Renal physiology II

Basic renal processes

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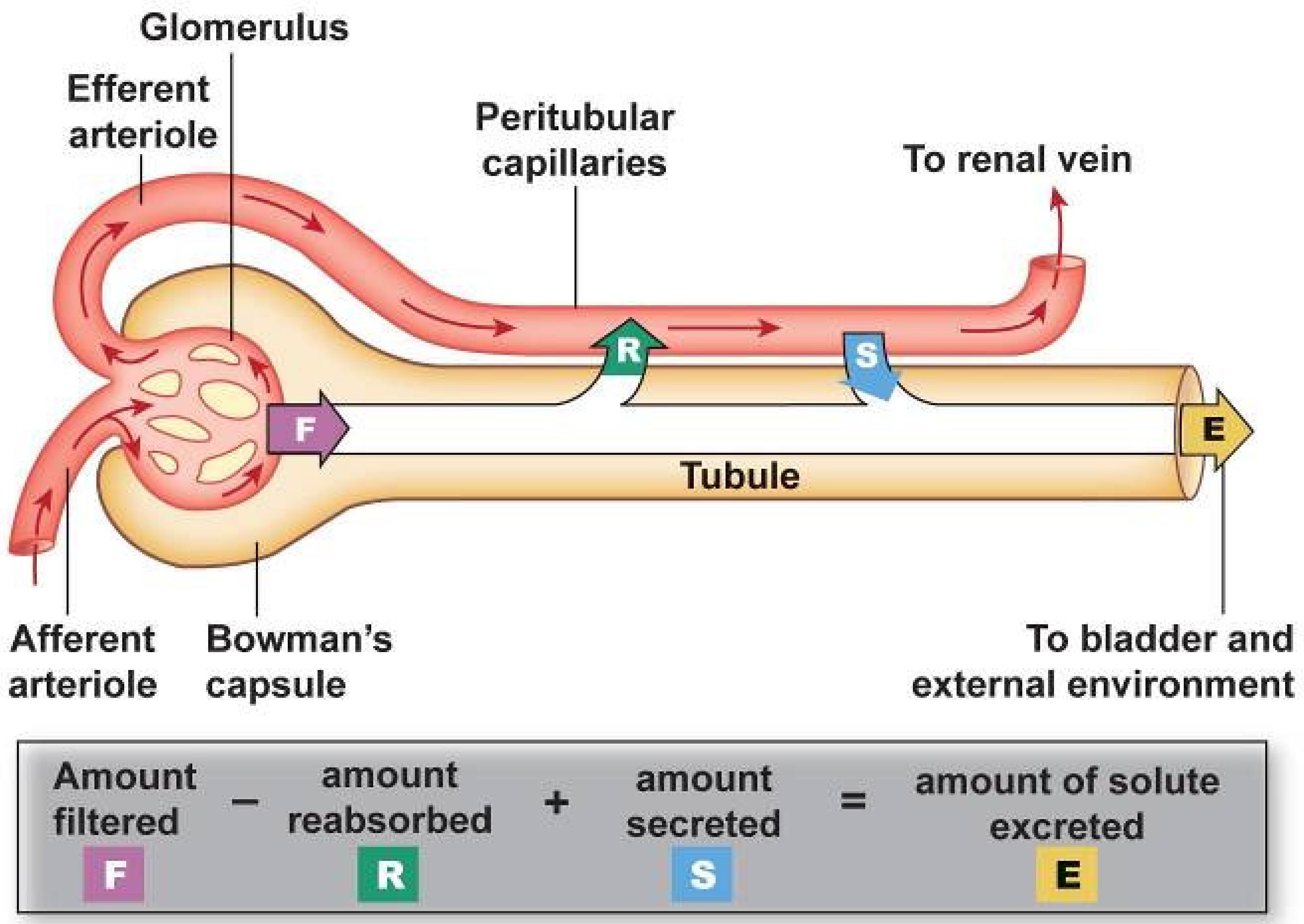
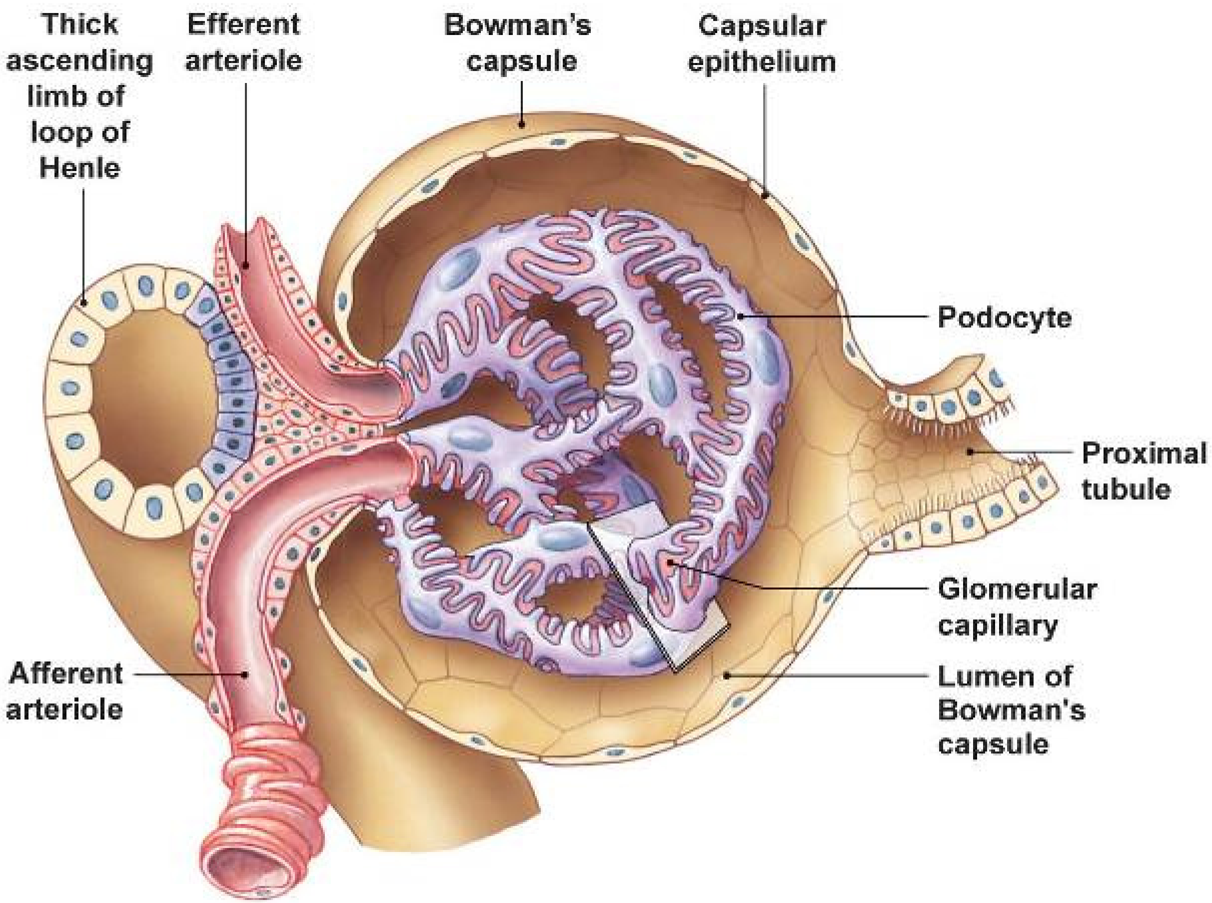
Basic renal processes

1. filtration
2. reabsorption
3. secretion

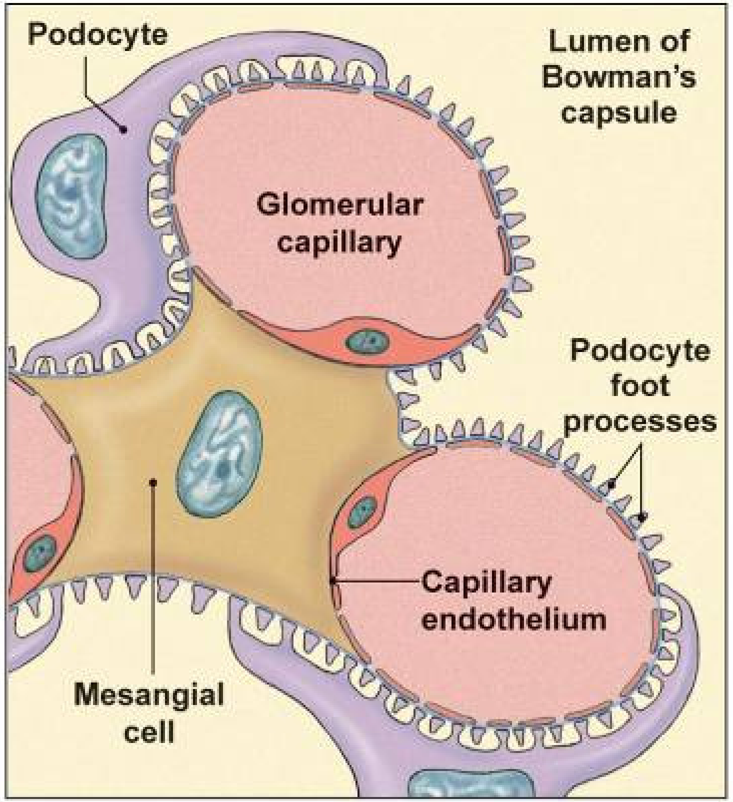


Glomerular filtration

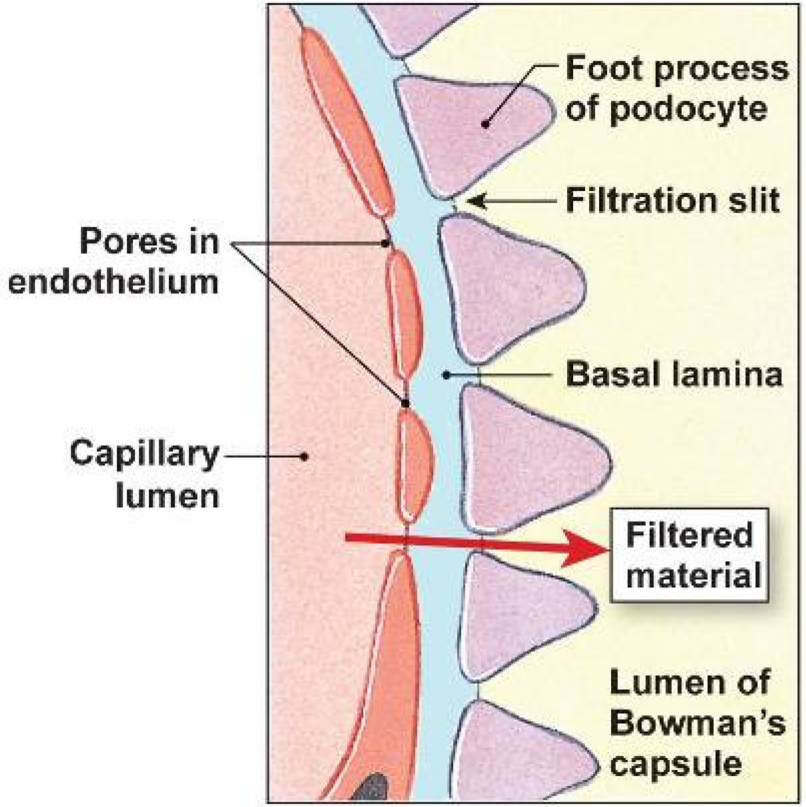


(a) The epithelium around glomerular capillaries is modified into podocytes.

The filtration apparatus



(c) Podocyte foot processes surround each capillary, leaving slits through which filtration takes place.



(d) Filtered substances pass through endothelial pores and filtration slits.

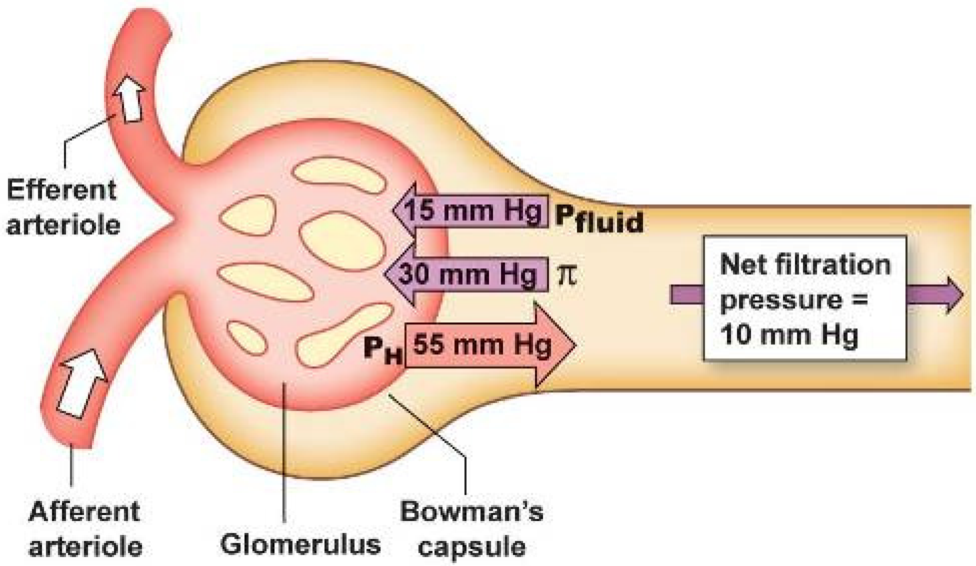
Permeability of the membrane

- substances < 4 nm freely filtered
- 8 nm cut-off point for neutral substances
- negative charge (due to sialoproteins) deter larger particles, eg., albumin (7 nm) which does not appear in filtrate
- loss of negative charge (nephritis and prolonged stress) – albuminuria
- haemoglobin (65 000 AMU) passes fairly easily
- large amounts of protein lost during nephrosis

Glomerular filtration

- volume filtered/min = glomerular filtration rate (GFR) = 125 ml/min
- of 1200 ml blood (650 ml plasma) circulating through the kidneys, 125 ml/min (180 l/day) is filtered
- filtration fraction = 19%
- filtrate is protein free

Effective filtration pressure (EFP)



P_H	–	π	–	P_{fluid}	=	net filtration pressure
55	–	30	–	15	=	10mm Hg

KEY

P_H = Hydrostatic pressure (blood pressure)

π = Colloid osmotic pressure gradient due to proteins in plasma but not in Bowman's capsule

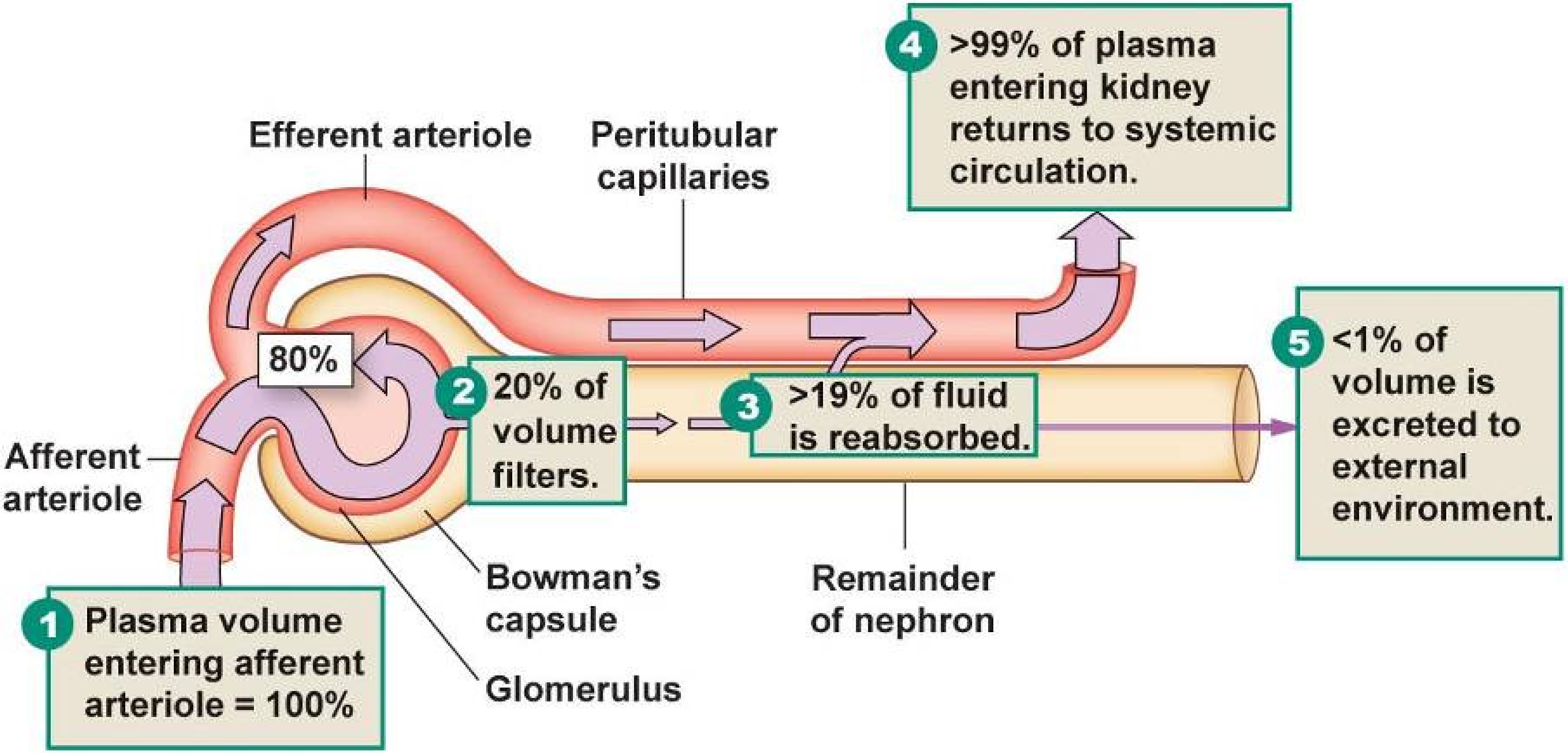
P_{fluid} = Fluid pressure created by fluid in Bowman's capsule

EFP = (55 + 0) - (30 + 15) = 10 mm Hg

GFR = K_f x EFP

K_f = ultrafiltration coefficient

The filtration fraction is 20%



Glomerular hydrostatic pressure (60 mm Hg) is regulated by:

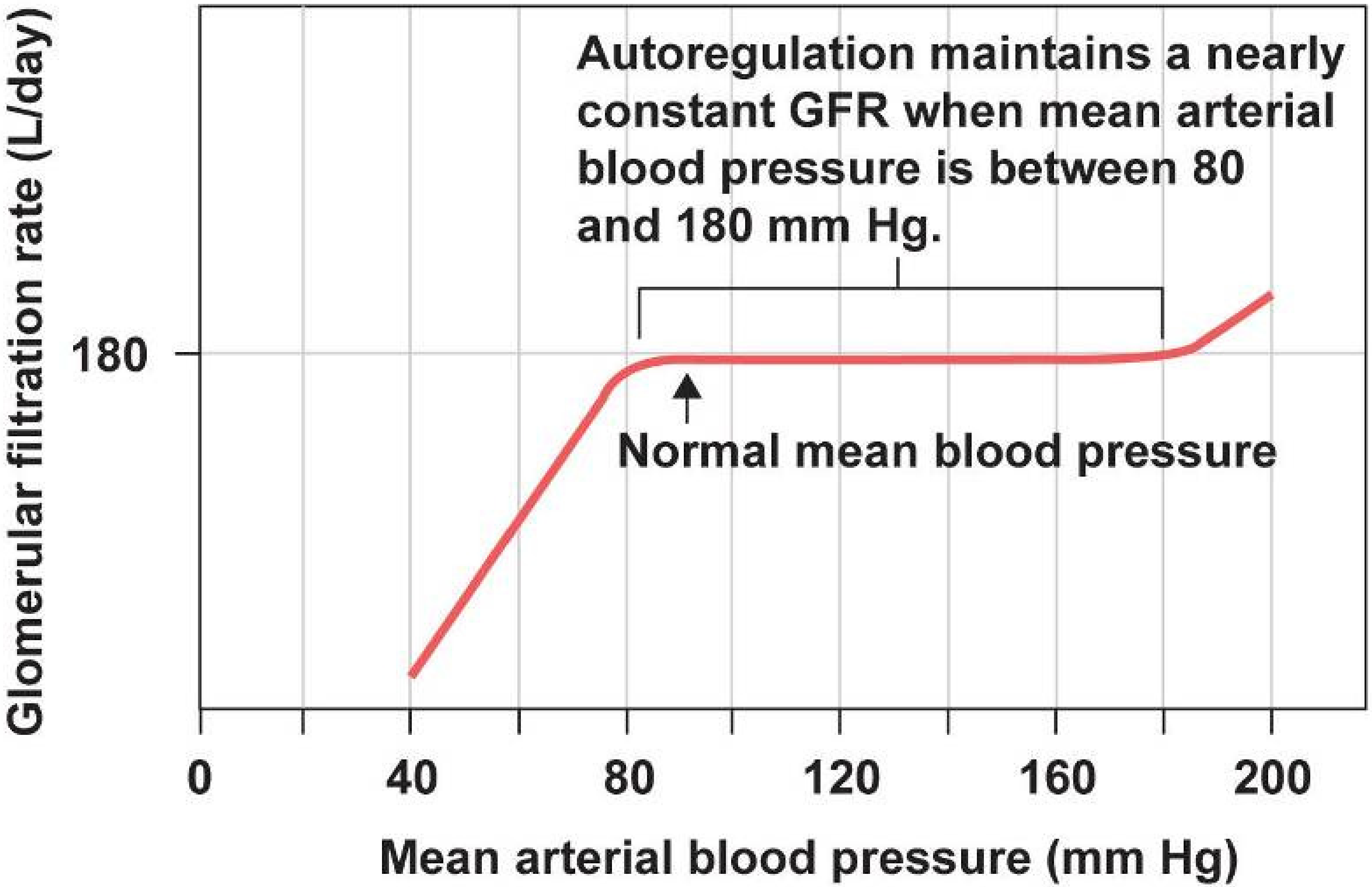
Autoregulation of renal blood flow

1. myogenic mechanism – afferent arteriole muscle contracts when stretched
2. tubuloglomerular feedback – increase in tubular flow causes the macula densa cells to send a chemical message to the neighboring afferent arteriole to constrict and decrease GFR

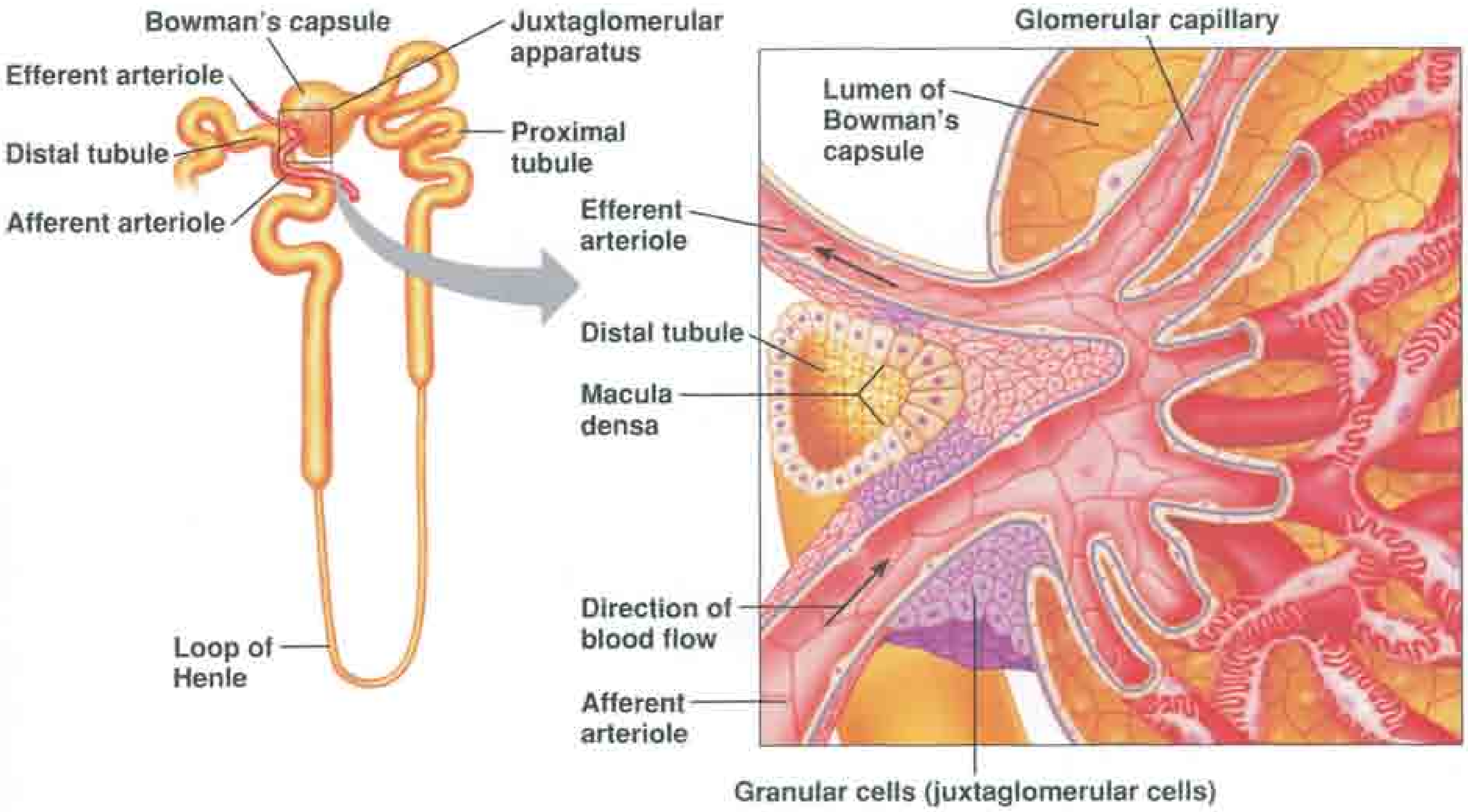
   vasoconstrictors – ATP and adenosine

   vasodilators – NO

Importance of autoregulation when arterial pressure changes



The juxtaglomerular apparatus

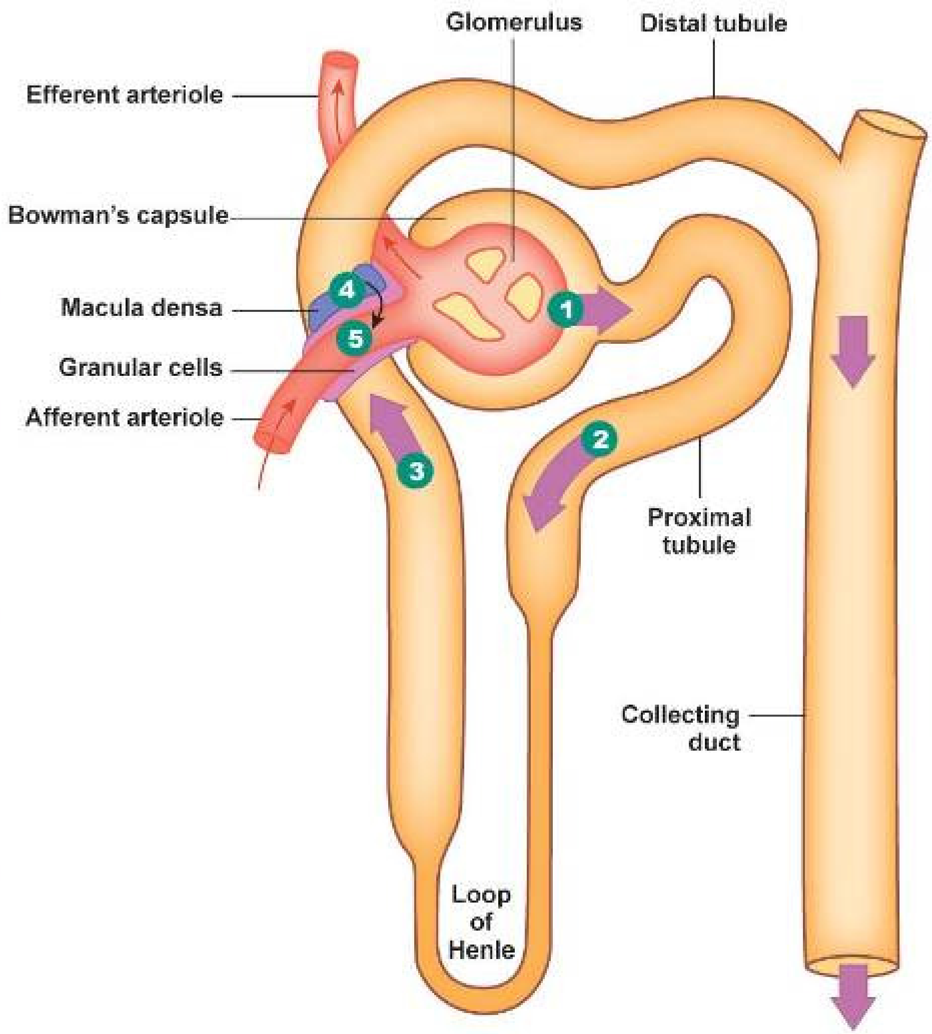


Tubuloglomerular feedback

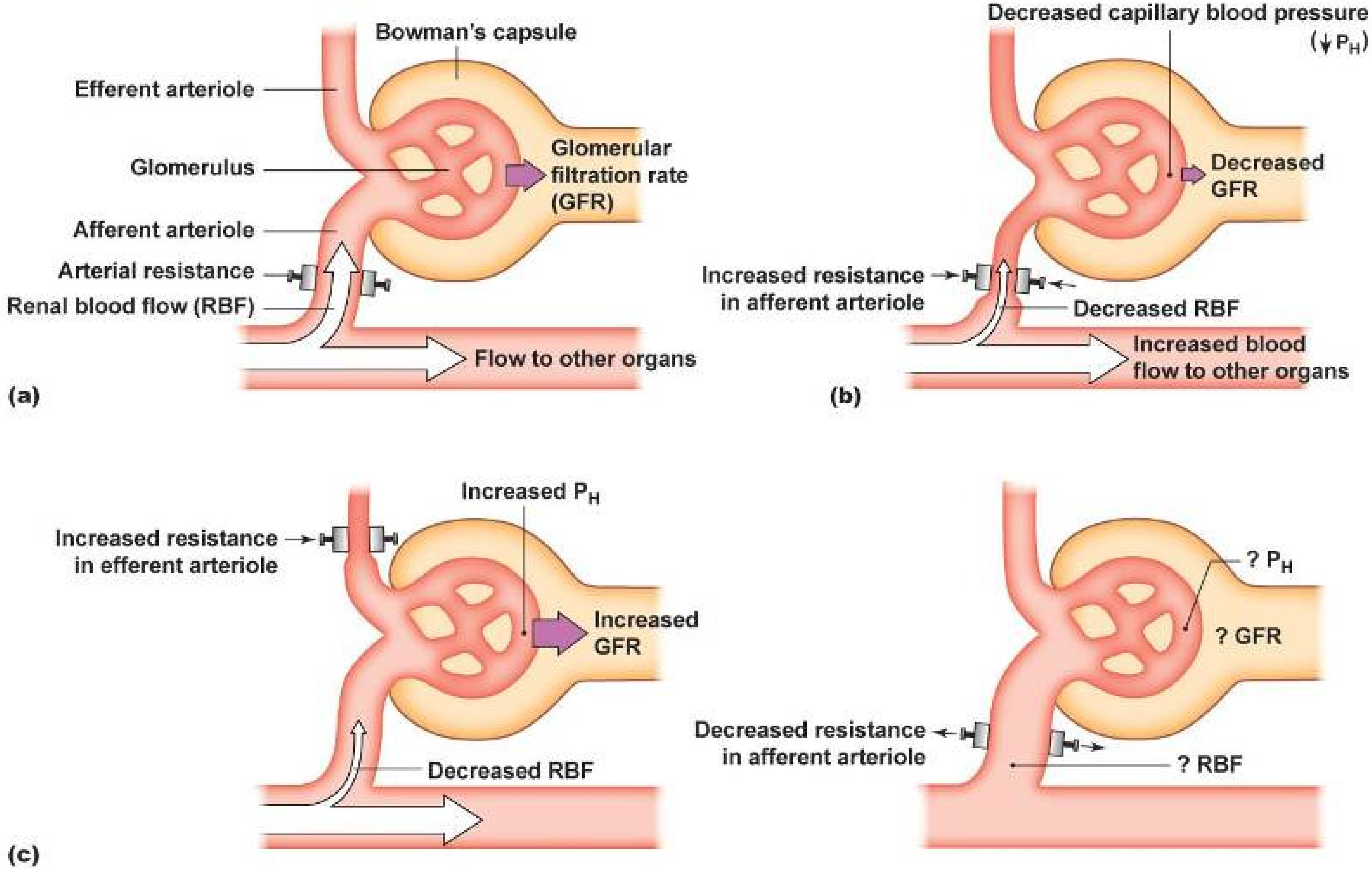
3. ↑ in [NaCl]

1. GFR increases.
   ↓
2. Flow through tubule increases.
   ↓
3. Flow past macula densa increases.
   ↓
4. Paracrine from macula densa to afferent arteriole
   ↓
5. Afferent arteriole constricts.
   ↓

Resistance in afferent arteriole increases.
↓
Hydrostatic pressure in glomerulus decreases.
↓
GFR decreases.



Arteriolar diameter changes renal blood flow and GFR



Regulation continued

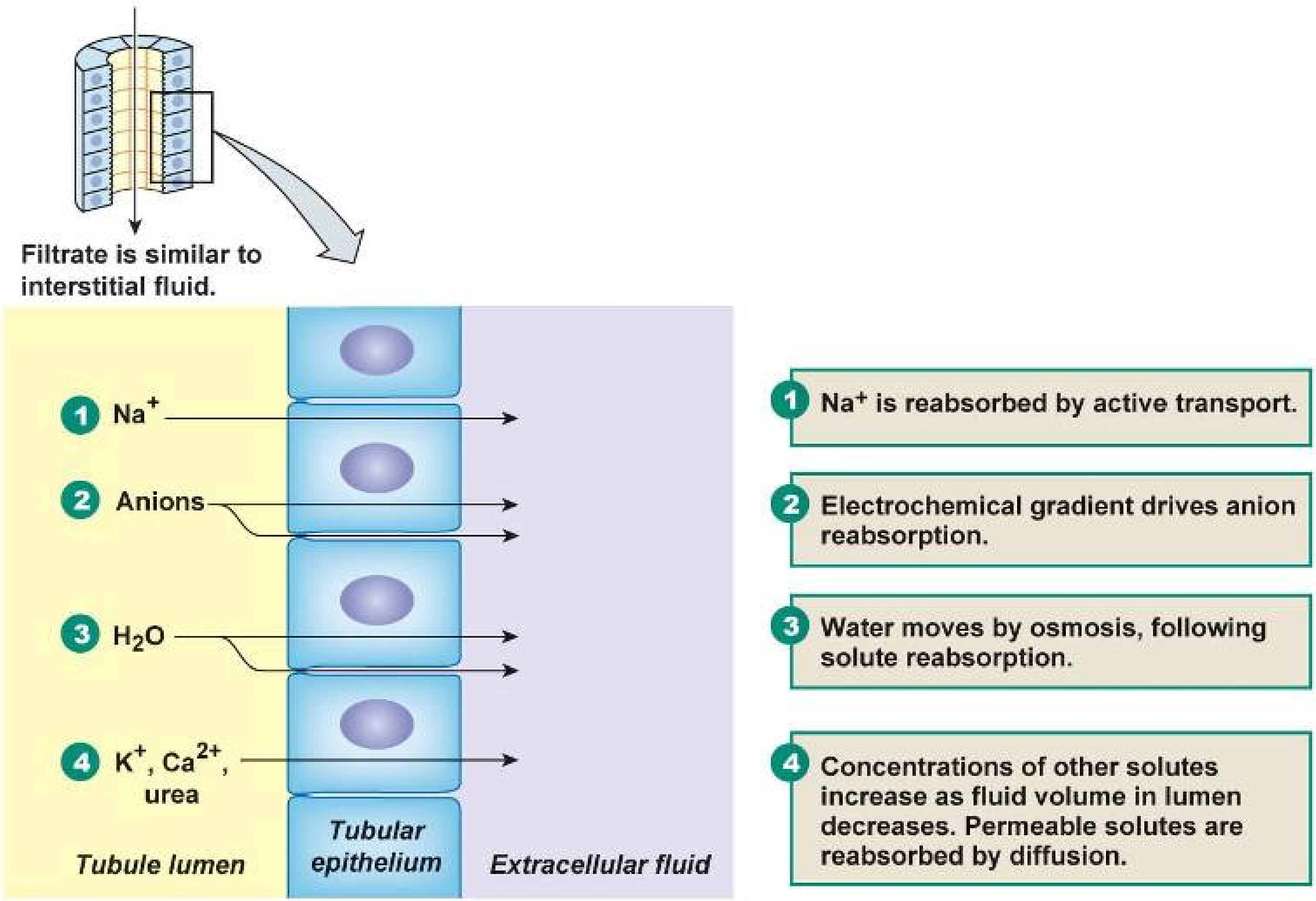
- sympathetic nerves and circulating catecholamines decrease GFR
  - α1-adrenergic constriction (seen in shock, exercise, stress)
- other vasoconstrictors decrease GFR
  - angiotensin II, endothelins, ADH (anti-diuretic hormone), TXA2
- renal vasodilators increase GFR
  - ANP (atrial natriuretic peptide), cAMP, bradykinin, NO, cortisol, dopamine, PGE2
  - protect kidneys against ischaemia

- COP in glomerular blood
  - in afferent arteriole 25-28 mm Hg
  - when COP decreases (high fluid intake, hypoproteinaemia) $\rightarrow$ GFR increases
- COP in Bowman's capsule
  - negligible, except during diseases that increase permeability or affects negative charge (nephritis) $\rightarrow$ GFR increases
- hydrostatic pressure in Bowman's capsule
  - 10-15 mm Hg
  - increases with ureter obstruction, due to back pressure and renorenal reflex

Summary: regulation of GFR

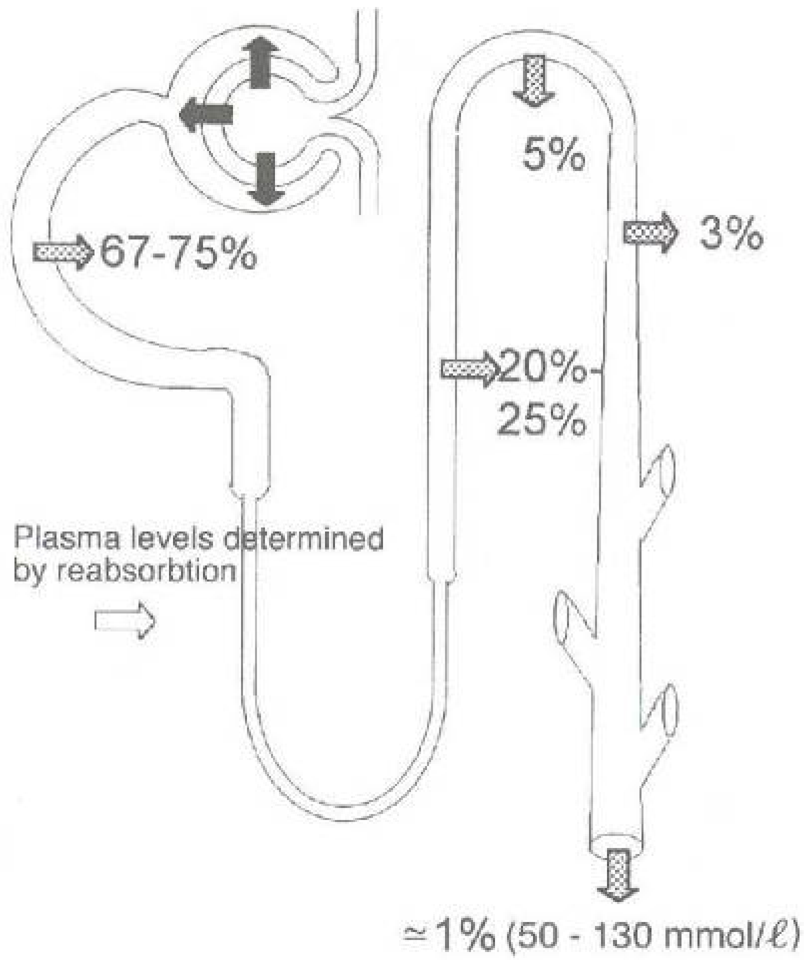
- BP in glomerular capillary
- hydrostatic pressure in Bowman's capsule
- integrity of glomerular filter and influence of the mesangial cells
- total area of filter bed
- measurement of GFR is done by determining the clearance of inulin or creatinine

Overview of reabsorption



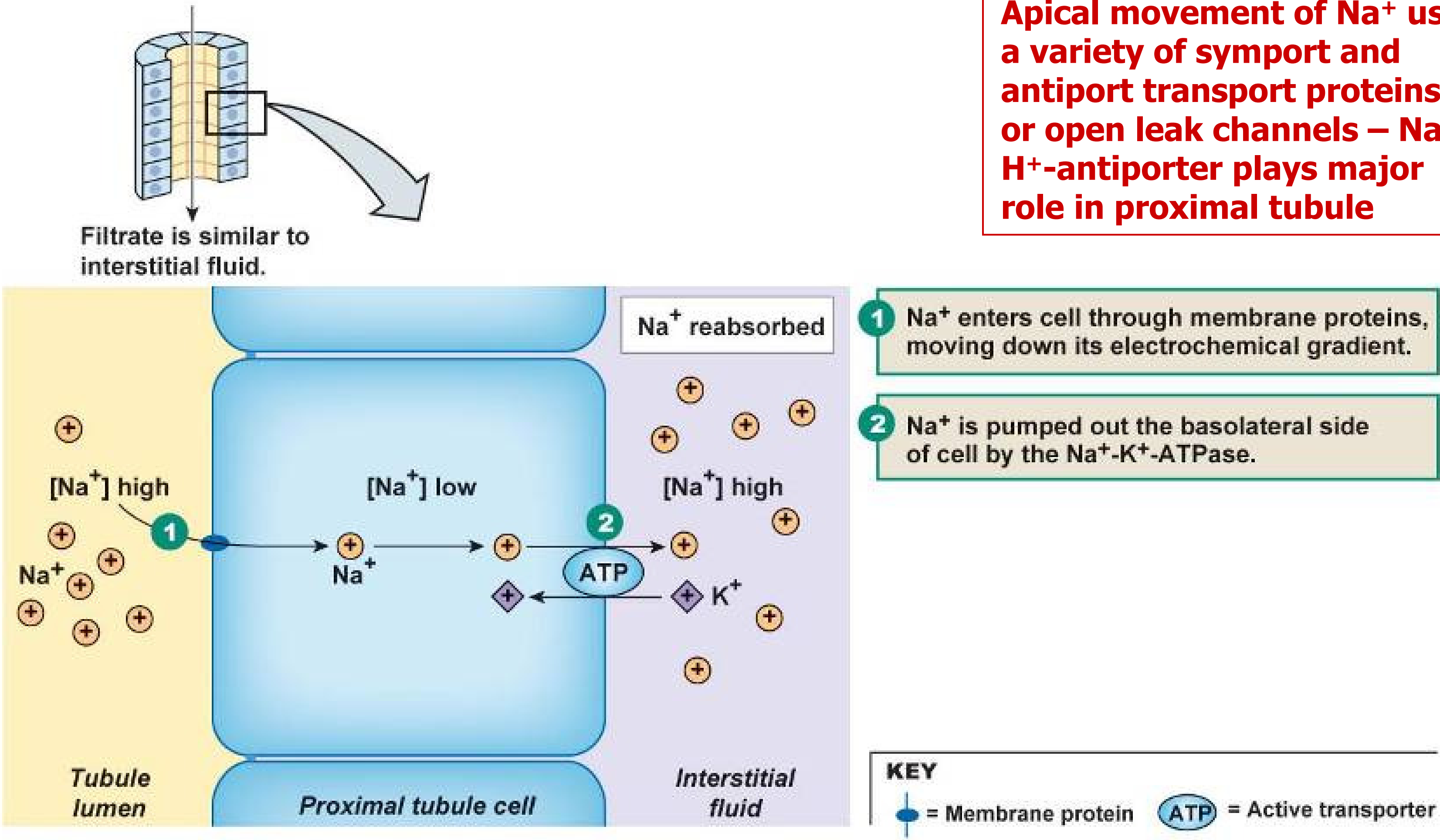
Handling of Na^+

- Na^+ freely filtered
- ERPF = 650 ml/min
- plasma $[Na^+]$= 140 mM
- plasma load = 140 x 0,65 = 91 mmol/min
- GFR = 125 ml/min
- tubular load = 140 x 0,125 = 17,5 mmol/min
- 99% reabsorbed
- urinary sodium = 50-130 mmol/l
- influenced by:
  - GFR
  - aldosterone
  - AT II
  - natriuretic hormone
  - sympathetic nerve activity

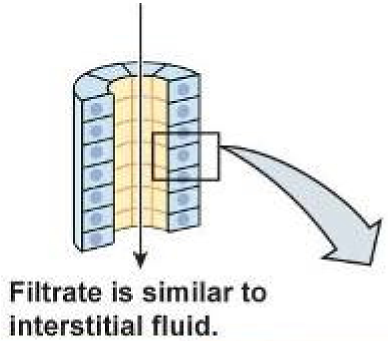


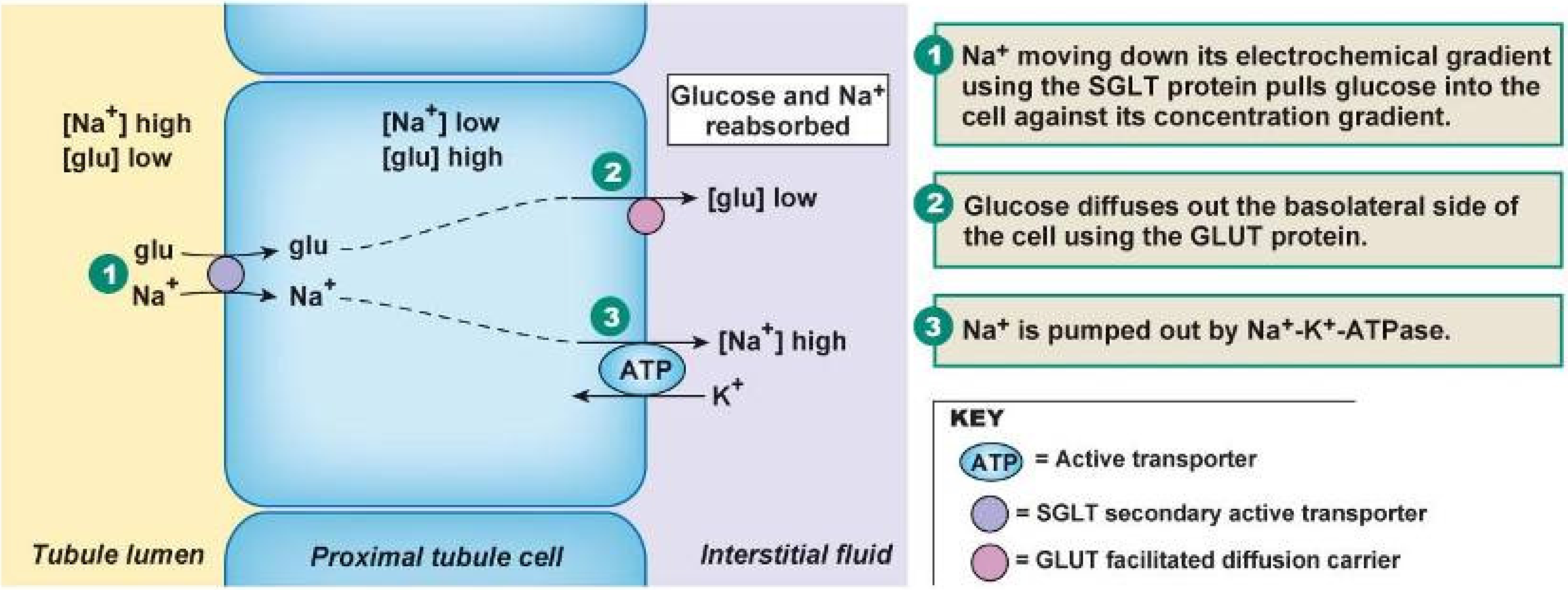
Na^+ reabsorption mechanisms in the proximal tubule

Apical movement of Na^+ uses a variety of symport and antiport transport proteins or open leak channels – Na^+-H^+-antiporter plays major role in proximal tubule

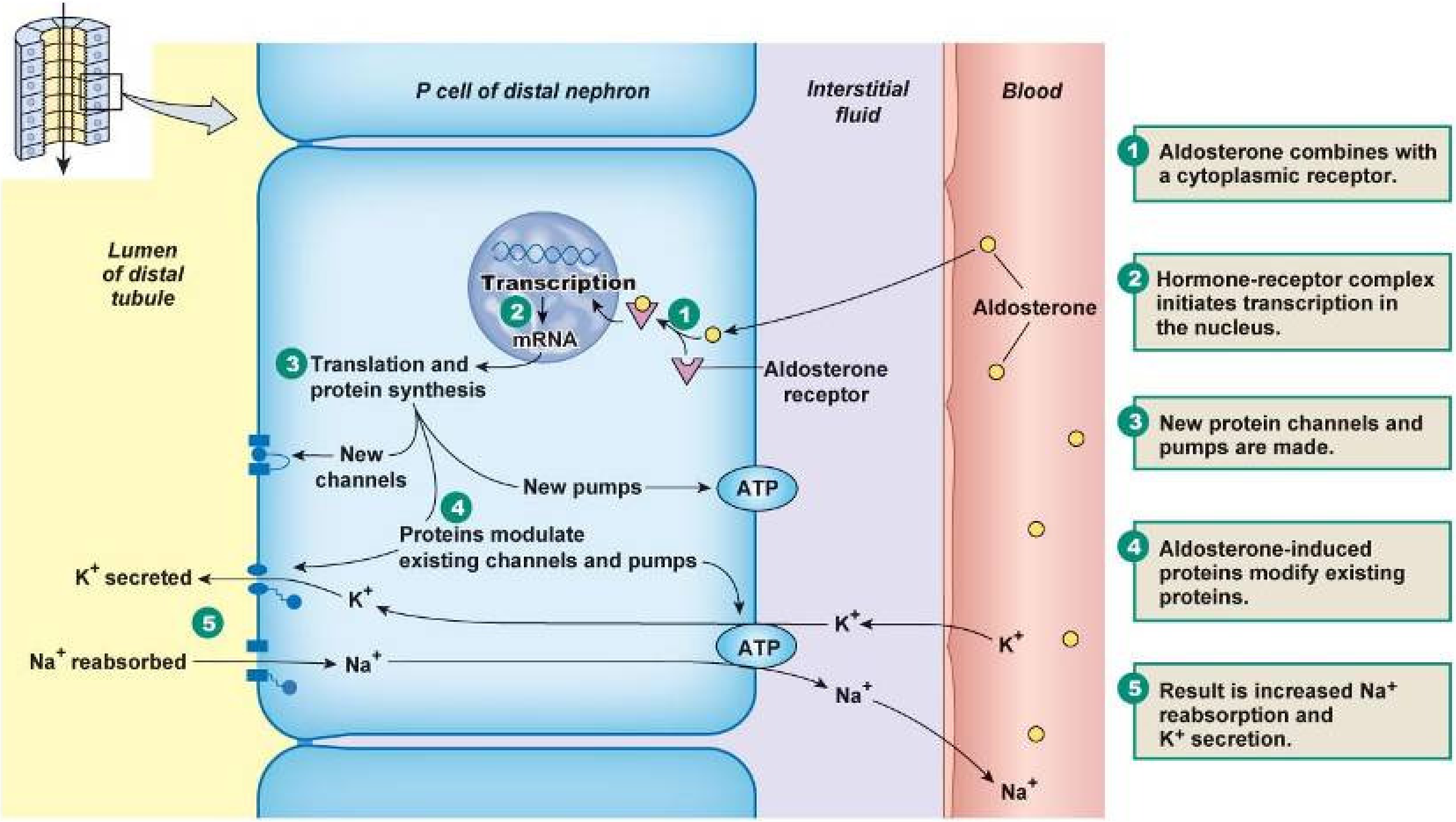


Including glucose, amino acids, ions and various organic metabolites.





Aldosterone action in principal cells



↑ Synthesis of Na^+ channels, Na^+/K^+-pump and citric acid cycle enzymes

- positive Na^+ balance
  - ↑ ECF Na^+
  - ↑ ECF volume
  - hypertension
  - edema

- negative Na^+ balance
  - ↓ Na^+ (hyponatraemia)
  - hypovolaemia
  - hypotension

- Na^+ reabsorption
  - driven by Na^+/K^+-ATPase in basolateral membrane of tubule, largest energy expenditure
  - reabsorption of glucose, amino acids etc. is coupled to Na^+ reabsorption

Handling of K^+

- K^+ in ICF = 150 mM, ECF 5 mM, NB for membrane potential
- [K^+] balance: determined by K^+ secretion (after total reabsorption)
- regulation of plasma [K^+]:

  $\uparrow$ in plasma [K^+] $\rightarrow$ epinephrine, insulin and aldosterone will cause cells to take up K^+
- alterations in plasma [K^+]

  acid-base balance – acidosis $\rightarrow$ results in movement of H^+ into cells and [K^+] out of cells, alkalosis the reverse

  $\uparrow$ osmolality of ECF $\rightarrow$ release of [K^+] by cells

  physical activity $\rightarrow$ K^+ is released from skeletal muscle

  cell lysis – hyperkalaemia

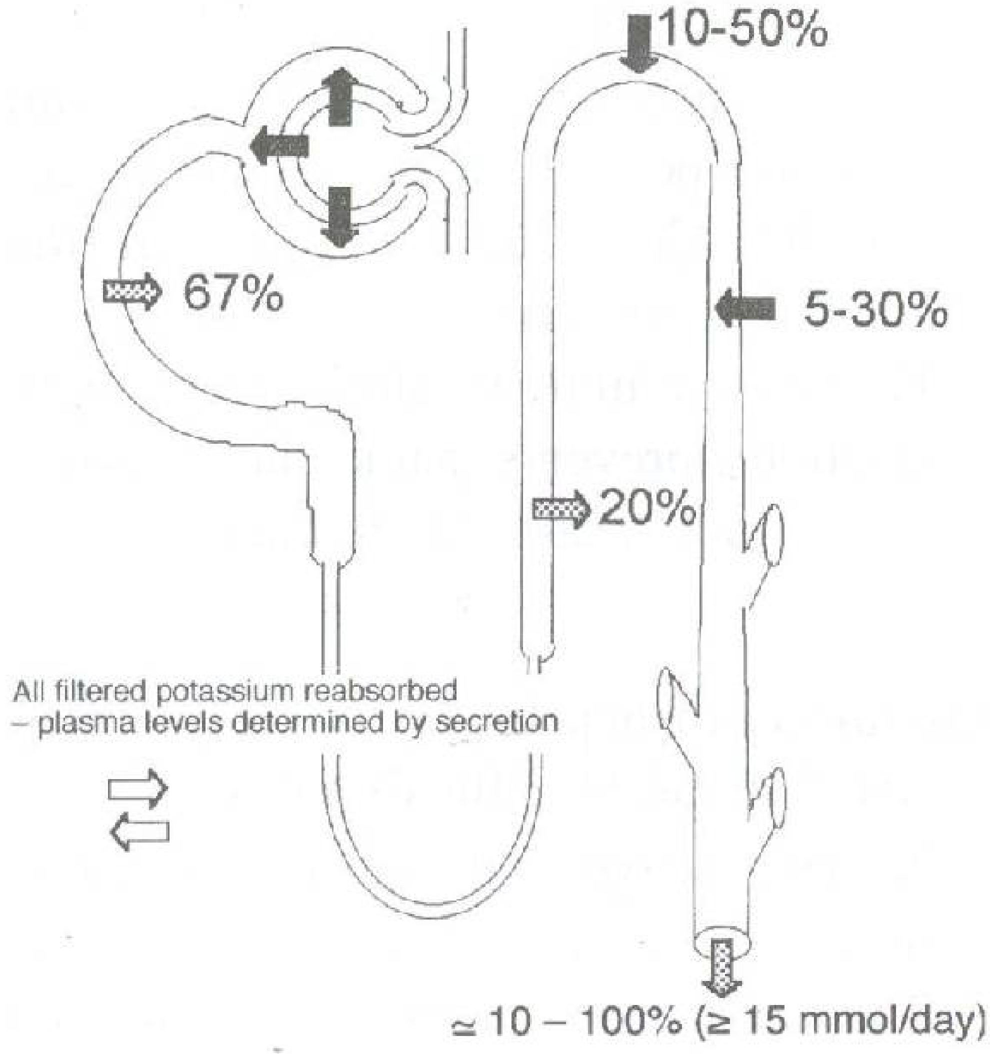
Handling of K^+ in the different segments

• K^+ freely filtered

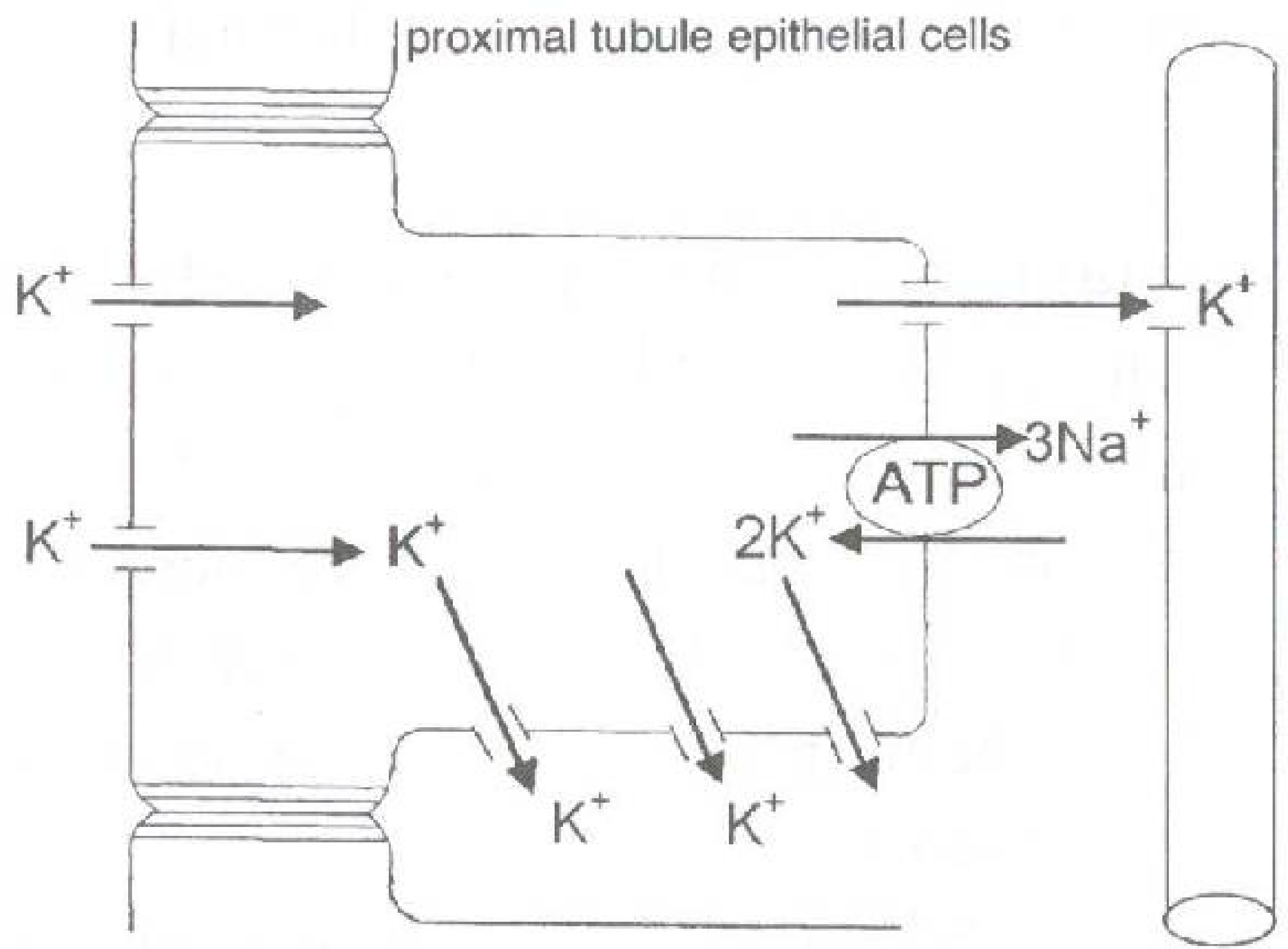
• ERPF = 650 ml/min
plasma [K^+] = 5 mmol/l
plasma load = 5 x 0,65
= 3,25 mmol/min

• GFR = 125 ml/min
tubular load = 5 x 0,125
= 0,625 mmol/min

• all filtered K^+
reabsorbed, excess
removed by secretion



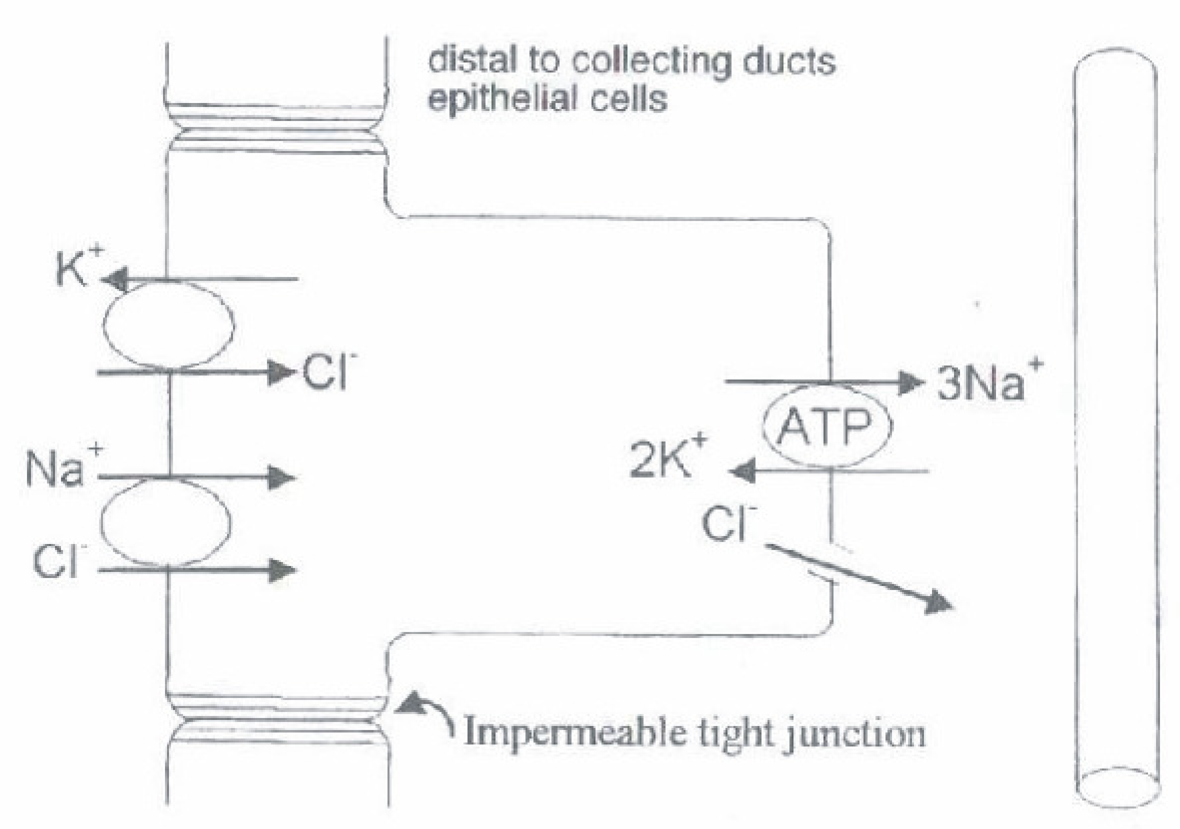
Potassium reabsorption in the proximal tubule



- Na^+/K^+-ATPase in basolateral membrane works against reabsorption!!
- K^+ does follow osmotic gradient through K^+ channels in LM and BLM

Early distal tubule

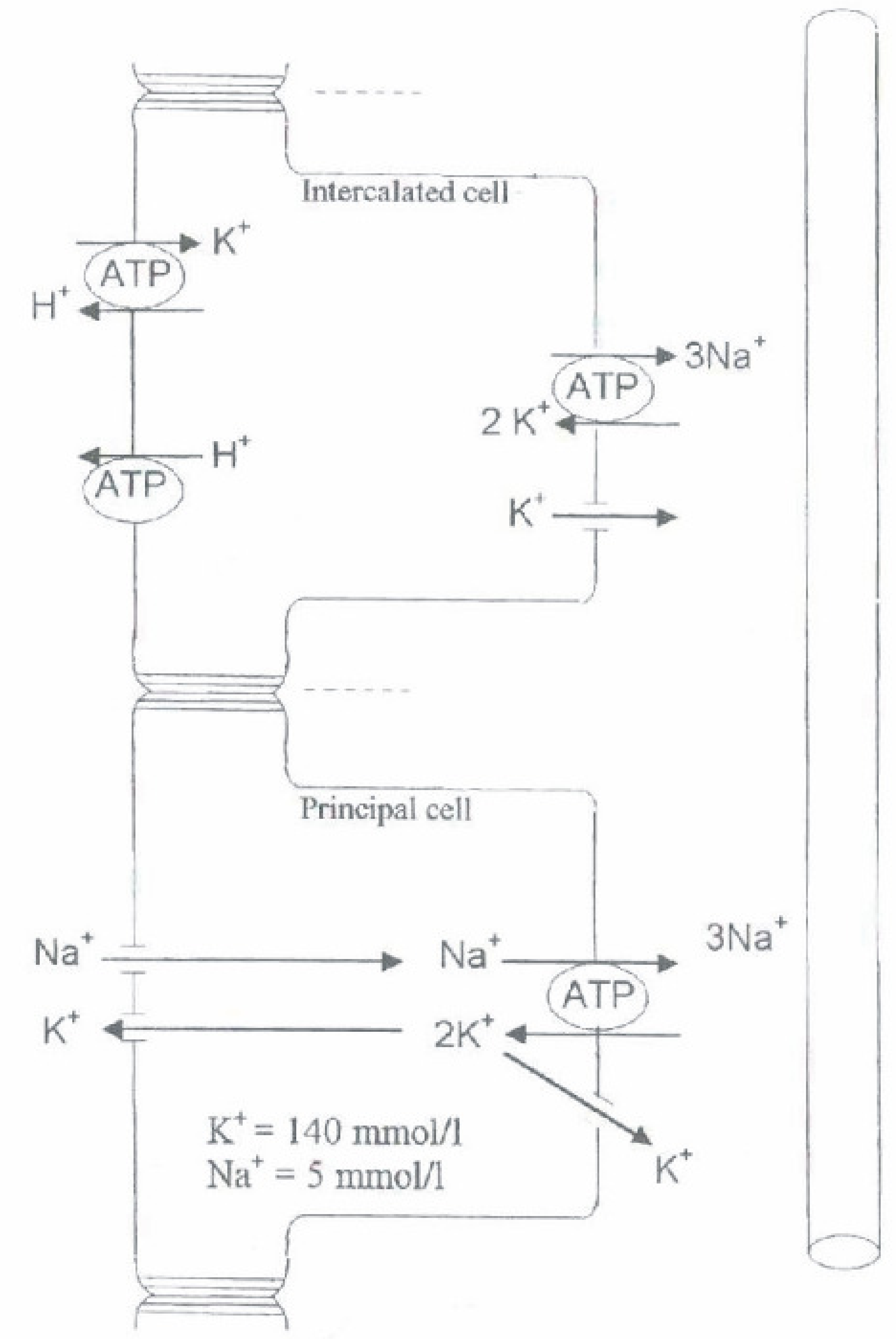
• secretion via secondary active K^+/Cl^- countertransport in luminal membrane
• no paracellular transport!



Distal to collecting tubule

- α-intercalated cells
- primary active countertransport in luminal membrane K^+ channels in basolateral membrane

- principal cells
- secretion, NB for plasma $[K^+]$
- Na^+/K^+-ATPase in basolateral membrane
- K^+ channels in luminal membrane very permeable



K^+ secretion increased by factors that increase K^+ channels or the electrochemical gradient

- aldosterone

  increases synthesis of basolateral membrane Na^+/K^+-ATPase and luminal membrane K^+ channels

- high ECF [K^+]

  leads to high ICF [K^+], results in depolarization and decreases excitability

- acid-base status

  alkalosis will increase ICF K^+ in exchange for H^+, leaves cells to compensate for ECF alkalosis

- diuretics

  loop and thiazide diuretics increase K^+ loss in urine, K^+ sparing diuretics decrease K^+ secretion

Handling of Cl^-

- Cl^- in filtrate slightly less than in plasma, due to negative charge which is repulsed by negative filtration membrane

- Na^+ reabsorption is the major determinant of Cl^- reabsorption, together they are major contributors to osmolality

Handling of Ca^{2+} by the proximal tubule (1), loop of Henlé (2) and distal tubules (3)

- proximal

67% reabsorbed by Na^{+}/Ca^{2+} countertransport

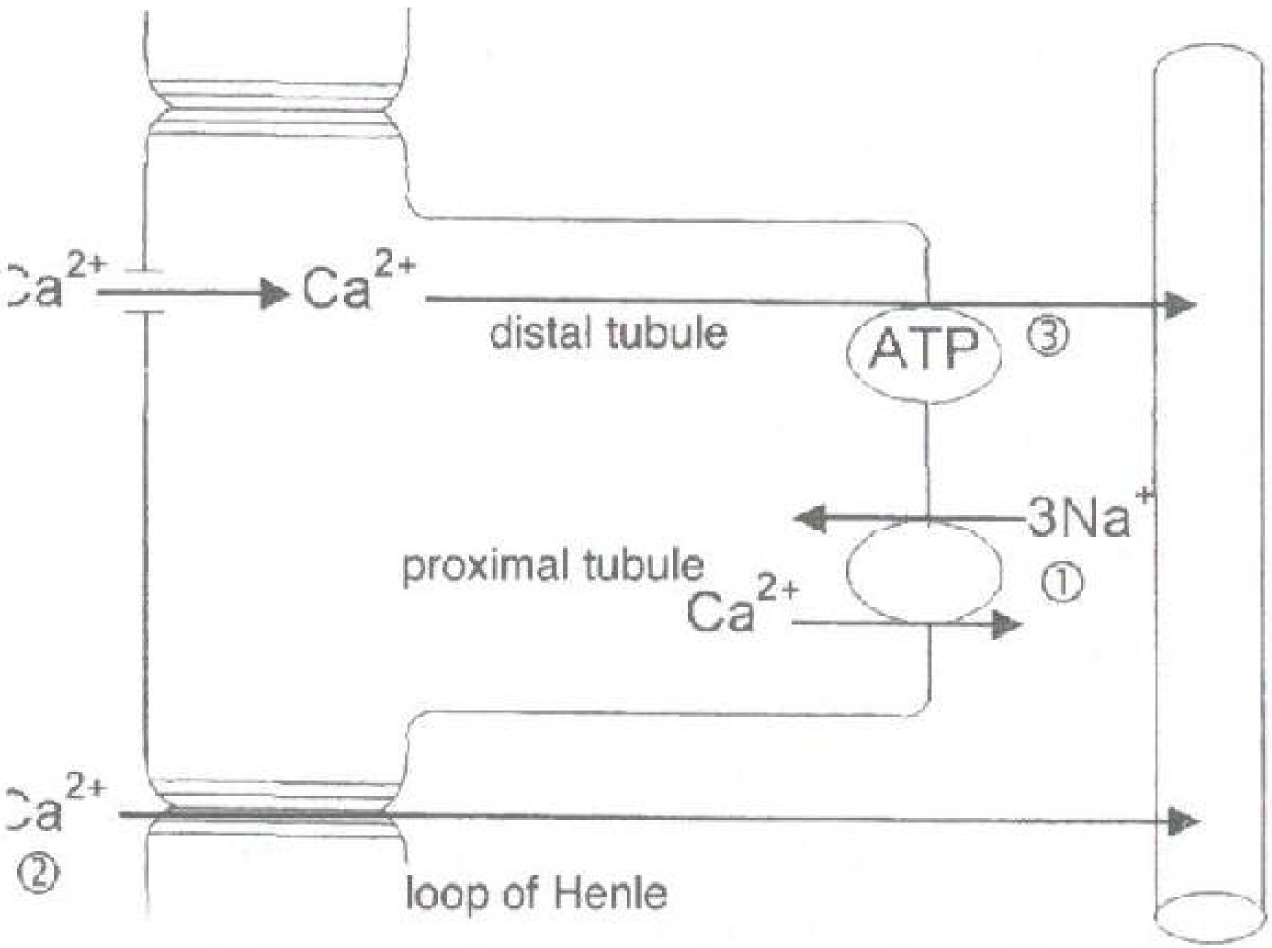
- loop of Henlé

25% by paracellular transport

- distal tubule

8% by active Ca^{2+}-ATPase in basolateral membrane

PTH and Vitamin D stimulate Ca^{2+}-ATPase



- plasma Ca^{2+} = 2.5 mmol/l
- GIT and bone also NB in blood Ca^{2+} levels
- 50% free, 40% bound to protein and 10% bound to citrate/phosphate
- acidosis increases ionised Ca^{2+}
- free Ca^{2+} and Ca^{2+} bound to citrate/phosphate is filterable
- renal load: 0,65 x 2,5 = 1,63 mmol/min
- tubular load 2,5 x 60/100 x 0,125 = 0,19 mmol/min

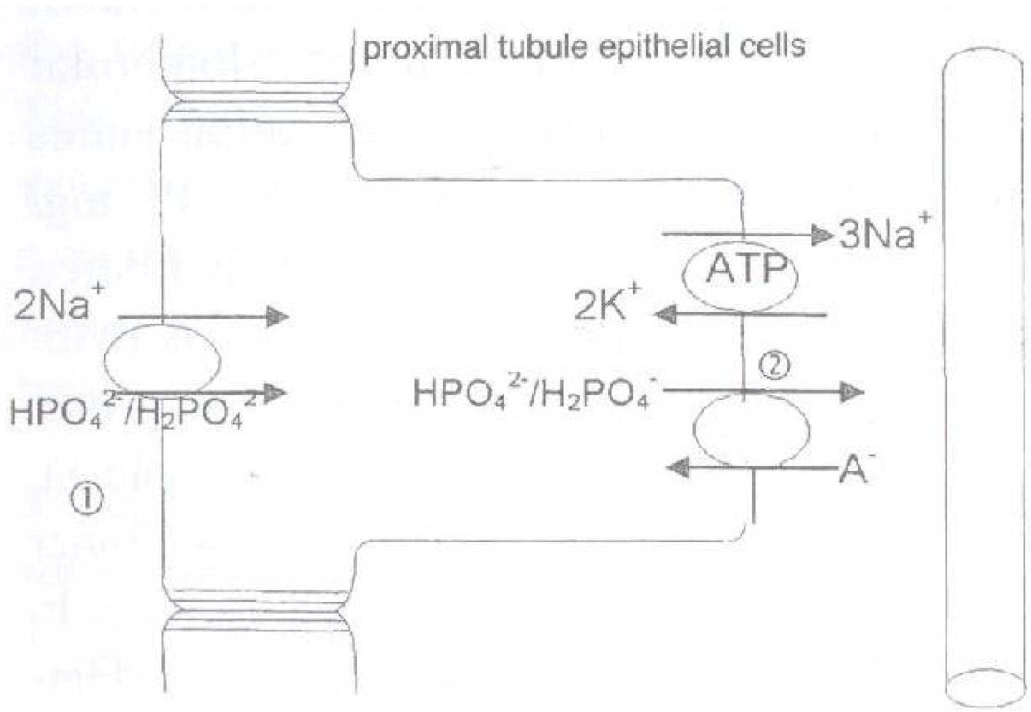
Handling of Mg^{2+}

- $[Mg^{2+}]$ in filtrate 70-80% of plasma
- 25% reabsorbed in proximal tubule
- majority reabsorbed by paracellular transport in ascending loop of Henlé
- hypermagnesaemia and hypercalcaemia damage paracellular shunts – impair reabsorption
- loop diuretics also impair reabsorption

Handling of phosphate

- plasma [phosphate] = 1,25 mmol/l as $HPO_4^{2-}/H_2PO_4^-$ of 4:1
- 10% bound to protein
- 80% reabsorbed in proximal tubule
- as soon as the luminal cotransporter is saturated, phosphate will appear in the urine

Handling of phosphate in proximal tubule



- secondary active transport in luminal membrane Na^+/phosphate cotransporter in luminal membrane
- determines T_m for phosphate
- inhibited by PTH which decreases T_m and increases phosphate excretion in the urine

- phosphate/anion countertransport in basolateral membrane

- no reabsorption/secretion in later segments

Handling of glucose

- glucose/Na^+ cotransporter in luminal membrane
- energy provided by Na^+/K^+-ATPase in basolateral membrane
- glucose carried over basolateral membrane by Glut 1 and Glut 2 (facilitated diffusion)
- as long as plasma glucose remains under the threshold, all will be reabsorbed

Handling of amino acids and proteins

- amino acids similar to glucose: amino acids/Na^+ cotransporter driven by Na^+/K^+-ATPase
- amino acids have different secondary active transport mechanisms to leave the cell along concentration gradient
- proteins filtered in small amounts; reabsorbed in proximal tubule by pinocytosis, digested by tubular cells, amino acids absorbed as such
- nephrotic syndrome: increases permeability of glomerular membrane – proteinuria

Urea, uric acid and creatinine

- urea
  - breakdown product of amino acids
  - plasma [urea] = 3-7,5 mmol/l, 860 mmol filtered daily, 50% reabsorbed by diffusion in proximal tubule
  - rest of tubule impermeable to urea, thus urine [urea] is about 70 times that of plasma – [200-400 mmol/l]
- uric acid
  - breakdown product of purine bases in nucleic acids
  - plasma [uric acid] = 0,18-0,45 mmol/l
  - 90% actively reabsorbed in the proximal tubule
  - probenecid, colchicine and allopurinol increase uric acid secretion and lessen gout symptoms
  - thiazide diuretics lessen excretion
- creatinine
  - very little reabsorbed but secreted again, netto all is excreted

Tubular secretion

- active secretion

  takes place by secondary active transport

  K^+, H^+ secretion are NB in pH control

  K^+, penicillin and other organic molecules are filtered, reabsorbed and secreted by the nephron

  secretion can speed up excretion as it removes substrates as they move through the peritubular capillaries

  probenecid competes with penicillin for active transport, thus slows down penicillin secretion – NB in antibiotic treatment