# Renal Physiology

Basics
2 kidneys
10-11 cm long
150g each
1 million nephrons/kidney
25% of cardiac output: RBF ~ 625ml/min/kidney
20% filtered: GFR ~ 125 ml/min (range 80-140ml/min)
Functions:

1. Excretion
    a. Metabolic endproducts
        Acid (organic or inorganic)
        Nitrogenous waste (urea)
        Nucleic acid turnover (uric acid/xanthine)
    b. Drugs/Toxins
        Filtration or secretion
        Often same disposal as acids
2. Maintenance of fluid volume
    Sodium and water regulation via RAA and in response to ADH
3. Maintenance of body fluid composiiton
    Na+, K+, Cl-, pH, Mg+, Ca+, phosphate, water
4. Hormonal regulation
    Renin
    Erythropoetin
    1,25 dihydrocholecalciferol

Glomerular filtration
Passive ultrafiltration of plasma across semipermeable glomerular membrane
Determinants of GFR:
Glomerular permeability (Lp)
Glomerular surface area (S)
Pushing pressure (difference in hydrostatic pressure)
Pulling pressure (difference in oncotic pressure)

GFR = LpS - (Δhydrostatic pressure - Δoncotic pressure)

(i) Glomerular permeability
Fenestrated negatively-charged (anionic) capillary endothelial cell layer with microvilli
Size and charge selective
Free filtration of water and neutral molecules less than 26 Angstroms
Some filtration of neutral/positively-charged molecules up to 60A
No filtration of highly-negative molecules (albumin) or >60A
(ii) Transglomerular hydraulic pressure
Autoregulation* of afferent and efferent arterioles acts to maintain glomerular blood pressure at a constant 50-60mmHg
Proximal tubular hydrostatic pressure effectively zero, except when downstream obstruction

(iii) Oncotic pressure

Constant at ~25mmHg

In normal conditions plasma proteins not filtered so Bowman's space oncotic pressure zero

Autoregulation of glomerular filtration

GFR preserved across wide range of blood pressure (80 – 180mmHg) due to 2 complimentary mechanisms:

(i) Afferent arteriolar myogenic stretch

Laplace's law governs that a rise in pressure/increase in radius (volume) increases wall tension

Myogenic tone of afferent arteriole 'pushes' back; conversely relaxes when pressure/radius, thereby regulating flow into glomerulus

(ii) Tubuloglomerular feedback (juxtaglomerular apparatus)

Macula densa cells in distal tubule monitor flow

Increased pressure – increased GFP – increased tubular flow

Leads to production of substances (endothelin, TXA2, AT2) from granular cells of juxtaglomerular apparatus, leading to constriction of afferent arteriole

NB. Granular cells of JGA secrete renin in predominantly in response to low tubular chloride rather than sodium. Sodium follows chloride, leading to a rise in ECF volume and blood pressure (see appendix)

Assesment of glomerular filtration

GFR cannot be measured directly – needs to be estimated. Methods comprise Plasma creatinine and other markers, mathematical formulae, and plasma clearance

(i) Plasma markers

Creatinine

Constant production in individual

10% secreted – therefore typically overestimates GFR

Patient to patient variation based on age, sex, muscle mass and race. Low production (little old ladies) overestimates GFR; high intake (bodybuilders) underestimates GFR

Mathematical formula used to 'normalise values':

(i) Cockcroft & Gault (individuals with normal function)

$$\mathrm{CrCl} = \frac{\{[(140 - \mathrm{age}) \times (\mathrm{IBW\ in\ kg})]}{[\mathrm{PCr(mg/dL)} \times 72]\}} \times 0.85\,(\mathrm{women})$$

Does not describe a linear relationship – see graph overleaf. Also calculates creatinine clearance, not glomerular filtration rate

(ii) MDRD (individuals with impaired renal function)

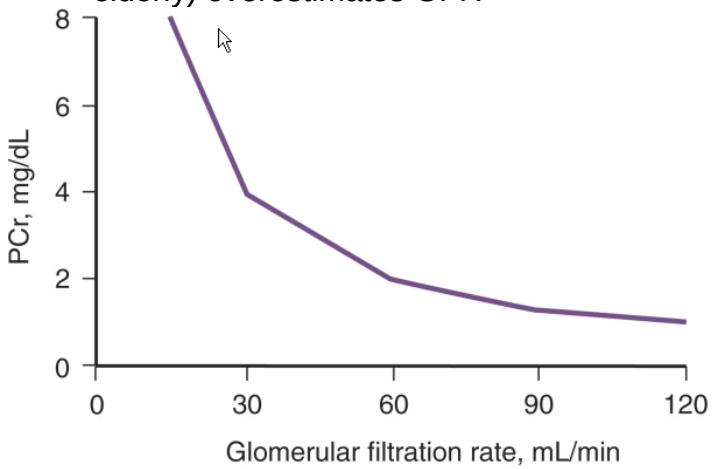
Modification of diet in renal disease (1999). Derived as a screening tool to identify patients with renal disease

$$GFR = 186 \times (PCr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

Calculates GFR not creatinine clearance
Underestimates eGFR at high values. Therefore a number of hospitals give eGFR of > 60ml/min rather than a figure for high filtration rates
Requires fudge factor for blacks – not calculated automatically
New formula CKD EPI set to supercede MDRD as better predictor across range of GFRs

Steady *reciprocal* relationship between GFR (or creatinine clearance) and serum creatinine (see below)

NB. Increased production (rhabdomyolysis, supplements) underestimates GFR
Reduced production (cirrhosis, reduced muscle mass, elderly) overestimates GFR




Urea
Freely filtered but up to 50% reabsorption by tubule

Cystatin C
Nucleic acid breakdown molecule. Constant production, unaffected by diet, not secreted, expensive

(ii) <u>Clearance</u>

Best way of estimating GFR is by measuring clearance of a substance from plasma.
Clearance = the amount of plasma that is completely cleared of a substance per unit time.

Cl = [U] x V / [P]

U = Urine concentration of substance
V = Volume of urine
P = Plasma concentration of substance

To be accurate the substance must:
Achieve steady state in plasma
Excreted solely by kidney
Freely filtered
Not secreted, reabsorbed or metabolised by tubule

Good example inulin, but impractical. Typically creatinine clearance, but secreted by proximal tubule, thus overestimates GFR by 10-20% at normal levels. Overestimation greater as renal function deteriorates – more creatinine secreted. Radiolabelled EDTA most accurate (DTPA can be used but slightly secreted). Typically single injection of $^{51}$Cr-EDTA, then measure blood levelsat specified intervals 2-5 hours after injection to demonstrate decay curve.

Tubular function

| | | |
|---|---|---|
| Proximal tubule | Major site of electrolyte and glucose reabsorption<br>Secretion of organic acids/drugs and toxins | |
| Loop of Henle | Generation of osmotic gradient for variable water reabsorption (countercurrent mechanism)<br>Additional NaCL reabsorption | |
| Distal tubule/ collecting duct | Hormone sensitive fine tuning | |
| | Aldosterone | NaCl reabsorption<br>K+ excretion |
| | ADH | Water reabsorption |
| | H+ excretion dependent on acid base status | |

Proximal Tubule

Divided into three segments: S1/S2 concerned with reabsorption, S3 predominantly concerned with secretion

Reabsorption

- 15% Mg ++
- 65% Na+ *, K+, Ca++
- 80% Water, phosphate, HCO3-
- 100% Glucose **, amino acids
- * **Na+ is the only solute actively reabsorbed** via basolateral Na+/K+ pump. Remainder passively reabsorbed down concentration, osmotic (water) or electrochemical gradients
- ** Glucose absorption threshold 200mg/dL
- Glutamine converted to ammonia throughout PCT

Secretion

- Drugs and toxins via active organic ion (cation or anion) pumps
- Liver often converts uncharged molecules to charged ones for excretion

Loop of Henle

Two purposes of LoH

- Reabsorption of 25-30% Na+
- Generation of vertical osmotic gradient

(i) Thin descending limb

- Highly water permeable (aquaporin 1 channels)
- Negligible solute transport

(ii) Thin ascending limb

- Minimal water permeability
- Passive NaCl and urea diffusion down concentration gradient

(iii) Medullary thick ascending limb

- Water impermeable
- 25-30% Na+ reabsorption

Passive transport into cell (Na+K+CLCL2 co transporter*)
Active transport out (basolateral Na-K ATPase)
*Targeted by loop diuretics

15% Ca++; 60% Mg++ reabsorption
Passive paracellular, driven by electrochemical gradient.
Dissipation of gradient by loop diuretics inhibits Ca++ and Mg++ absorption

10-20% HCO3- reabsorption

Minimal K+ reabsorption
Recycling of K+ in TALH crucial to generate electrochemical gradient

Countercurrent mechanism (300-1200 mosm/l)
NaCl and urea (50% from loop; 50% from collecting duct) make interstitium hypertonic. Water osmotically absorbed from TDLH = more concentrated urine at hairpin = more diffusion of solute = more diffusion of water, etc. Under ADH, urea and water diffuse into interstitium. Water rapidly reabsorbed by vasa recta (also aquaporins in *cortical* collecting duct) thereby preserving concentration gradient

Production of Tamm-Horsfall mucoprotein

<u>Distal tubule</u>

Divided into DCT and connecting tubule
Principle cells – aldosterone dependent secretion of K+/absorption of Na+
Intercalated cells – hormone-independent absorption of K+

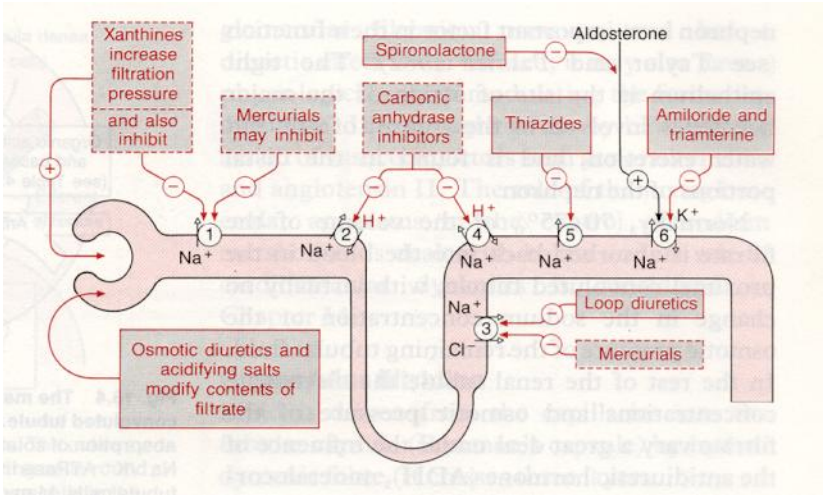
Distal convoluted tubule:
5-10% Na+ absorption
Passive Na+K+CL2CL2 co-transport, driven by basolateral Na+/K+ ATPase
Co-transporter inhibited by thiazide diuretics
Na+ absorption dependent on luminal [Na+]. – frusemide increases Na+ absorption by DCT (net Na+ loss however)

10-15% Ca+ reabsorption
Passive, independent of Na+ absorption
Driven by basolateral Na+/Ca+ pump (Ca+ out).
Reduced intracellular Na+ 2' thiazides postulated as a reason for hypocalciuric effect but exact mechanism unknown

Connecting tubule:
Sodium absorption and potassium loss under influence of aldosterone
K+ secretion rate influenced by sodium delivery, and urine flow rate.
Tubular damage impairs potassium secretion (interstitial nephritis etc.)

| | Proximal nephron | LOH | Distal nephron |
|---|---|---|---|
| Na+ reabsorption* | 67% | 25% | 8% |
| Water reabsorption* | 65% | 15% | 20% |
| Ca++ reabsorption | 65% | 15% | 15% |
| Mg++ reabsorption | 15% | 60% | 10% |

* maximum values



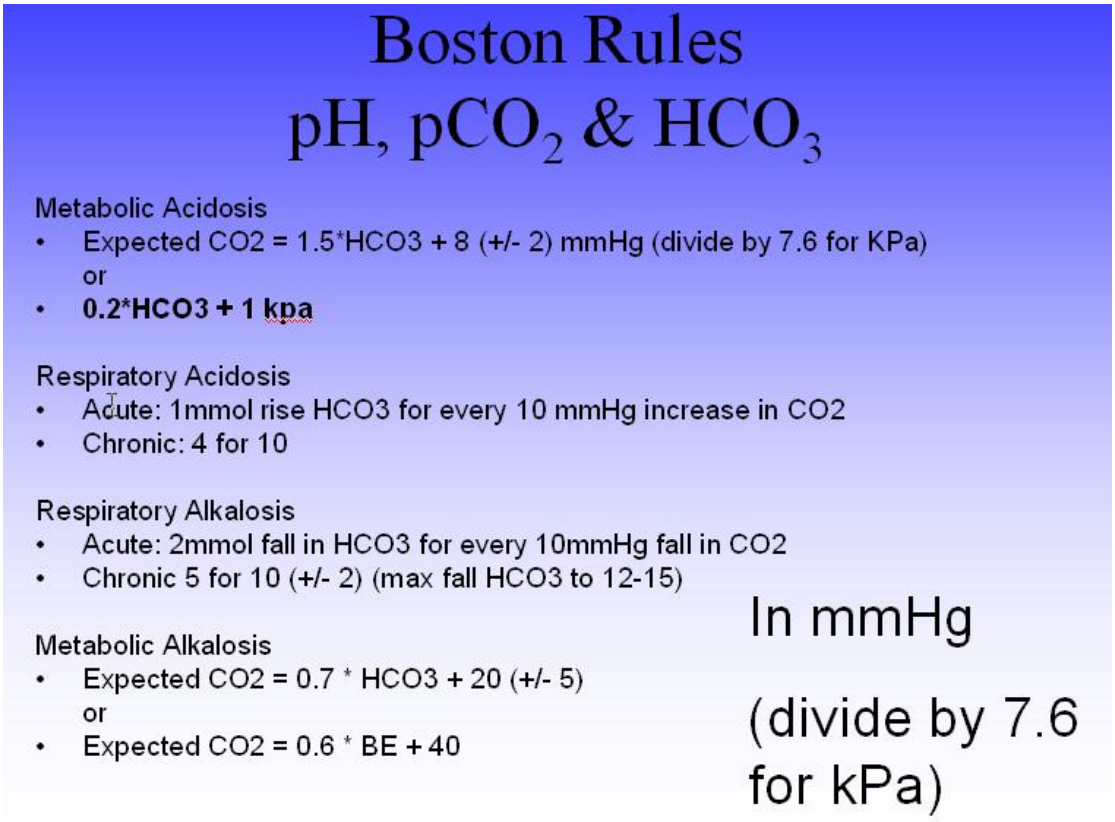

Diuretics

| | |
|---|---|
| Loop diuretics | inhibit Na+K+CL-CL- pump in TALH<br>Organic acids requiring secretion into PCT for effect. In renal failure more competition for secretion from accumulating toxins. Explains usage of large doses (250mg-1g) for effect in renal failure<br>Up to 25% increased sodium excretion<br>Loss of NaCL, water, K, Mg and Ca |
| Thiazide diuretics | inhibit NaCL co-transport in DCT<br>5-10% increased sodium excretion<br>Loss of NaCl, water. Loss of K by increasing sodium load to DCT. |
| Potassium-sparing | Spironolactone, amiloride, triamterine<br>5% increased sodium excretion<br>Spironoloctone competes with aldosterone for intracellular mineralocorticoid receptor – inhibits Na-K ATPase<br>Amiloride/triamterine directly blocks sodium channels |

Acid-base balance

pH 7.35 – 7.45
Tightly controlled by buffers
HCO3/CO2 principal buffer system
Lungs excrete CO2 rapidly
Kidney
- Reclamation of all filtered HCO3
- Excretion of H+ with generation of HCO3
  - Mechanisms:
    - glutamine into NH4 and HCO3 in PCT
    - H-ATPase in DCT excretes H+ and generates HCO3 (H+ buffered by PO4 or as free acid)

Determining appropriateness of compensation




Anion gap and Metabolic acidosis

Na + K – Cl – HCO3 Normal < 15-20*
High > 15-20*

* Depends on lab measurement. Newer ion-specific techniques more accurate. New classification HIGH = 12 or above

Blood electrochemically neutral. 'Positive' anion gap because more unmeasured anions than cations. Unmeasured cations magnesium, calcium and gamma globulins. Unmeasured anions sulphates, albumin and phosphate. Where a pure loss of bicarbonate occurs, chloride released to 'bridge the gap'. In situations where new acids are produced electrochemical neutrality is maintained (salicylate plus H+), thus chloride remains unchanged

| | |
|---|---|
| High anion gap | Lactic acidosis<br>Ketoacidosis<br>Salicylate poisoning |
| Normal anion gap | Gut losses (Vomiting, fistula, diarrhoea)<br>Renal losses (RTA)<br>Chloride ingestion/administration |

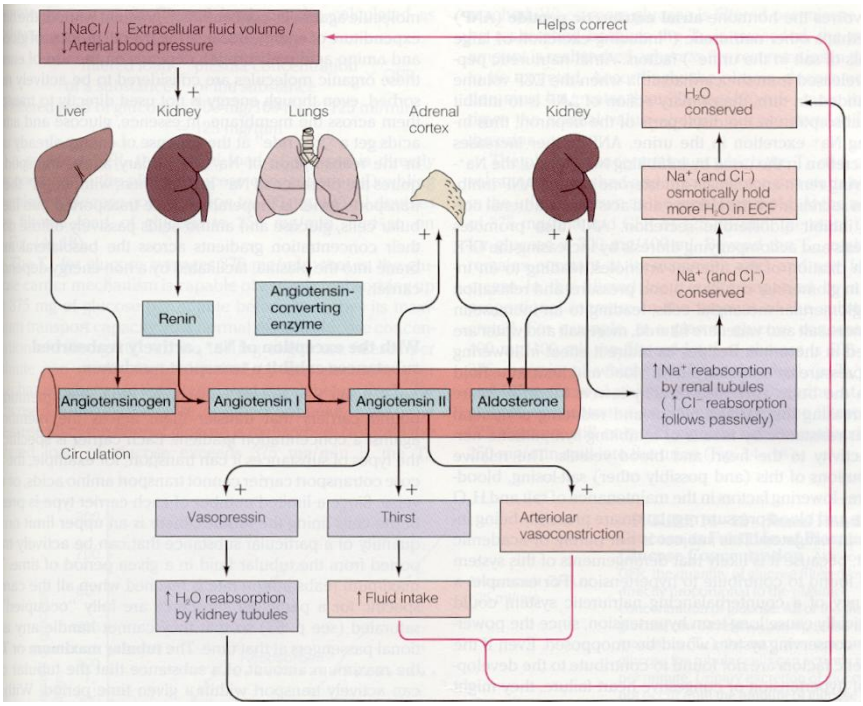
NB Renal tubular acidosis (RTA)
Family of diseases characterized by failure of tubular H+ secretion and urinary acidification:

| | |
|---|---|
| Type 1 | distal failure of H+ secretion<br>Diagnostic triad<br>Hyperchloraemic metabolic acidosis<br>High urinary pH (>5.5)<br>Low serum HCO3<br>Associated low sodium, hyperaldosteronism, with low potassium (and low citrate)<br>**Calcium phosphate stone disease** – Rx with sodium bicarbonate |
| Type 2 | Proximal failure of bicarbonate reabsorption<br>Same triad as above, with low sodium and potassium<br>Citrate normal - no stone disease<br>Usually children - growth retardation and osteomalacia (Tiny Tim) |
| Type 3 | Actually type 1 |
| Type 4 | Impaired distal H+ and K+ secretion. As above but with hyperkalaemia |

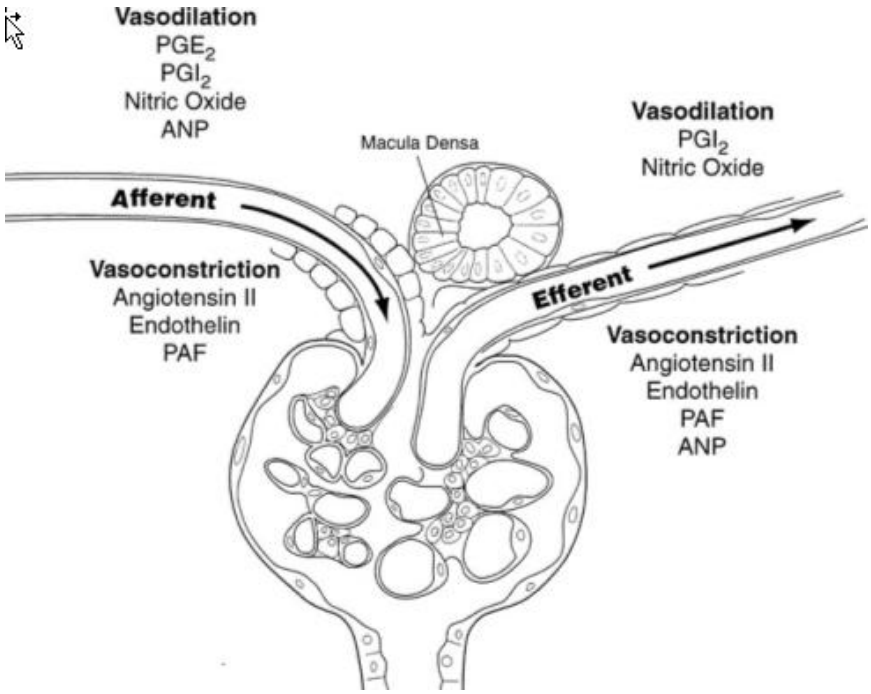
Metabolic alkalosis

Ingested alkali normally rapidly excreted by kidney. Persistent alkalosis usually due to impairment of HCO3 excretion from kidney, typically due to chloride deficiency. Replacement of Cl usually reverses alkalosis.
Chloride responsive = Gut losses and diuretics (90% - often with paradoxical aciduria due to aldosterone action) - low urinary Cl
Chloride unresponsive = mineralocorticoid excess leading to acid and potassium loss from tubule. Normal urinary Cl (>15 MEq/l)

## Homeostasis and renin-angiotensin axis




NB. Control of renin release is rate-limiting step in RAA axis

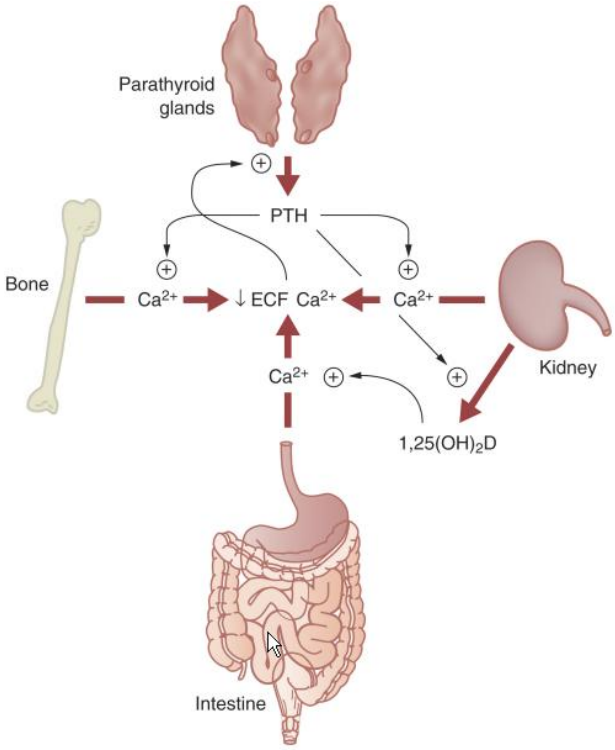



| Vasoconstrictors | Vasodilators |
|---|---|
| Angiotensin 2 | Nitric oxide |
| Vasopressin | Carbon monoxide |
| Noradrenaline | PGE2/PGI2 |
| Endothelin | Acetylcholine |
| Platelet activating factor | Serotonin |

| ANP | Glucocorticoids |
|---|---|
| Angiotensin 2 | mediates effects via AT1 receptor – efferent constriction>> afferent vasoconstriction |
| Endothelin | Highly potent vasoconstrictor released from endothelial cell membrane |
| ANP | Atrial natriuretic peptide (Cogan 1990)<br>Released in response to increased intravascular volume<br>Effects<br>Increased GFR (dilatation AE and constricts EA)<br>Inhibits juxtaglomerular apparatus (decreased renin, AT2 and aldosterone) = natriuresis<br>Inhibits vasopressin release and effects = diuresis<br>Prevents phase 3 (shutdown) in bilateral UO vs. unilateral UO by maintaining AE dilatation |
| Nitric oxide | Synthesised by endothelial NOS (eNOS) and released from endothelium |
| Carbon monoxide | Produced as a byproduct of heme metabolism by Heme oxygenase (HO). Exerts renoprotective effect vs ischaemia, especially in renal medulla |

<u>Calcium homeostasis</u>

Major source of cholecalciferol is dermal synthesis from cholesterol
Other source from diet
Initial 25a-hydroxylation in liver
Second 1a-hydroxylation in kidney to form 1,25 dihydroxy-cholecalciferol (calcitriol)
Acts on gut to increase calcium and phosphate reabsorption. Acts on bone to increased calcium resorption




PTH – acts on kidney to stimulate calcium reabsoprtion and phosphate excretion

Calcium in plasma bound to albumin (46%), complexed with citrate/phosphate (7%) or ionized/free (47%). Acidosis displaces Ca from albumin increasing free ionized calcium. Reverse in alkalosis. May not be identified as serum calcium estimation measures total calcium, not ionized forms.

Erythropoeisis

EPO produced by interstitial cells of kidney in response to low oxygen tension. HIF-1a and HIF-2a stabilised in hypoxic conditions to assemble apparatus for promoting transcription of EPO. Anaemia in renal failure simple secondary to loss of functioning interstitial cells.