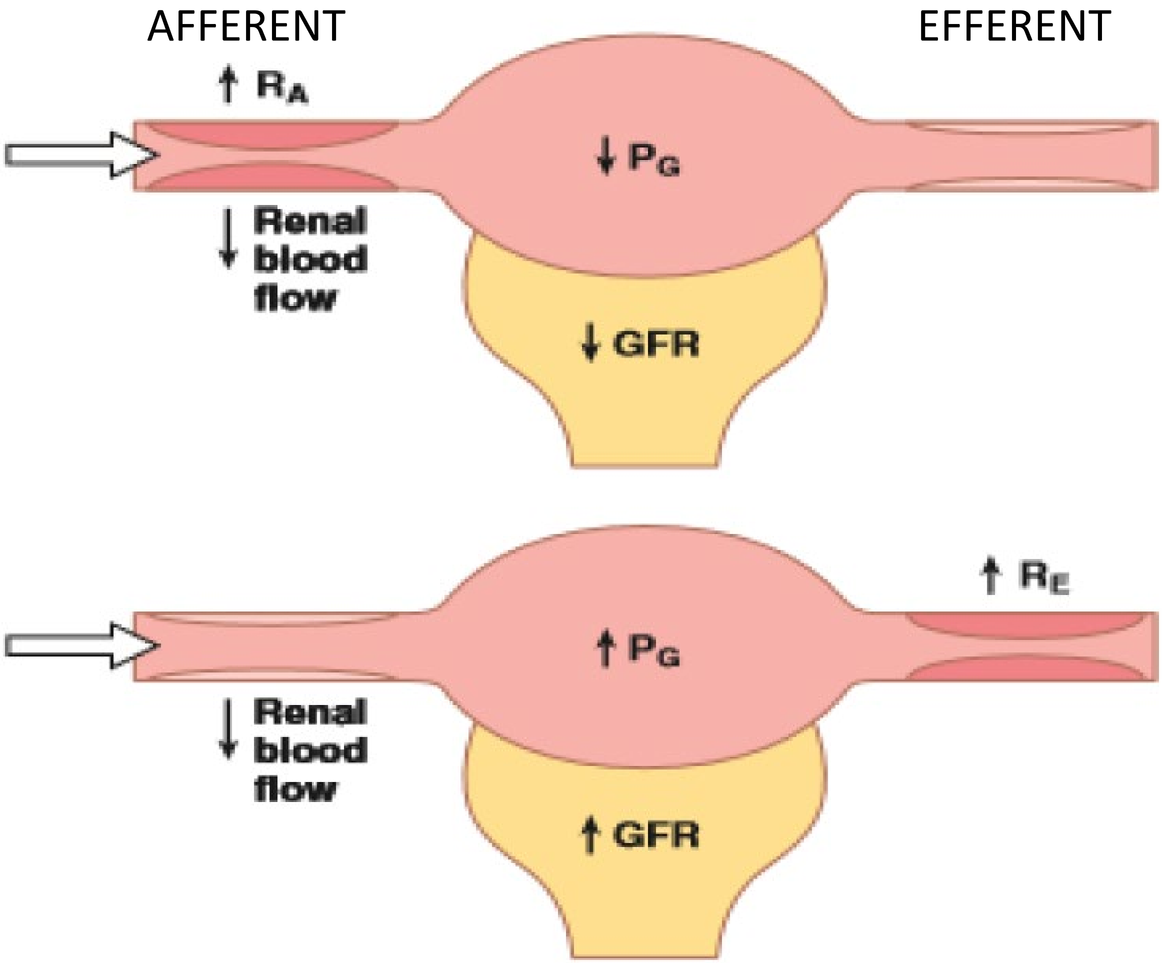
- All renal blood vessels innervated by sympathetic nerves
- Only strong sympathetic activation will cause constriction of renal arterioles
- Most important in severe, acute disturbances, e.g. severe haemorrhage, defense reaction

# Autacoid/hormonal control

- Adrenaline/epinephrine and noradrenaline/norepinephrine
  - Same effect as SNS activation
  - Constrict renal arterioles; ↓ GFR
- (Endothelin; ↓ GFR)
- Angiotensin II
  - Produced when BP decreases
  - Preferentially constricts efferent arteriole → maintenance of normal GFR
- Nitric oxide
  - Vasodilatory, ↑ GFR
- Prostaglandins
  - $PGE_2$ & $PGI_2$
  - Vasodilatory, oppose vasoconstriction, maintenance of normal GFR

# Autacoid/hormonal control – what could possibly go wrong?


# Tubuloglomerular feedback

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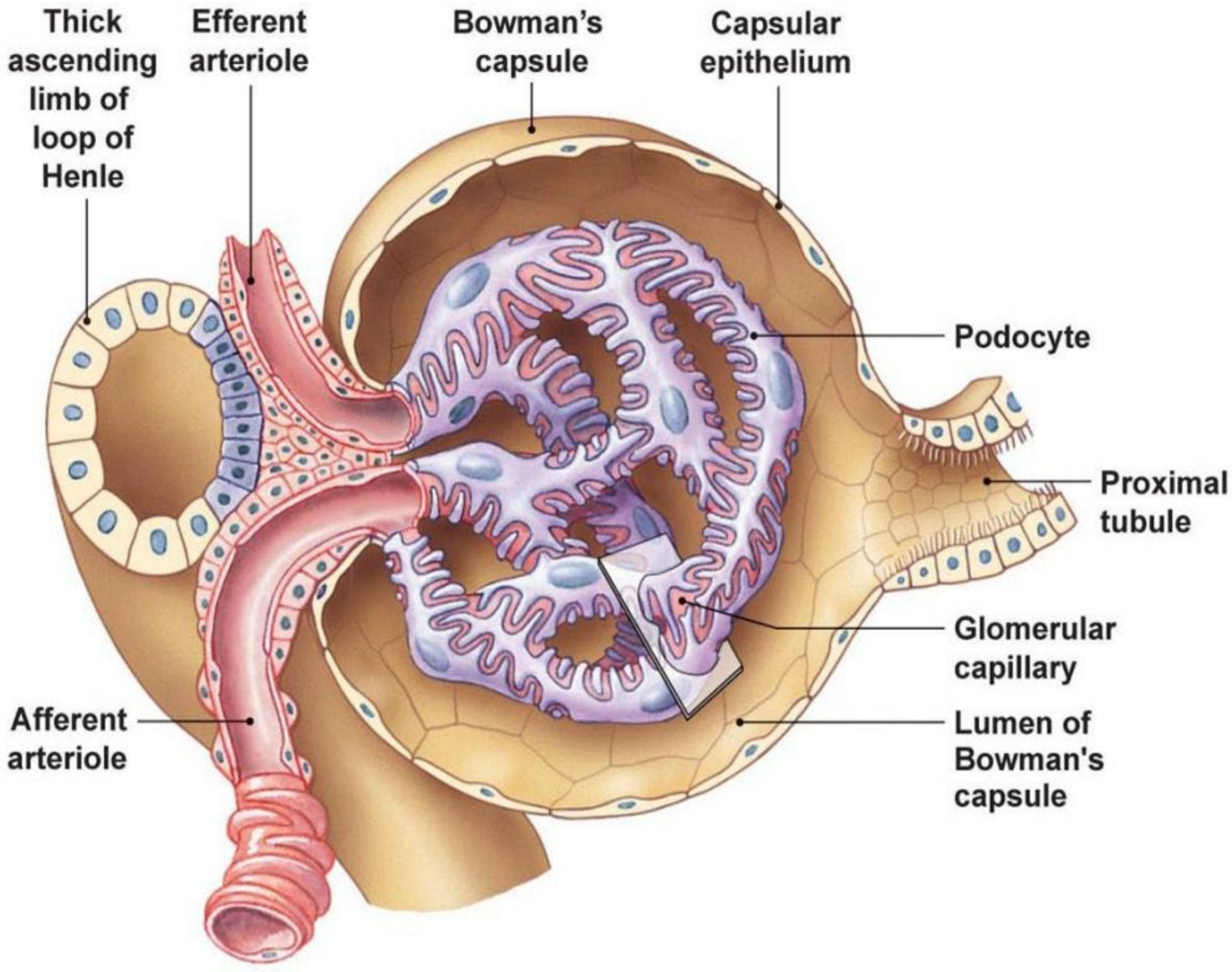
- Juxtaglomerular apparatus/complex
  - Juxtaglomerular cells
  - Macula densa
- Macula densa senses $Na^+$ & $Cl^-$ concentration in distal tubule



↓ arterial pressure

↓ glomerular hydrostatic pressure

↓ GFR

↓ flow rate in LoH

↑ reabsorption of $Na^+$ & $Cl^-$

↓ $Na^+$ & $Cl^-$ at macula densa

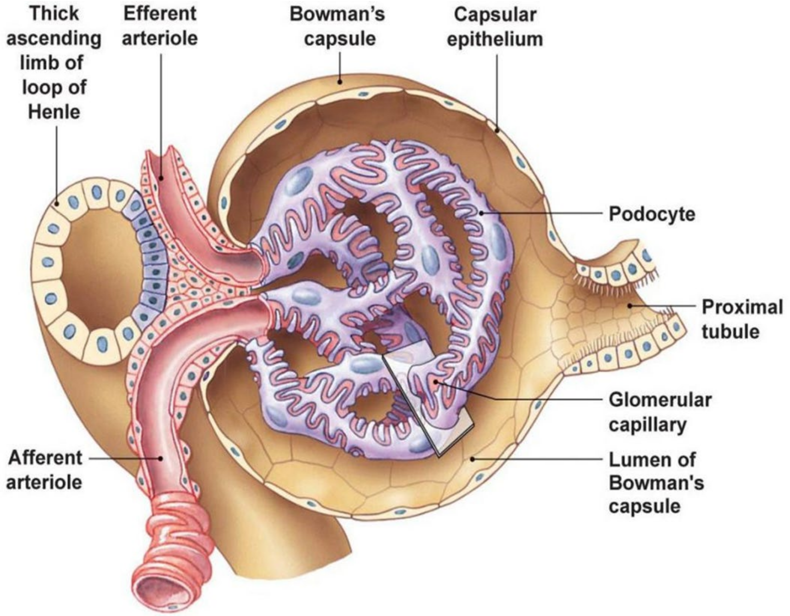
afferent arteriolar dilation

↑ renin release from JG cells

↑ production ATII

constriction of efferent arteriole

↑ GFR



# Tubular reabsorption and secretion

- **Large quantities, highly selective**
- Small changes in GFR or tubular reabsorption/secretion can mean huge changes in overall urinary excretion
- MOST of what is filtered at the glomerulus is reabsorbed
- Tubules fine-tune reabsorption and secretion

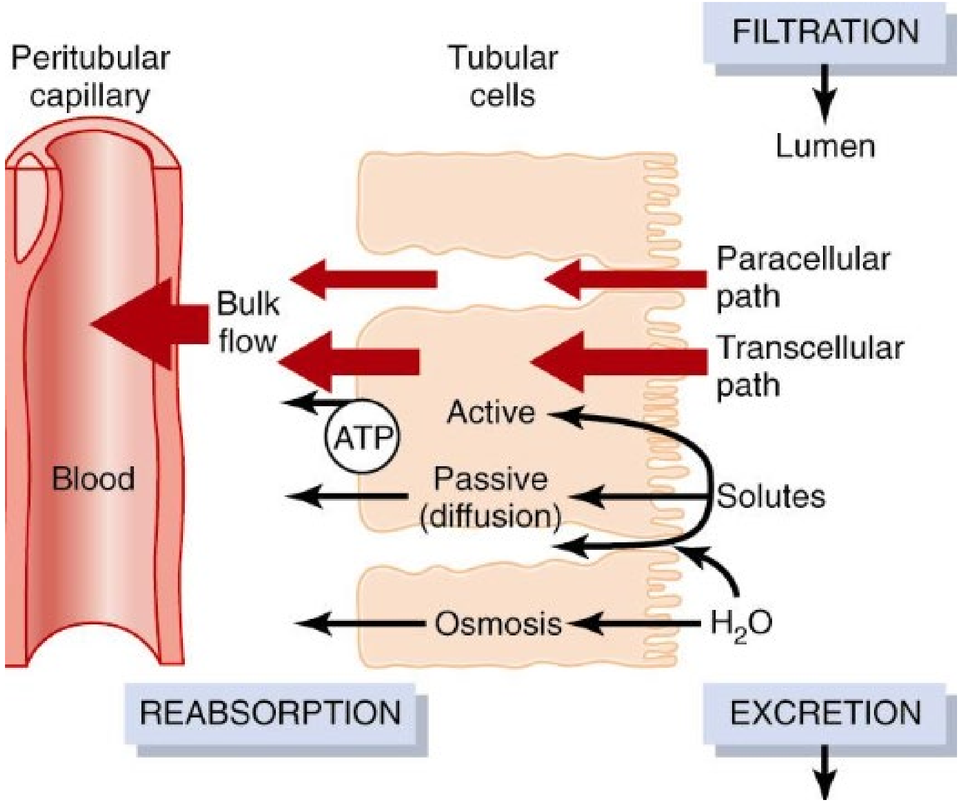
# Tubular reabsorption and secretion

- % filtered load reabsorbed of different substances:

| **Substance** | **% filtered load reabsorbed** |
|---|---|
| Glucose | 100 |
| Bicarbonate | >99.9 |
| $Na^+$ | 99.4 |
| $K^+$ | 87.8 |
| $Cl^-$ | 99.1 |
| Urea | 50 |
| Creatinine | 0 |

# Tubular reabsorption and secretion

- Substances have to move between tubule and capillaries
- Several different mechanisms as to how tubules reabsorb and secrete substances
  - Active or passive
  - Paracellular or transcellular
- Active transport
  - Primary or secondary

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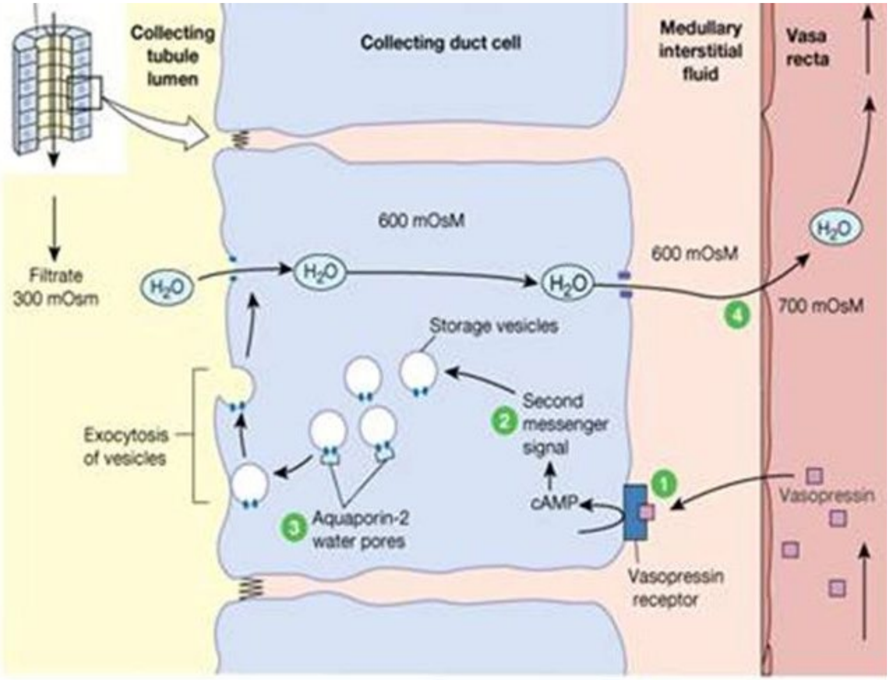
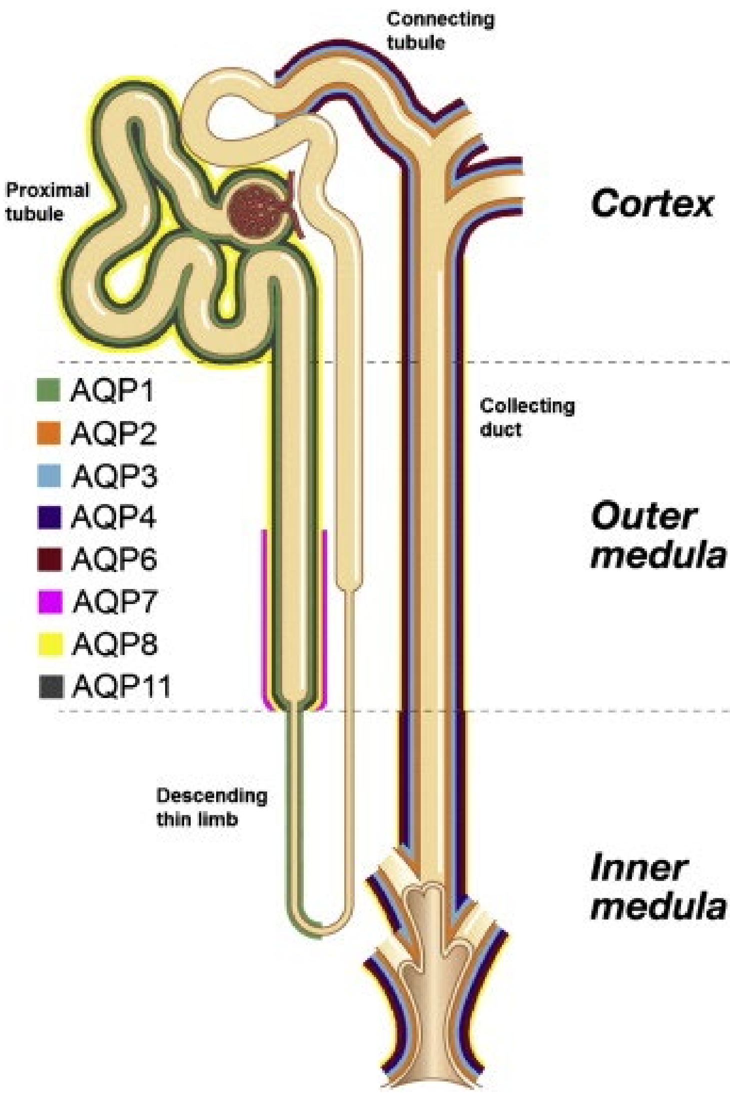
# Coupling $Na^+$ and water reabsorption

- Active transport of sodium out of tubule creates osmotic gradient
- Drives water reabsorption
- $Na^+$ main driver as greatest quantity
- Parts of tubule that are highly permeable to water
- Water moves through **aquaporins** and **tight junctions**



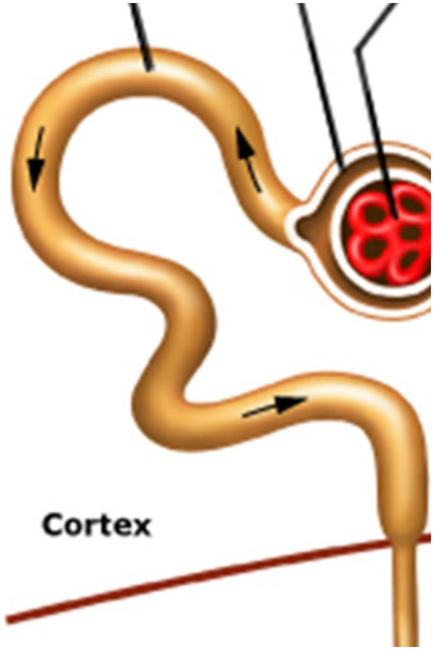



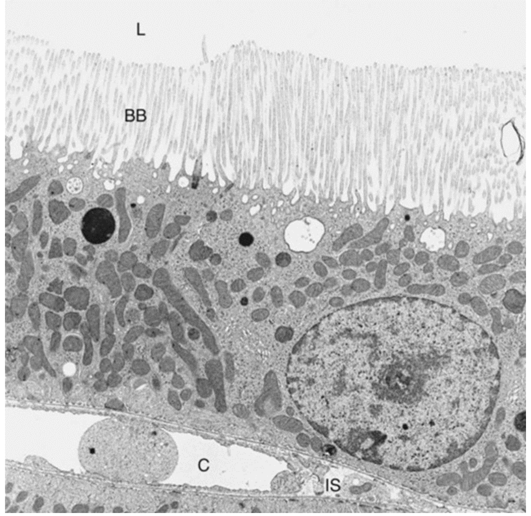
# Passive diffusion of solutes

- Negative ions diffuse along electrical potential gradients
  - Active transport of $Na^+$ → paracellular diffusion of $Cl^-$, (urea)
- Urea permeates tubule less readily than water
  - 50% reabsorbed, 50% excreted in urine
- Creatinine
  - Large molecule, does not cross tubule
  - No reabsorption

# Proximal tubule

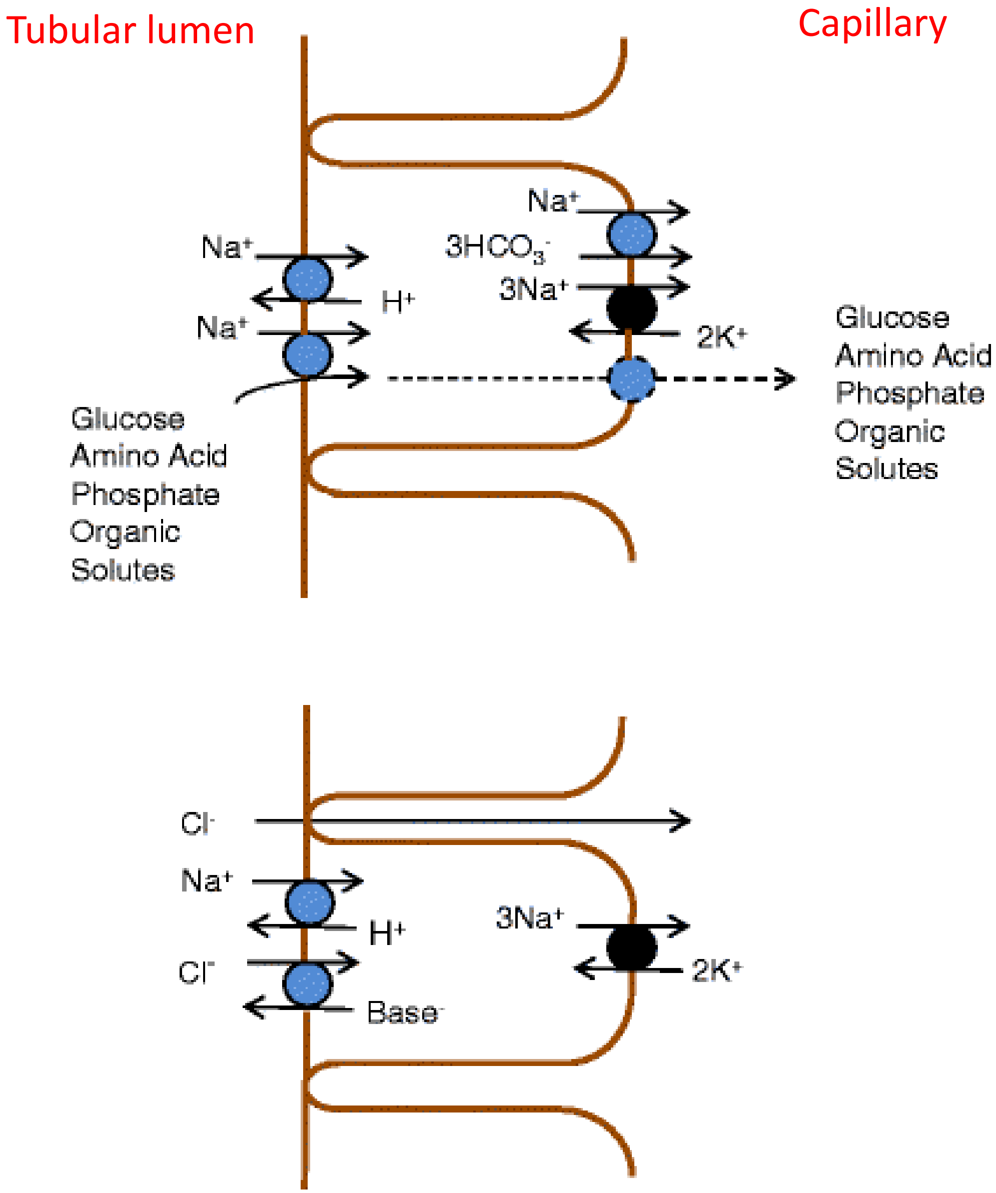
- Reabsorption
  - ≈ 65% filtered $Na^+$, $Cl^-$ and water
  - Co-transport of $Na^+$ with glucose and amino acids, $Cl^-$
  - Counter-transport of $Na^+$ with $H^+$ secretion
  - $HCO_3^-$, $K^+$, water also reabsorbed
- Secretion
  - H+
  - Organic acids and bases
  - Catecholamines



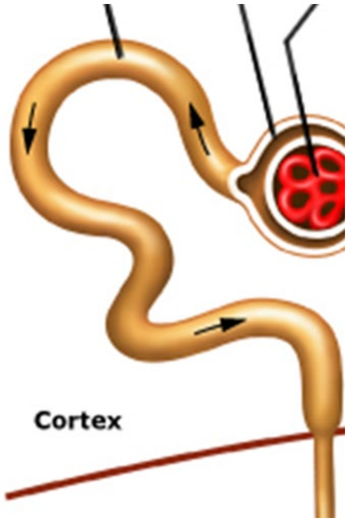

Klein; Cunningham 6th Edition, 2020

Proximal Tubule Cell




Gattineni & Baum, 2015

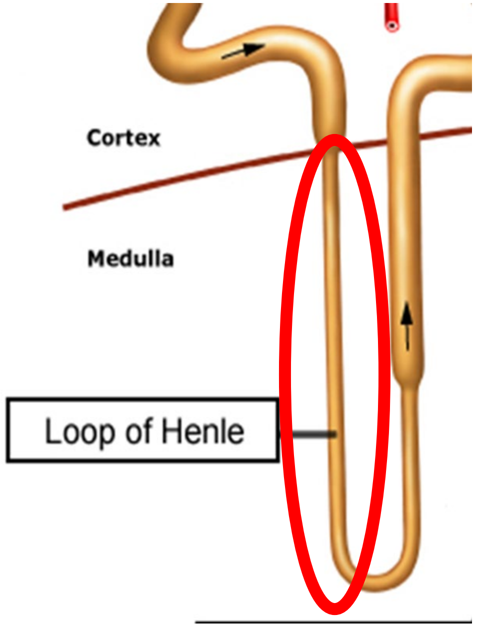
# Proximal tubule

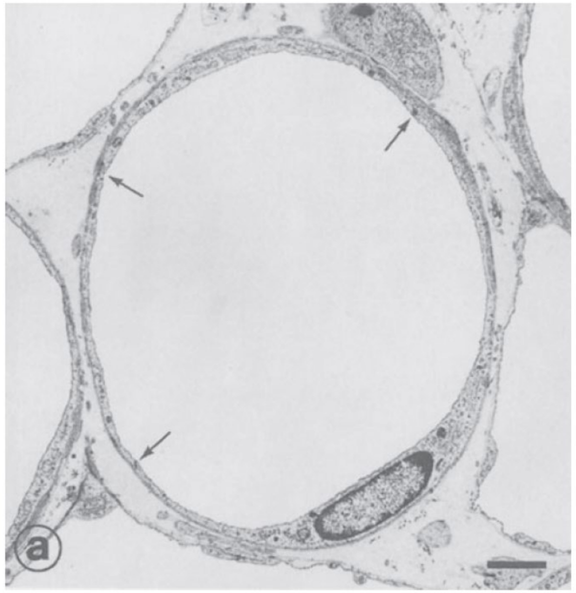



- Glucose
    - Transport maximum – filtered load exceeds ability to reabsorb
    - Glucose will appear in urine before all nephrons at transport maximum
    - Plasma glucose concentration 9.0-10.0 mmol/L
    - Glucose in tubular fluid keeps osmotic gradient – more water stays in tubule

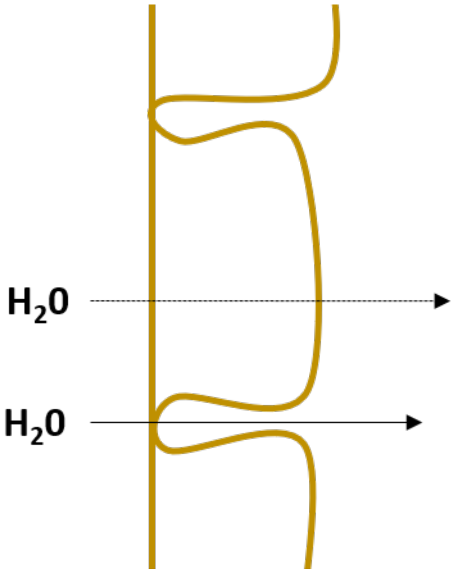
# Thin descending loop of Henle

- ≈20% filtered water reabsorbed
- Simple diffusion only
- Highly permeable to water
- Moderately permeable to most solutes
  - Urea
  - $Na^+$
- **Main effect is movement of water out of the tubule**



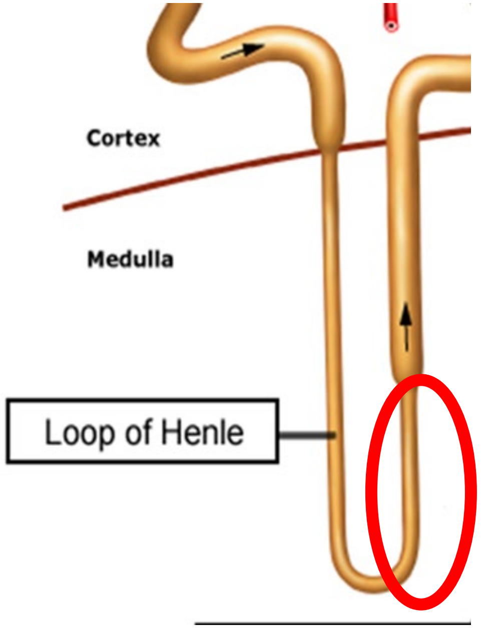



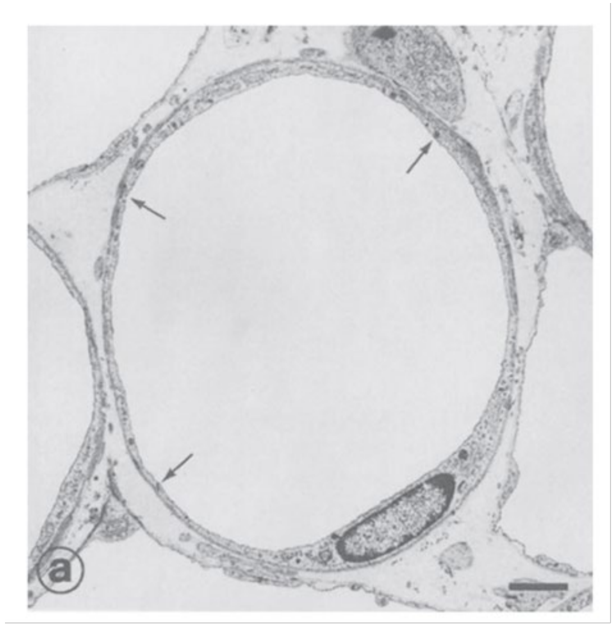
Bachmann & Kriz, 1999



# Thin ascending loop of Henle

- Impermeable to water
- Very small amount of solute reabsorption

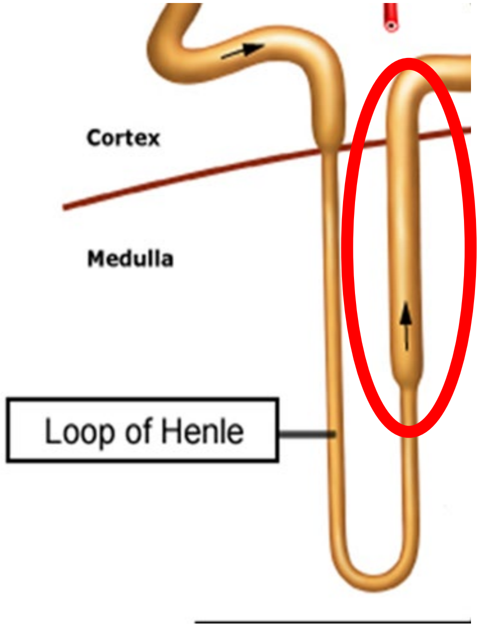


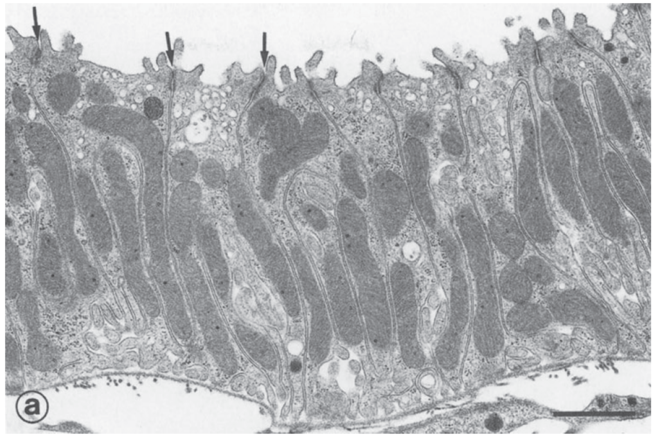



Bachmann & Kriz, 1999

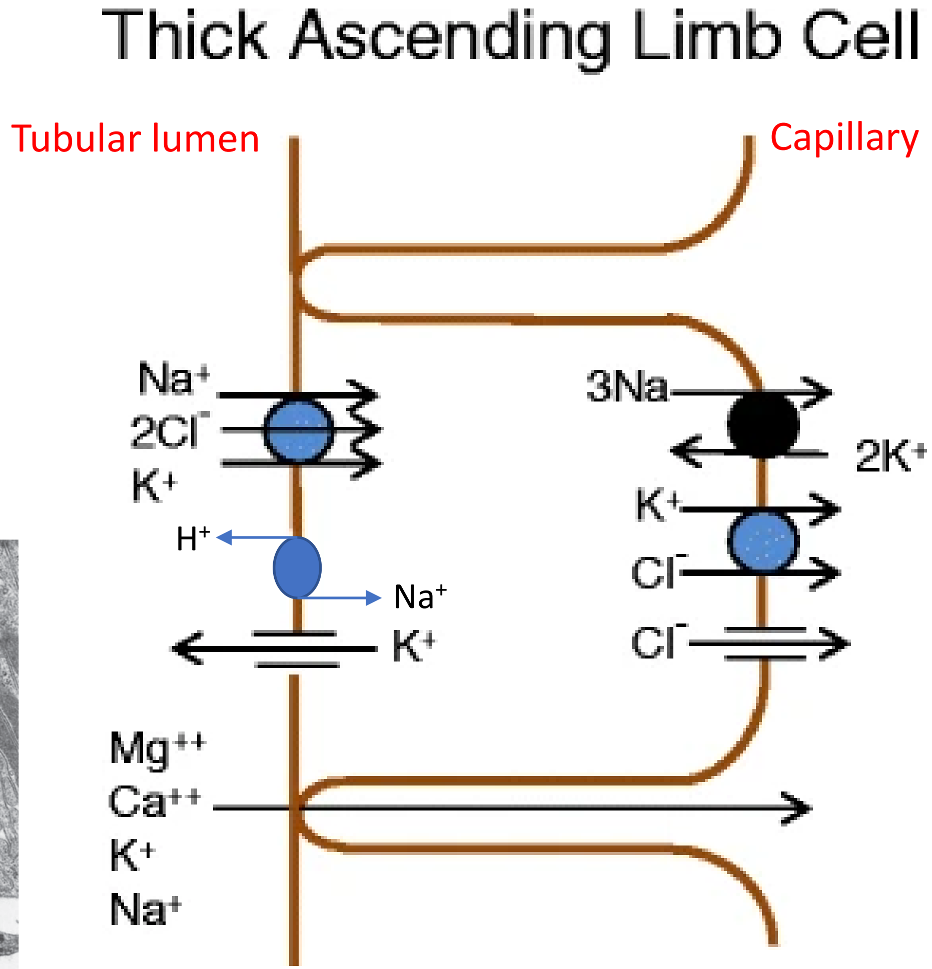
# Thick ascending loop of Henle

- Reabsorption
  - ≈25% filtered $Na^+$, $K^+$ and $Cl^-$ reabsorbed
  - **$Na^+$, $Cl^-$, $K^+$ co-transport** (NKCC2 transporter)
- Secretion
  - Also $Na^+$-$H^+$ counter-transport; $H^+$ secretion
- **Impermeable to water**



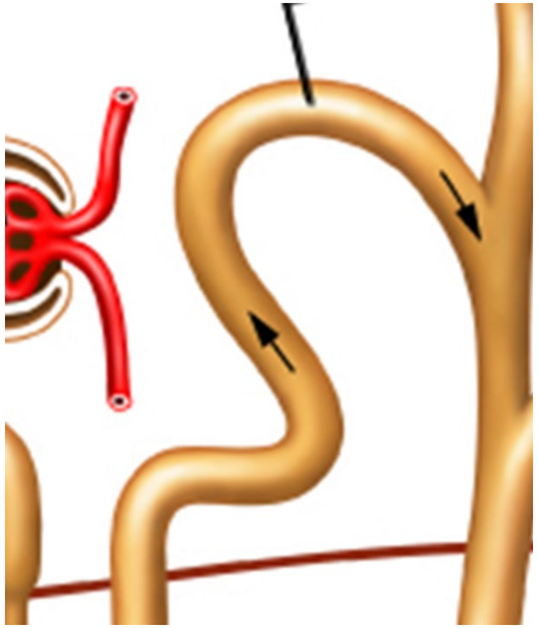

Bachmann & Kriz, 1999




Gattineni & Baum, 2015

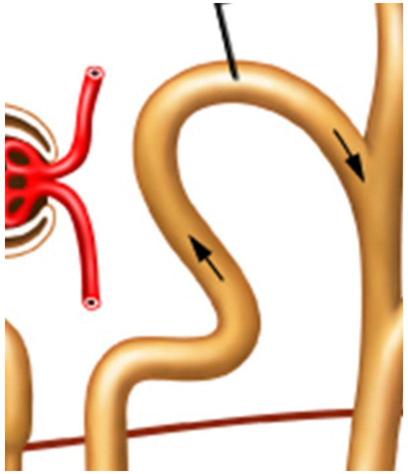
# Distal tubule – first half

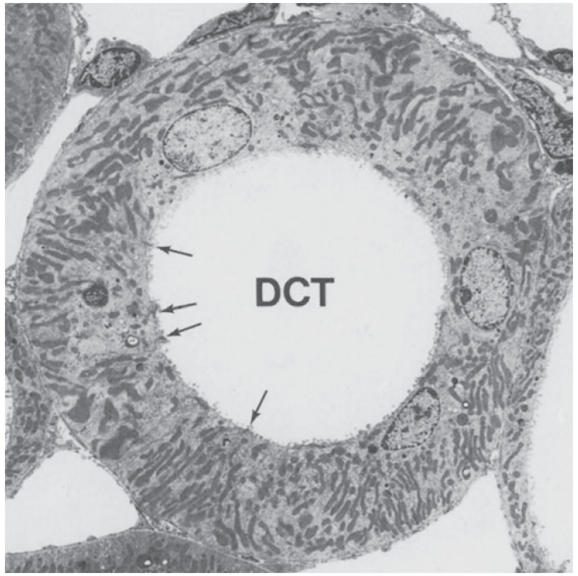
- Macula densa
  - No role in reabsorption/secretion
  - Detection of $Na^+$ and $Cl^-$ concentrations



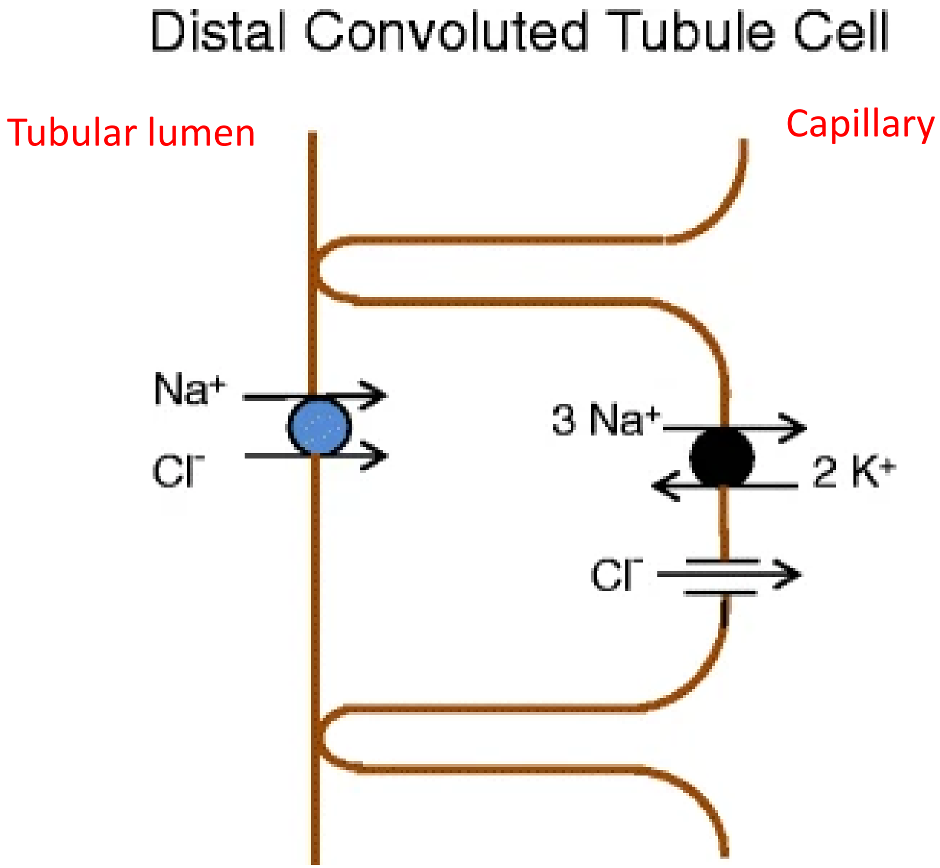
# Distal tubule – first half

- Reabsorption
  - ≈5% filtered $Na^+$ and $Cl^-$ reabsorbed
  - Similar functions to thick ascending loop of Henle
- Also impermeable to water



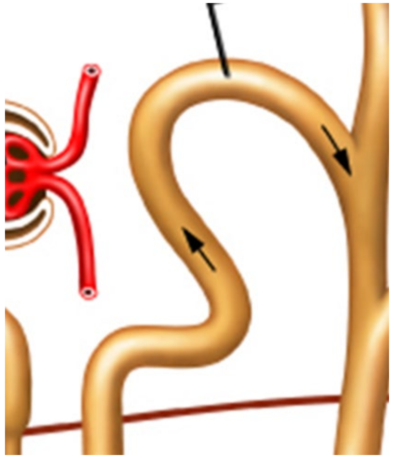



Bachmann & Kriz, 1999

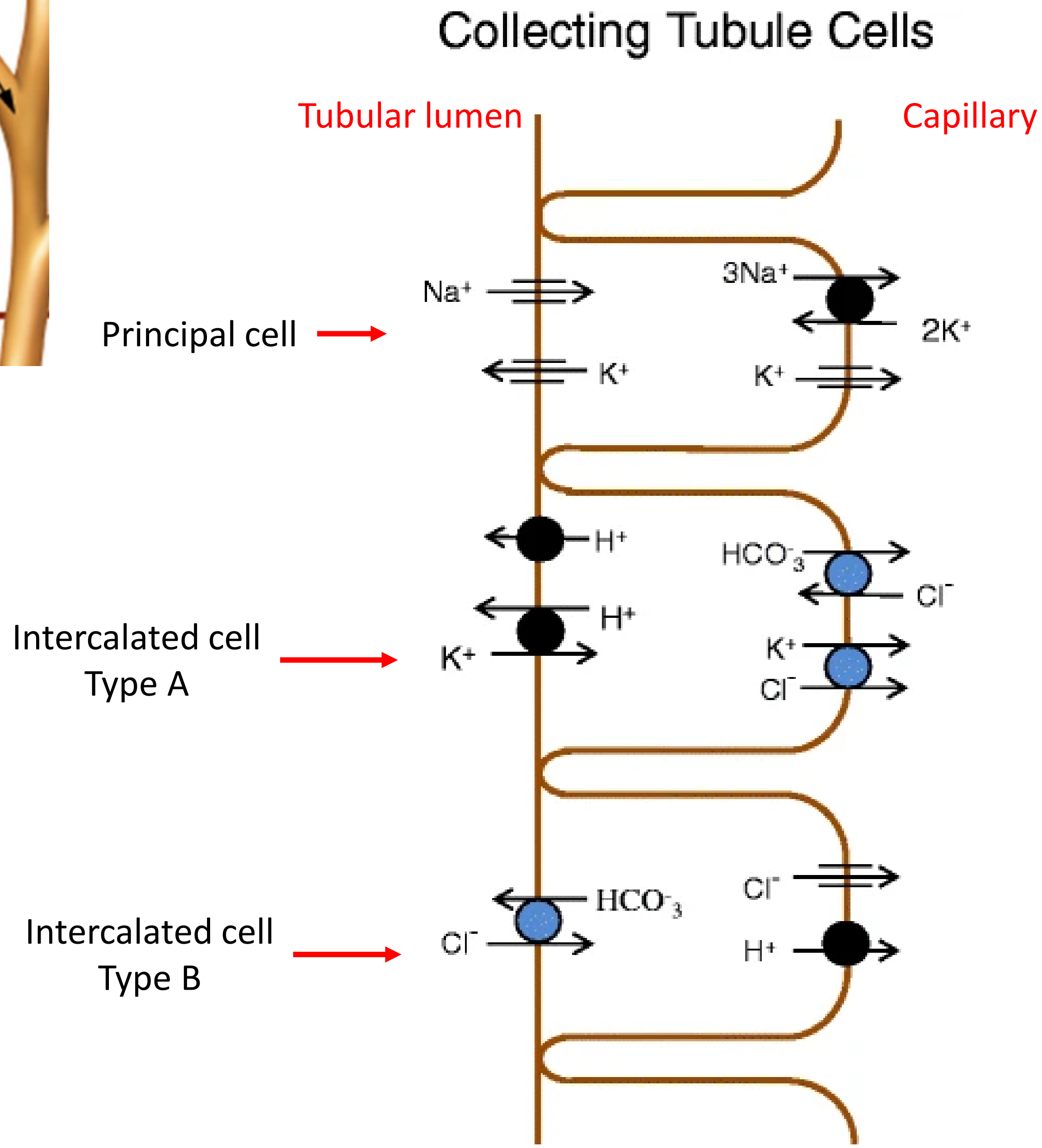



Gattineni & Baum, 2015

# Distal tubule – second half & cortical collecting tubules

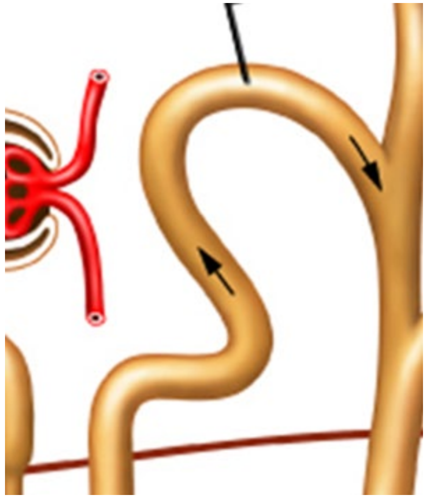


- Principal cells
  - Reabsorption – $Na^+$ (aldosterone)
  - Secretion – $K^+$
- Intercalated cells – acid-base
- Intercalated cells – type A
  - Secretion – $H^+$
  - Reabsorption – $HCO_3^-$
- Intercalated cells – type B
  - Opposite function to type A
  - Reabsorption – $H^+$
  - Secretion – $HCO_3^-$




Gattineni & Baum, 2015

# Distal tubule – second half & cortical collecting tubules



- Impermeable to urea
- Water reabsorption
  - ADH (vasopressin)

# Medullary collecting duct

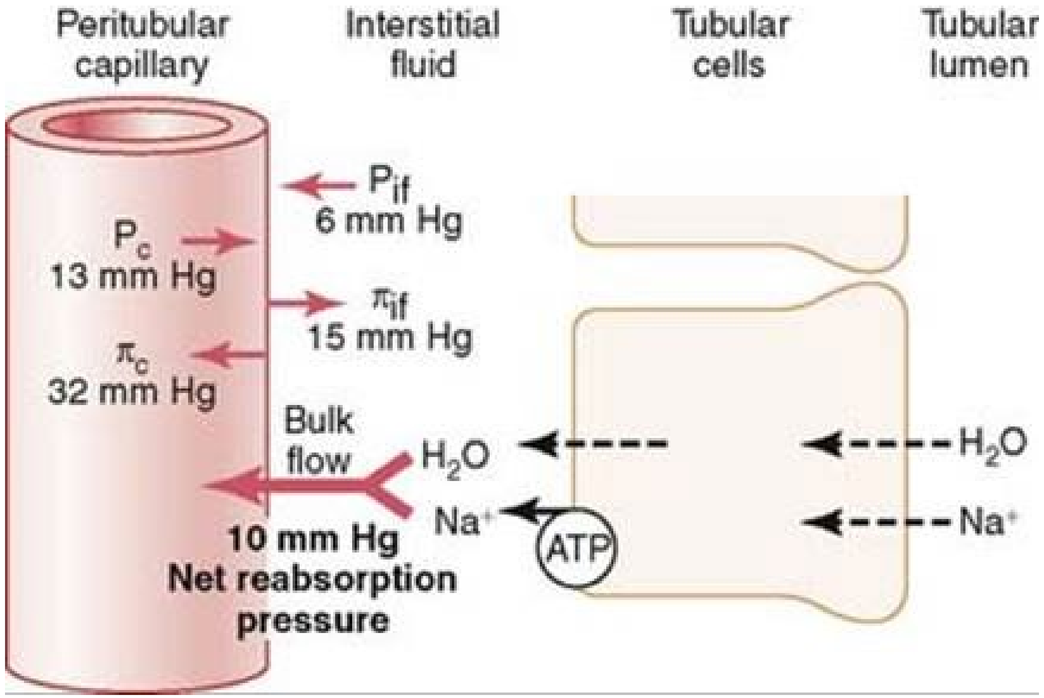
- <5% water and $Na^+$ reabsorbed here
- Final site urine processing
- Water permeability controlled by ADH
- Permeable to urea (some reabsorption)

# Regulation of tubular reabsorption

- Glomerulotubular balance
    - Proximal tubules increase their absorption rate when flow through the tubules is increased
    - ↑ GFR → proportional ↑ proximal tubular reabsorption
    - Keeps % reabsorption constant
    - Also occurs in other segments (mainly loop of Henle)
    - Prevents overloading of distal tubule
    - Works alongside other autoregulatory mechanisms (tubuloglomerular feedback)
    - Independent of hormonal control

# Regulation of tubular reabsorption

- Fluid physical forces
  - Hydrostatic and colloid osmotic pressures in the tubules, interstitial fluid and peritubular capillaries

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# Calcium reabsorption

- Proximal tubule
  - 60-70% filtered $Ca^{2+}$ reabsorbed here
  - Mostly passive, paracellular, along electrical and chemical gradients
- Thick ascending loop of Henle
  - 20% filtered $Ca^{2+}$ reabsorbed here – also passive, paracellular diffusion
- Distal tubule
  - 10-20% filtered $Ca^{2+}$ reabsorbed here
  - Transcellular
- Reabsorption in thick ascending loop of Henle and distal tubule under control of parathyroid hormone

# Phosphate reabsorption

- Majority reabsorbed in proximal tubule
- Influenced by PTH

# Wastes

- Creatinine
  - All filtered, none reabsorbed
- Urea
  - Some reabsorbed
- Ammonia
  - Produced in kidney

# Measuring the kidney's handling of solutes: fractional excretion

- Plasma vs. urine concentration of solutes, measured in comparison to a substance that is filtered but not reabsorbed (usually creatinine).
- Tells us about whole body concentration of solutes (mainly electrolytes) based on how much the kidney is reabsorbing or secreting them
- Eg. for FEx of sodium:

$$FEx = [(\text{urinary } Na^+/\text{plasma } Na^+) \times (\text{plasma creatinine}/\text{urine creatinine})] \times 100$$

# Normal values – fractional excretion

| **Substance** | **% filtered load reabsorbed** |
|---|---|
| Glucose | 100 |
| Bicarbonate | >99.9 |
| $Na^+$ | 99.4 |
| $K^+$ | 87.8 |
| $Cl^-$ | 99.1 |
| Urea | 50 |
| Creatinine | 0 |

# Normal values – fractional excretion

| **Substance** | **% filtered load reabsorbed** | **Fractional excretion (%)** |
|---|---|---|
| Glucose | 100 | 0 |
| Bicarbonate | >99.9 | <0.1 |
| $Na^+$ | 99.4 | <1 |
| $K^+$ | 87.8 | 12.2 |
| $Cl^-$ | 99.1 | 0.9 |
| Urea | 50 | 50 |
| Creatinine | 0 | 100 |