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)

\[ EFP = (55 + 0) - (30 + 15) = 10 \text{ mm Hg} \]

GFR = \( K_f \times \text{EFP} \)

\( K_f \) = ultrafiltration coefficient

**KEY**
- \( P_H \) = Hydrostatic pressure (blood pressure)
- \( \pi \) = Colloid osmotic pressure gradient due to proteins in plasma but not in Bowman’s capsule
- \( P_{\text{fluid}} \) = Fluid pressure created by fluid in Bowman’s capsule

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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

Autoregulation maintains a nearly constant GFR when mean arterial blood pressure is between 80 and 180 mm Hg.

Normal mean blood pressure
The juxtaglomerular apparatus

- Bowman's capsule
- Efferent arteriole
- Distal tubule
- Afferent arteriole
- Juxtaglomerular apparatus
- Proximal tubule
- Loop of Henle
- Glomerular capillary
- Lumen of Bowman's capsule
- Macula densa
- Direction of blood flow
- Afferent arteriole
- Granular cells (juxtaglomerular cells)
Tubuloglomerular feedback

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.

3. ↑ in [NaCl]

Resistance in afferent arteriole increases.
Hydrostatic pressure in glomerulus decreases.
GFR decreases.
Arteriolar diameter changes renal blood flow and GFR

(a) Efferent arteriole
Glomerulus
Afferent arteriole
Arterial resistance
Renal blood flow (RBF)

(b) Decreased capillary blood pressure (\( \downarrow P_H \))
Decreased GFR
Increased resistance in afferent arteriole
Decreased RBF
Increased blood flow to other organs

(c) Increased P_H
Increased GFR
Decreased RBF
Increased resistance in efferent arteriole

? P_H
? GFR
? RBF

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• sympathetic nerves and circulating catecholamines decrease GFR
  \(\alpha_1\)-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

Regulation continued
• COP in glomerular blood
  in afferent arteriole 25-28 mm Hg
  when COP decreases (high fluid intake, hypoproteinaemia) → GFR increases

• COP in Bowman’s capsule
  negligible, except during diseases that increase permeability or affects negative charge (nephritis) → 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

1. **Na⁺ is reabsorbed by active transport.**
2. **Electrochemical gradient drives anion reabsorption.**
3. **Water moves by osmosis, following solute reabsorption.**
4. **Concentrations of other solutes increase as fluid volume in lumen decreases. Permeable solutes are reabsorbed by diffusion.**
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\textsuperscript{+} reabsorption mechanisms in the proximal tubule

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

1. Na\textsuperscript{+} enters cell through membrane proteins, moving down its electrochemical gradient.
2. Na\textsuperscript{+} is pumped out the basolateral side of cell by the Na\textsuperscript{+}-K\textsuperscript{+}-ATPase.

**Key**
- Membrane protein
- ATP = Active transporter
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
  \(\uparrow\) ECF Na\(^+\)
  \(\uparrow\) ECF volume
  hypertension
  edema

• negative Na\(^+\) balance
  \(\downarrow\) 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⁺]:
  ↑ in plasma [K⁺] → epinephrine, insulin and aldosterone will cause cells to take up K⁺
• alterations in plasma [K⁺]
  acid-base balance – acidosis → results in movement of H⁺ into cells and [K⁺] out of cells, alkalosis the reverse
  ↑ osmolality of ECF → release of [K⁺] by cells
  physical activity → 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 \times 0.65
  = 3.25 mmol/min

- GFR = 125 ml/min
  tubular load = 5 \times 0.125
  = 0.625 mmol/min

- all filtered K\(^+\) reabsorbed, excess removed by secretion
Potassium reabsorption in the proximal tubule

- \( \text{Na}^+/\text{K}^+ \)-ATPase in basolateral membrane works against reabsorption!!
- \( \text{K}^+ \) does follow osmotic gradient through \( \text{K}^+ \) channels in LM and BLM.
Early distal tubule
• secretion via secondary active $\text{K}^+/\text{Cl}^-$ 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$^{2+}$

- $[\text{Mg}^{2+}]$ 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 $\text{HPO}_4^{2-}/\text{H}_2\text{PO}_4^-$ 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 \([\text{urea}] = 3-7.5 \text{ mmol/l}\), 860 mmol filtered daily, 50% reabsorbed by diffusion in proximal tubule
  - rest of tubule impermeable to urea, thus urine \([\text{urea}]\) is about 70 times that of plasma – \([200-400 \text{ mmol/l}]\)

- **uric acid**
  - breakdown product of purine bases in nucleic acids
  - plasma \([\text{uric acid}] = 0.18-0.45 \text{ mmol/l}\)
  - 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