RENAL PHYSIOLOGY AND PHARMACOLOGY

RENAL AND FLUID AND ELECTROLYTES

Renal physiology

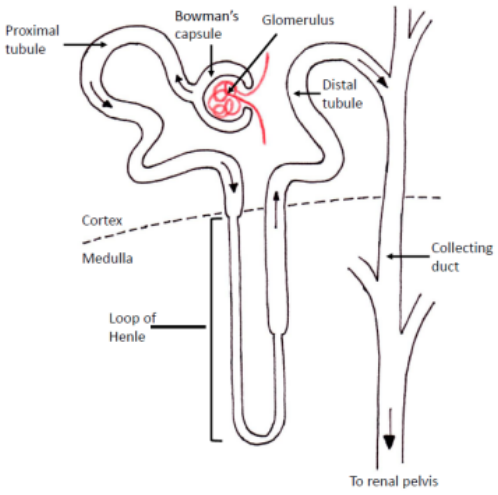
Functions of the kidney: MAKEUP

1. **Excretion of metabolic waste and foreign substances**
   a. Filtration of metabolic waste products e.g. urea from protein, uric acid from nucleic acids; Cr from muscle
   b. Filtration of drugs
2. **Regulation of water + electrolyte balance**
   a. Homeostatic mechanism
   b. 180L of fluid and other substances filtered per day
   c. countercurrent mechanism – concentration of urine
   d. renal tubules reabsorb Na, H2O, K, Ca, Mg, and Cl either actively or passively
3. **Regulation of plasma osmolality**
   a. Sensors: osmoreceptors, baroreceptors (high pressure + volume), intrarenal mechanisms
   b. Controller: hypothalamus
   c. Effectors: ADH, RAAS, ANP, SYNS
4. **Regulation of acid base balance**
   a. Excretion of acid: secreted H buffered by PO4 + formation of NH4
   b. Reabsorption of HCO3 → for CO2 homeostasis
5. **Regulation of BP**
   a. RAAS
   b. ECF vol regulation
6. **Endocrine function**
   a. Vit D: role in Ca2+ homeostasis
   b. EPO: stimulate RBC production
   c. RAAS
   d. Prostaglandins esp. PGE2 + prostacyclin – potent renal vasodilators
   e. Bradykinin – potent renal vasodilator
7. **Gluconeogenesis**
   a. Renal cortex contains glucose 6 phosphatase → able to release glucose in times of need

Describe the functional anatomy of the kidneys and urinary tract

Gross anatomy of the kidneys

- Paired organs located in the retroperitoneal space T12-L3
- Fibrous capsule
- Consists of: outer cortex; inner medulla; pelvis (subdivided into major + minor calyxes)
- Innervation of the kidney is by SY noradrenergic nerves



Functional anatomy of the kidney

Nephron = functional unit of the kidney

- Each kidney contains: 1-1.5million nephrons
- 2 types: cortical +Juxtamedullary
- made up of single layer epithelial cells separated by a basement membrane
- Nephron consists of:
  - Glomerulus:
    - network of capillaries invginated in BC in renal cortex
    - afferent arteriole + efferent arteriole
    - Layers control filtration: glomerular capillary endothelium; basement membrane; Podocytes; Mesangial cells
    - Produces ultrafiltrate
  - Proximal tubule
    - 2 parts: convoluted (pars convoluta) + straight (pars recta)
    - main role: reabsorption of electrolytes + water; secretion; regulation of acid-base
  - Loop of Henle
    - Descending + ascending limb (thick + thin)
    - cortical nephrons (85%): short LoH
    - juxtamedullary (15%): long LoH
  - JGA
    - Final part of LoH adjacent to arterioles
    - 3 components: granular cells (renin secretion), macula densa cells (sense tubular [NaCl]), extraglomeruluar mesangial cells
  - Collecting ducts
    - drain urine into calyces
- Fluid in bowmans capsule passes along: PCT, loop of henle, DCT, CD

Glomerulus + function

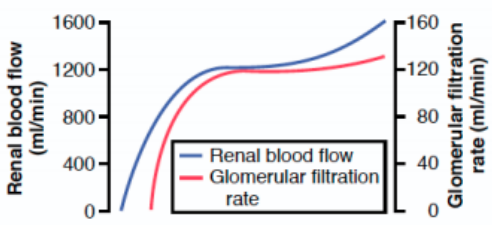
- 3 distinct layers
- glomerular capillary endothelium
  - highly specialised endothelium with fenestrations to ↓filter thickness
  - prevents cellular components of blood from coming into contact with BM
- glomerular BM
  - made of CT; -vely charged
  - acts as filter
- bowmans epithelial cells (podocytes)
  - epithelial cells with foot processes → large SA
  - maintain BM + phagocytic functions

Explain the physiology of renal blood flow

- RBF = vol of blood passing through kidneys per unit time
- Kidneys receive ~25% of CO = ~1250ml/min
  - Cortex: 500ml/min/100g
  - Outer medulla: 100ml/min/100g
  - Inner medulla: 20ml/min/100g
  - High blood flow: required for production of large amounts of renal filtrate → urinary excretion of waste products
- Renal circulation is unique:
  - supplied by renal artery from aorta; drained by ≥1 renal vein to IVC
  - Renal artery → afferent arterioles → glomerular capillaries → efferent arterioles
  - Vasa recta (peritubular capillaries): arise from efferent arterioles; supply renal medulla + countercurrent flow
  - Cortex: 2 sets of arterioles (afferent + efferent) + 2 sets of capillaries (glomerular + peritubular)

Determinants of RBF:

- **RBF = Part – Pven / R**
  - Part = renal arterial pressure ~ = MAP 100mmHg
  - Pven = venal venous pressure ~= IVC ressure 4mmHg
  - main control for RBF = R (renal vascular resistance) → main determinant of R = tone of afferent + efferent arterioles



Regulation of RBF

1. **Autoregulation**
   - RBF autoregulated within MAP 70-170mmHg
   - 2 main mechanisms = myogenic control + tubuloglomerular feedback
   - **1. Myogenic mechanism**
     - Afferent arteriole smooth muscle contraction in response to transmural **stretch**/ tension.
     - ↑RPP → ↑transmural pressure → reflex smooth muscles arteriolar constriction → ↑resistance → maintain RBF
     - ↓RPP → afferent arteriole smooth muscle relaxation → ↓vascular resistance
     - Fast acting; protects glomeruli from short fluctuations in BP
   - **2. Tubuloglomerular feedback**
     - JGA monitors fluid flow through DCT + adjusts GFR accordingly (ΔRBF are secondary)
     - Sensing unit = macula densa
     - Basically: ↑Na + Cl at macula densa → stimulates adenosine production
     - ↑RPP → ↑glom cap pressure → GFR ↑s → ↑rate of delivery of Na + Cl ions to macula densa
     - ↑[Na+] sensed by macula densa cells through Na/K/2Cl cotransporter. Intracellular movement of Na, K, Cl ions coupled to osmotic movement of H2O into macula densa cell → cellular swelling ∝ to GFR
     - Adenosine released ∝ degree of cell swelling →
       1. afferent arterioles vasoconstrict → ↑renal vascular resistance → ↓RBF
       2. glomerular mesangial cells contract → ↓surface area for filtration → ↓GFR
       3. granular cells inhibited from secreting renin
2. **Neuronal control**
   - ↑SNS tone → intrarenal β1 Rs → ↑renin release → ↑ATII → vasoconstriction
   - ↑SNS → adrenaline release by adrenal medulla → α Rs → vasoconstriction → ↓RBF
3. **Hormonal control**
   - **RAAS**
     - renin released from granular cels of JGA in response to:
       - ↓tubular flow (sensed by macula densa)
       - ↓afferent arteriolar pressure
       - SYNS through β1 receptors
     - Renin cleaves angioteninsogen → angiotensin I → angiotensin II by ACE → ATII effects:
       - Efferent > afferent vasoconstriction → ↑RPP
       - ↑SVR → ↑BP
       - ↑aldosterone → DCT + CD → ↑Na + H2O reabsorption
       - Thirst + ↑ADH release + ↑SYNS (NA release)
   - **ANP**: vasodilate afferent arteriole → ↑RBF
   - **Prostaglandins** → vasodilate → ↑RBF
4. **High blood amino acid/ glucose level**
   - High filtered aa/ glucose load → ↑reabsorption in PT with Na → ↓NaCl reaches distal tubules → macula densa → ↓adenosine → vasodilation → ↑RBF

Describe glomerular filtration and tubular function

Glomerular filtration rate

- GFR = volume of filtrate formed per unit time
- ~125ml/min = 180L/day
- glomerular filtration
  - comprised of plasma ultrafiltrate – large proteins remain in plasma
  - occurs within renal corpuscle: bowmans capsule + capillaries invaginating capsule (afferent + efferent arterioles)

Degree to which solutes are filtered is dependent on 2 physical properties:

1. **MW**
   - MW <7000 Da freely filtered: e.g. small ions, glucose, urea, amino acids, hormones
   - MW <70 000 Da are partially filtered: albumin (0.02%)
   - MW >70000 not filtered: e.g. hydrophobic hormones of steroids + thyroid
2. **Electrical charge**
   - filtration barrier contains polyanions → repel –vely charged macromolecules
   - BM: heparin sulphate proteoglycan molecules
   - foot processes: sialoglycoproteins

Determinants of GFR/ the rate at which filtration occurs depends on:

- GFR = Kf x NFP

1. Filtration coefficient (Kf)

- Product of intrinsic permeability of glomerular capillary (filter) + surface area available for filtration
- Kf denotes: hydraulic permeability x surface area
- Contraction / relaxation of mesangial cells alters SA and Kf → ∝ ΔGFR
- Rate of filtration = Kf x NFP

2. Net filtration pressure (NFP)

- NFP = magnitude of forces favouring or opposing filtration
- Described by Starling's forces:
  - Relationship between hydrostatic + colloid pressures within glomerular capillary + bowmans capsule
  - **NFP = [P_C-P_B] - [π_C - π_B]**
  - = [48mmHg – 10mmHg] - [25mmHg]
  - **Pc (hydrostatic pressure in glomerular capillaries) ~48mmHg**
    - Affected by Δrenal arterial pressure or resistance
    - ↑Pc:
      - ↑renal arterial pressure
      - ↓afferent arteriolar resistance (afferent dilation)
      - ↑efferent arteriolar resistance (efferent constriction)
      - → ↑GFR
    - ↓Pc
      - ↓renal arterial pressure
      - ↑afferent arteriolar resistance (afferent constriction)
      - ↓efferent arteriolar resistance (efferent dilation)
      - → ↓GFR
  - **P_B (hydrostatic pressure in bowmans capsule) ~10mmHg**
    - ↑P_B → ↑intratubular pressure eg obstruction → ↓GFR
  - **πB (oncotic pressure in bowmans capsule) = 0mmHg**
  - **π_C (glomerular capillary oncotic pressure) = ~25mmHg**
    - π_C at beginning of glom cap = oncotic pressure of systemic arterial plasma
    - progressive ↑π_C along capillary as H2O filters out of vascular space → ↑protein left behind → ↓NFP → ↓GFR
    - ↑π_C: ↑systemic plasma oncotic pressure

Arteriolar		Afferent	Efferent
P_{GC}	mmHg	60	58
P_{BC}	mmHg	15	15
π_{GC}	mmHg	**21**	**33**
NFP	mmHg	**24**	**10**

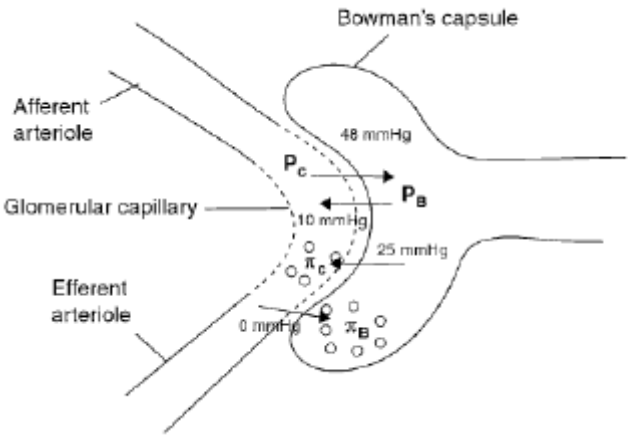


Figure 1.5.3a. The hydrostatic and oncotic forces acting on the glomerulus. Where, P_C = hydrostatic pressure of glomerular capillary, P_B = hydrostatic pressure of Bowman's capsule, Π_C = oncotic pressure of glomerular capillary and Π_B = oncotic pressure of Bowman's capsule.

Therefore GFR is affected by:

- Effect of afferent/ efferent arteriolar tone
  - Afferent tone:
    - ↑tone → ↓PG → ↓NFP → ↓GFR: mediated by adenosine, ATII, adrenaline
    - ↓tone → ↑PG → ↑NFP →↑GFR: mediated by ANP, NO, PG
  - Efferent tone
    - ↑tone → ↑PG → ↑NFP → ↑GFR: ANP, adrenaline, ATII
    - ↓tone → ↓PG → ↓NFP → ↓GFP
- Tubuloglomerular feedback
- MAP
- Kf
- Plamsa oncotic pressure
- Reflection coefficient
  - Normally omitted in starling equation as =1 in normal nephron
  - Protein losing nephropathy will ↓reflection coefficient → leaky to protein → ↓plasma oncotic pressure + ↑interstitial oncotic pressure → ↑↑GFR

Filtration fraction (FF)

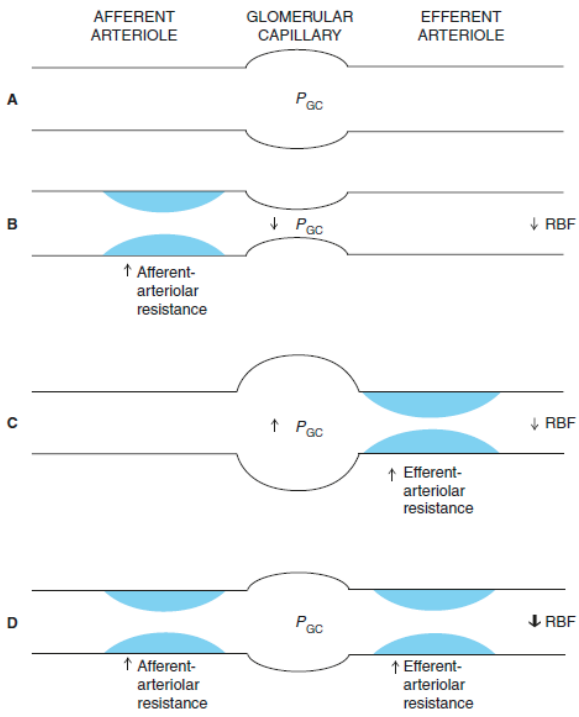
- the fraction of plasma entering the glomerular capillary that is filtered
- ~15-20% RPF
- only the plasma component of blood can take part in filtration
- FF = GFR / RPF
  - RPF can be calculated if RBF + Hct are known
  - RPF = RBF x (1- Hct)

Describe the forces acting across the glomerular capillary membrane. Explain how afferent and efferent arteriolar tone affect glomerular filtration rate: PAST QUESTION

Forces - See above

Afferent + efferent arteriolar tone and effect on GFR

- P_{GC}
  - GFR directly proportional relationship to PGC: ↑PGC → ↑GFR; ↓PGC → ↓GFR
  - Afferent constriction:
    - ↓PGC → ↓GFR
    - ↓RBF → ↑filtration fraction → ↑π_c → ↓GFR
  - afferent dilation:
    - ↑PGC → ↑GFR
    - ↑RBF → ↓filtration fraction → ↓π_c → ↑GFR
  - Efferent constriction:
    - ↑PGC → ↑GFR
    - ↓RBF
  - Efferent dilation
    - ↓PGC → ↓GFR
    - ↑RBF
- Autoregulation
  - Afferent + efferent arteriolar tone = autoregulated between MAP 75-170mmHg to maintain constant GFR via myogenic + tubuloglomerular feedback mechanism
  - Glomerulotubular balance: NaCl reabsorption in proportion to GFR
  - Also affected by: autonomic, hormonal (ATII, ANP), and disease states



Tubular function

Tubular function

- Kidneys produce 150-180L of protein free filtrate per day (125ml/min)
- Tubules process this filtrate by:
  - Reabsorbing 99% of Na and H2O
  - Conserving essential nutrients (glucose, amino acids etc.)
  - Eliminating potential toxins, organic bases and acids, excess K, and exogenous compounds

Tubular reabsorption

- Most substances must cross 2 plasma memebranes
  - Luminal (or apical) membrane
  - Basolateral membrane
- Transport mechanisms
  - transcellular
    - simple diffusion: transfer of substances down EC gradient
    - facilitated diffusion: transfer of substances down EC gradient via specific transmembrane proteins
    - primary active transport: transfer down EC gradient via specific transmembrane protein which consumes ATP
    - secondary active transport: transfer of multiple ions/ molecules by transmembrane protein; one down EC gradient → provides energy for other substrate against EC gradient
    - endocytosis: invagination of CM
  - paracellular
    - simple diffusion
    - solvent drag: transfer of small ions or molecules by mass movement of H2O (solvent) through pores
- Bulk flow or simple diffusion into the peritubular capillaries = final common step for all reabsorbed substances
- Reabsorption regulated by physical + hormonal influences
  - Glomerulotubular balance
  - RAAS, ANP, ADH

Tubular secretion

- initial step = simple diffusion/ bulk flow from peritubular capillaries to interstitial fluid → into tubule via simple diffusion (tight junctions) or active transport through cells

Tubular metabolism

- e.g. synthesis of HCO3 and ammonia from glutamine

Cellular transport by location

- Basolateral membrane: only site of primary active transport
- Luminal membrane: site of diffusion, facilitated diffusion, and secondary active transport

Proximal tubule

- Most metabolically active cells in the kidney; high O2 consumption
- Reabsorbs 70% Na and H2O
- Complete reabsorption of amino acids and glucose (cotransported with Na)
- Almost complete reabsorption of HCO3 and excretion of H through carbonic anhydrase catalyzing reaction between CO2 and H2O
- Reabsorb PO4

Descending LoH

- Do not carry out active transepithelial ion transport
- Act as important passive equilibriators in the process of countercurrent multiplication

Thick ascending LoH

- Extensive transepithelial reabsorption of Na (up to 25% total), and Cl

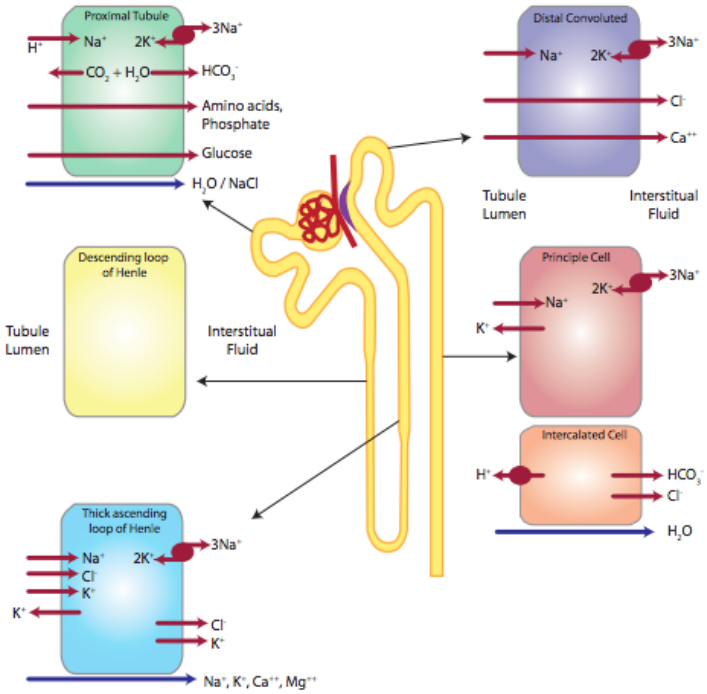
- Smaller fluxes of K, Mg2+, and Ca2+
- Impermeable to water under all conditions → this allows the countercurrent to be established
- This is where loop diuretics (frusemide) work

Distal convoluted tubule

- Extends from macula densa to CCT
- Na reabsorbed with Cl
- Little K or H2O movement
- Ca2+ reabsorption (modulated by PTH)
- Thiazides act here and ↑Ca2+ reabsorption

Cortical collecting duct

- Reabsorption of 2-3% filtered Na, Cl
- K (principle cell) and acid excretion (intercalated cell)
- All of these processes stimulated by aldosterone
- H2O permeability variable – dependent on ADH creating aquaporins
- Amiloride and spironolactone act here → sparing of K and acids



Reabsorption by substance

	PCT	Descending Thin Limb	Ascending Thin Limb	Ascending Thick Limb	DCT	CD	Other
Histology	**Simple columnar epithelium**, lots of apical microvilli with canaliculi, basal infoldings with mitochondria Central nuclei Large cells (3-5 nuclei around lumen)	**Squamous epithelium**	**Squamous epithelium**	Similar in structure to DCT	**Simple cuboidal epithelium** No microvilli Basal infoldings with mitochondria Apical nuclei Pale compared to PCT	Pale **principal cells** & dark **intercalated cells** As progresses into medulla → Taller columnar cells with no intercalated cells	Basal mitochondria – typical of ion pumpers (eosinophilic) All epithelium will be cytokeratin positive
Na^+ (freely filtered)	**60-70% reabsorbed** Apical: **Na^+/H^+ exchanger**, cotransport with glucose, AAs, PO_4^{3-} Basolateral: **Na^+/K^+-ATPase** **Paracellular transport**	**Impermeable**	**Reabsorption passive & paracellular**	**25% reabsorbed** Apical: **$Na^+/K^+/2Cl^-$ cotransporter**, **Na^+/H^+ exchanger** Basolateral: **Na^+/K^+-ATPase** **Paracellular**	**5% reabsorbed** Little paracellular Apical: **Na^+/Cl^- cotransporter** (*inhibited by diuretics/thiazides*) Basolateral: **Na^+/K^+-ATPase**	**3% reabsorbed** by principal cells Apical: Epithelial Na^+ channels (**ENaC**) create negative lumen (*inhibited by amiloride*) Basolateral: **Na^+/K^+-ATPase**	1) Principal determinant of **ECF volume** 2) Reabsorption closely coupled with water in PCT, dissociated in distal segments 3) Basolateral exit always via Na^+/K^+-ATPase 4) Urinary excretion 100mmol/day (0.4%)
Cl^- (freely filtered)	**Reabsorption** Early PCT: **Paracellular** 2° negative lumen gradient of Na^+ Late PCT: **Transcellular** Apical: **Counter-transport** with another anion Basolateral: **Cl^- channels** or **K^+/Cl^- cotransporter**	**Impermeable**	**Reabsorption passive & paracellular**	**Reabsorption** Apical: **$Na^+/K^+/2Cl^-$ cotransporter** Basolateral: **Cl^- channels** & **Cl^-/HCO_3^- exchanger**	**Reabsorption** Apical: **Na^+/Cl^- cotransporter** Basolateral: **Cl^- channels**	**Reabsorption** Principal cells: **Paracellular** (negative lumen from Na^+) Beta-intercalated cells: Transcellular using apical **Cl^-/HCO_3^- exchanger** Basolateral: **Cl^- channels**	Most filtered Na^+ reabsorbed with Cl^-
Water	**65% reabsorbed** **Paracellular** reabsorption through 'leaky' tight junctions **Transcellular** through aquaporins (transcellular > paracellular)	**15% reabsorbed - Moderately permeable**	**Impermeable**	**Impermeable**	**Impermeable**	**5-24.4% reabsorbed** **↑ Permeability with ADH (vasopressin)**	Water transport always passive
			Used for solute reabsorption				
K^+ (freely filtered)	**55% reabsorbed** Early PCT: Lumen negative, impairs somewhat Late PCT: Positive lumen enhances through **K^+ channels**	**30% reabsorbed in Loop of Henle**			**Beyond LoH, depends on overall K^+ balance**		1) Urinary excretion from 1-3% to 150% 2) Medullary recycling: K^+ reabsorbed in IMCD & thin & thick ascending exceeds K^+ secreted in descending → K^+ trapped in interstitium – secreted in K^+ overload
		Passive paracellular secretion driven by high K^+ in medullary interstitium	High luminal K^+ drives passive **paracellular reabsorption**	**Reabsorption**: Positive lumen drives paracellular Transcellular via apical **$Na^+/K^+/2Cl^-$ cotransporter** & basolateral **K^+ channels**	2% reabsorbed during K^+ depletion	**6% reabsorbed** during K^+ depletion in IMCD **IMCD**: Reabsorbs regardless of overall K^+ balance **α-intercalated**: Reabsorb K^+ by **H^+/K^+-ATPase** with exit through **K^+ channels** **Principal**: Secrete via **K^+ channels** (ROMK) & **K^+/Cl^- cotransport**	

	PCT	Descending Thin Limb	Ascending Thin Limb	Ascending Thick Limb	DCT	CD	Other
Urea (freely filtered)	**50% reabsorbed** Paracellular: Mainly by **solvent drag** Some transcellular	UT2 – Secretes urea Taken up in IMCD	More urea **secretion** (urea delivery to the initial portions of CD – **110% remains**)			**Reabsorption** Apical: Uptake via **UT1 transporter** Basolateral: Exit via **UT4** **40% remains**	At low rates of urine flow, reabsorption ↑ & secretion ↓
Glucose (freely filtered)	**Completely reabsorbed (98% PCT & remaining 2% in rest of nephron segments)** Early PCT: **SGLT2** (Na^+/glucose cotransporter apically) & **GLUT2** (facilitated diffusion basolaterally) Takes up glucose until ratio inside to out is 70:1 (high capacity, low affinity) Late PCT: **SGLT1** (uses $2Na^+$/glucose) & **GLUT1** (facilitated diffusion basolaterally)						SGLT's saturable (T_m systems) – Abnormally high levels of glucose overwhelm reabsorptive capacity Plasma glucose 200mg/dL or 10-12mmol/L
Amino Acids (freely filtered)	**Completely reabsorbed (>98% in PCT & remaining in rest of nephron)** Not individual transporters – Cysteine (basic) transporters (without these get cystinuria) & neutral AA transporters (without these get Hartnup's disease) Apical: Uptake with Na^+ or AA channels (facilitated diffusion) Basolateral: Facilitated diffusion with Na^+/AA cotransport or counter-transport						
Peptides/ Proteins	**Completely reabsorbed (>98% in PCT & remaining in rest of nephron)** Small peptides filterable & most hydrolysed by peptidases on luminal membrane of PCT Some resistant to hydrolysis & enter proximal cells via peptide cotransporters Larger proteins either undergo endocytosis (broken down by lysosomes) or transcytosis (not degraded)						
Phosphate (not freely filtered – 10% bound to proteins)	**80% reabsorbed** Apical: **Na^+/PO_4^-** transport → Makes lumen more negative ($2Na^+/1PO_4^-$) (PTH downregulate expression) Basolateral: Not understood					**10% reabsorbed** Not understood	**10% excreted** Balances with amount absorbed in GIT
Calcium (not freely filtered – 40% bound to proteins)	**65% reabsorbed** Majority **solvent drag** – Induced by Na^+ & H_2O reabsorption Voltage driven in PCT Apical: Through **Ca^{2+} channel** Basolateral: **Na^+/Ca^{2+} counter-transport** & **Ca^{2+}/H^+-ATPase**			**25% reabsorbed** ½ paracellular, ½ transcellular Apical: Epithelium Ca^{2+} channels Basolateral: Same as PCT	**8% reabsorbed** Transcellular	**1.5% reabsorbed**	**0.5% excreted** Uptake closely related to Na^+ uptake
H^+/HCO_3^-	**80% HCO_3^- reabsorbed** HCO_3^- comes in through CAIV Apical: **H^+ secretion** → **Na^+/H^+ exchange**, **H^+-ATPase pumps** Basolateral: HCO_3^- reabsorbed → **Na^+/HCO_3^- transport** (early), **Cl^-/HCO_3^- exchanger** (late) High intracellular HCO_3^- drives HCO_3^- out of cell			**10% HCO_3^- reabsorbed** Apical: **H^+** **Secretion**: **Na^+/H^+ exchange**, **H^+-ATPase pumps** Basolateral: HCO_3^- exits in **Cl^-/HCO_3^- exchanger**	**Remaining 10% HCO_3^- reabsorbed** Apical: **H^+ secretion** through **H^+-ATPase pumps** &/or **H^+/K^+-ATPase pumps** Basolateral: **Cl^-/HCO_3^- exchanger** Aldosterone: 1) Stimulates Na^+ reabsorption in CD (negative lumen favours H^+ secretion) 2) Stimulates H^+-ATPase Aldosterone independent: Acidosis stimulates insertion of **H^+-ATPase** (alkalosis inhibits)		**H^+ secretion & HCO_3^- reabsorption always take place together in kidney** Net acid excretion = (titratable acidity + ammoniagenesis) – HCO_3^- secretion

	PCT	Descending Thin Limb	Ascending Thin Limb	Ascending Thick Limb	DCT	CD	Other
Ammonia	**Most NH_3 doesn't come from glomerular filtration → Generated in PCT** 1 Glutamine → $2NH_4^+$ & reabsorb $2HCO_3^-$	Secretion of NH_4^+ in cortical thin descending limb Medullary portion of descending limb & thin ascending limb → Net passive NH_3 reabsorption into interstitium (combine with H^+ to form NH_4^+) **NH_4^+ recycling**		Reabsorption Apical: NH_4^+ uptake through **$Na^+/K^+/2Cl^-$ cotransporter** or K^+ channels (substitutes as K^+) Basolateral: NH_4^+ exit through non-ionic diffusion		NH_4^+ enters basolaterally by non-ionic diffusion or **Na^+/K^+-ATPase** → Then secreted into lumen & excreted Lateral transport from LoH to medullary CD allows some to bypass cortical CD	If taken up by vasa recta, it's detoxified in liver which eventually depletes HCO_3^- Not ideal therefore NH_4^+ removed in thick ascending limb **60% of net acid excreted through NH_4^+**
Magnesium	25% reabsorbed Paracellular & transcellular				65% reabsorbed Stimulated by PTH, glucagon, calcitonin & ADH	5% reabsorbed	
Hormones	**ANP**: ↑ NFP & GRF, ↑ Na^+ excretion, ↑ PO_4 excretion **SNS**: Stimulation of Na^+/H^+ exchanger enhances Na^+ reabsorption via Na^+/K^+-ATPase **Ang2**: Stimulates Na^+/H^+ counter-transport, stimulates Na^+ & H_2O reabsorption **PTH**: ↓ PO_4 reabsorption & ↑ excretion by downregulating apical transporter expression *Ca^{2+} handling in PCT not subject to hormonal control			**Aldosterone**: Stimulates $Na^+/K^+/2Cl^-$ cotransporter **PTH**: Stimulates apical Ca^{2+} uptake	**Aldosterone**: Stimulates Na^+/Cl^- cotransporter **PTH**: Stimulates apical Ca^{2+} uptake	**Collecting Ducts** **ANP**: Inhibits Na^+ reabsorption in IMCD **ADH**: ↑ # open Na^+ channels in apical principal cells, stimulates insertion of UT1, ↑ H_2O reabsorption with insertion of aquaporins **Aldosterone**: Stimulates Na^+ & Cl^- reabsorption & K^+ secretion in principal cells by activation of apical Na^+ channel & basolateral Na^+/K^+-ATPase **PTH**: Stimulates apical Ca^{2+} uptake	
Aldosterone: Stimulates Na^+ reabsorption & K^+ secretion by renal tubule **RAAS** & ↑ $[K^+]$: Stimulate aldosterone secretion **ANP**: Powerful vasodilator & causes diuresis by enhancing the renal excretion of Na^+ → Lowers effective circulating volume **ADH**: ↑ H_2O reabsorption in medullary collecting ducts							

Explain the counter-current mechanisms in the kidney

- "Medullary concentrating gradient "
- physiological process which sets up a concentration gradient from cortex through to medulla
- allows formation of concentrated urine

1. Counter current mechanism → creates concentrated medullary interstitium:

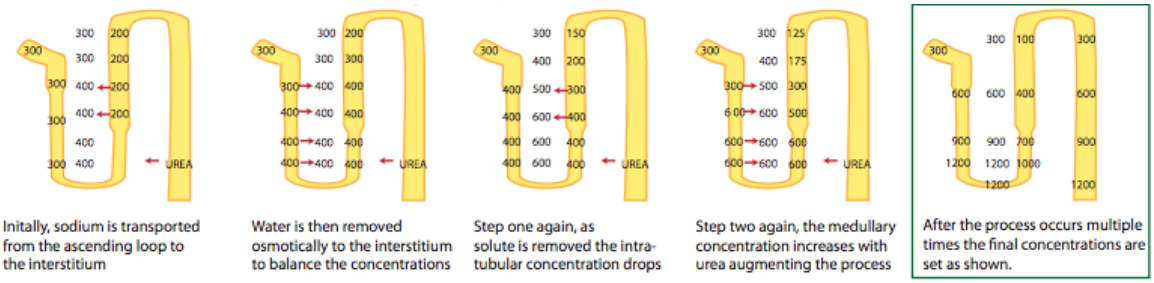
- Requires differential permeabilities in the 2 limbs to water and solutes in LoH
  - **Ascending limb**
    - Impermeable to H2O
    - Permeable to NaCl + urea
    - Thin ascending limb: **passive** NaCl reabsorption
    - Thick ascending limb: **active** NaCl reabsorption via
      1. Na/K/2Cl-symporter and Na/H antiporter on the luminal side *and*
      2. Na/K/ATPase on basolateral side of membrane → maintains Na+K gradient
  - **Descending limb:**
    - permeable to H2O
    - Impermeable to urea
    - low permeability to NaCl
- Mechanism
  - **Ascending limb NaCl reabsorption** → ↑NaCl in medullary interstitium
    - As ascending limbs impermeable to H2O → filtrate entering DCT = hypo-osmolar + renal medullar interstitium hyper-osmolar
  - **Descending limb H2O reabsorption**
    - Fluid entering descending limb = isotonic (300mOsm/kg)
    - Descending limb = permeable to H2O →H2O reabsorbed down concentration gradient
  - Process repeats + amplifies conc gradient of medullary interstitium (300→1200mOsmol/L at tip)
- final concentration = dependent on:
  - length of loop
  - capacity of the active pumps in thick ascending LoH
  - rate of flow
- Ultimately:
  - Na + Cl out of ascending loop by diffusion + active transport
  - H2O diffuse out of the descending loop

2. Counter Current Exchange system (vasa recta) → maintains intersisital osmotic gradient

- vasa recta = blood vessels supplying LoH + CD
- direction of blood flow = opposite to tubular flow
- maintain concentration gradient → counter-current exchange between descending + ascending vessels
  - Ensures blood flow doesn't wash away interstitial medullary gradient
  - Na + urea recirculate → diffusing out of ascending limb → into descending limb of vessel
  - Water bypasses; diffusing out of descending limb → into ascending limb of vessel
- Passive process; reliant on movement of water from counter current multipliers

3. Recycling of urea

- Accounts for ~650mOsm
- Urea = freely filtered at glomerulus
  - 40% filtered urea → cleared into urine
  - remaining urea contributes to high omolarity of medullary interstitium (~50%)
    - PCT: reabsorption of urea due to solvent drag
    - *Thin* LoH: urea secreted into tubular fluid via facilitated diffusion
    - *LoH, DCT, CCD* = impermeable to urea → urea reaching inner medullary CD has luminal [urea] = 650mmol/L
    - CD: urea reabsorbed by facilitated diffusion via uniporter stimulated by ADH



Describe the functions of the loop of Henle, including the physiological mechanisms involved: PAST QUESTION

- loop of henle = portion of nephrom between PCT and DCT that is responsible for creating ↑interstitial osmotic fradient in renal medulla necessary for formation of concentrated urine
  - 85% cortical nephrons
    - short LoH
    - thick ascending limb **passive** Na reabsorption
  - 15% juxtamedullary nephrons
    - long LoH extending into renal medulla
    - thick ascending limb **active** Na reabsorption via Na/K/2Cl cotransporter

Functions

- generate high medullary osmotic gradient → used by medullary CD to form concentrated urine
- reabsorb water (30% filtered in descending)
- reabsorb electrolytes (Na, K, Cl in ascending)
- secrete urea (in thin ascending)

Mechanism
- Countercurrent mechanism → see above
- Vasa recta → see above
- Concentration of urine in medullary collecting duct
  - In absence of ADH → CD relatively impermeable to water → dilute urine formed
  - In presence of ADH → aquaporin insertion into luminal surface of CD → H2O reabsorbed into medullary interstitium → concentrated urine

Explain the mechanisms involved in the regulation of renal function

Regulation of renal function

Neural + hormonal
- Neural:
  - Originate in: SY coeliac plexus
  - Major control over renal blood flow, glomerular filtration, and release of vasoactive substances (RAAS)
- Hormonal:
  - Originate in adrenal gland, pituitary gland, and heart
    - Adrenal gland:
      1. Adrenal cortex: secretes steroid hormones aldosterone + cortisol
      2. Adrenal medulla: secretes catecholamines adrenaline + noradrenaline
      3. Aldosterone is main regulator of Na and K excretion by the kidney
    - Pituitary:
      1. Secretes ADH (vasopressin)
      2. ADH is major regulator of water excretion via influence on renal vasculature + collecting duct principal cells
    - Heart
      1. ANP: contribute to signalling ↑excretion of Na+ by the kidneys
- Intrarenal chemical messengers
  - Nitric oxide

Hormones that regulate tubular reabsorption

	Production	Stimulus	Site of action	Effect
ADH	Nonapeptide from post pit	Hypovolaemia Hypotension ↑plasma tonicity ATII Stress	Cortical + medullary CD	- **↑H2O reabsorption:** bind V2 Rs on BL membrane of principal cells in CD → ↑cAMP → insert aquaporins in membrane - **↑urea reabsorption** → ↑ADH-urea transporters → ↑osmotic gradient tubular fluid vs medulla - **vasoconstriction**: V1 Rs → ↑afterload - **Form concentrated urine** - **Thirst**

ATII	Renin released from JGA	SNS stimulation
		↓intrarenal pressure
			eff > aff arterioles
			PCT
			Adrenal
			Hypothalamus
				- renin cleaves angiotensinogen → ATI → lungs (ACE) → ATII → adrenals → ↑aldosterone
				- **↓GFR**
				  ○ mesangial cell constriction → ↓glom SA → ↓Kf → ↓GFR
				  ○ afferent > efferent constriction → ↓GFR
				- **Vasoconstriction**
				  ○ **peripheral** : via AT1R, GPCR Gq: ↑MAP
				  ○ **constricts peritubular capillaries:** → ↓capillary pressure → ↓fluid reabsorption
				- **Tubular absorption**
				  ○ **Direct effect: ↑Na/H2O reabsorption** CD
				  ○ Indirect effect: ↑aldosterone
				  ○ ↑K excretion from CD
				- **central effect**
				  ○ **Stimulate ADH release**
				  ○ **Thirst**
				- **SNS stimulation**
				- **-ve feedback on renin production**

Aldosterone	Adrenal cortex (zona glomerulosa)	↑ATII ↑K ACTH	CD	- ↑Na/H2O reabsorption in DCT + CD via.. - binds MR in principal cells → upregulate + activate basolateral Na-KATPase → conc gradient for Na+ reabsorption - upregulates apical ENaC → ↑permeability to na+ → ↑reabsorption - ↑K excretion
ANP	RA	Atrial stretch (↑CVP)	Efferent + afferent arteriole CD	- dilation afferent arteriole/ constriction efferent arteriole → ↑GFR → ↑H2O, solute filtered. - Inhibit RAAS - ↓ADH - Na absorption proportional to GFR, therefore ↑reabsorption Na → glomerulotubular balance
SYNS				- ↑HR, ↑contractility, ↓venous capacitance → **↑CO, ↑VR, ↑SVR, ↑MAP** - **vasoconstriction**: constrict afferent + efferent arterioles (α1 effect) - **↑renin release (β1 effect)** → ↑RAAS → ↑salt + water reabsorption
ACTH	Post pit	Upregulated in hypovolaemia shock	-	- stimulates cortisol release → effect on catecholamines → maintains MAP - stimulates aldosterone release

Outline the endocrine functions of the kidney

Endocrine functions

1. **Hormones produced by the kidney**
   a. Calcitriol
      i. Calcitriol, or1,25 dihydroxycholecalciferol = final step in activation of vit D (vit D not synthesized in kidney but biotransformed)
      ii. Acts to ↑plasma Ca2+ → ↑ bone reabsorption, ↑tubular Ca2+ reabsorption, ↑intestinal Ca2+ absorption, ↑tubular PO4 reabsorption (antagonised by PTH)
   b. Erythropoietin
      i. Glycoprotein hormone produced in interstitial renal cells in response to arterial hypoxaemia
      ii. Stimulates maturation of erythroid precursors in bone marrow
   c. Prostaglandins
      i. Esp. PGE2 and prostacyclin
   d. Angiotensin II
2. **Enzymes released by the kidney which directly contribute to the production and release of hormones**
   a. Renin
      i. Enzyme cleaved from prorenin in granular cells of JGA
      ii. Released in response to ↓ renal perfusion
      iii. Release controlled by: afferent arteriolar baroreceptors (hypotension); macula densa (↓NaCl uptake), SY response, ATII, ANF (inhibition)
      iv. Cleaves circulating angiotensinogen to ATI (rate limiting step in production of ATII) → stimulates release of ADH + aldosterone
   b. Kallikreins
      i. Serine proteolytic enzymes in plasma and tissue
      ii. Produce kinins from kinogens
      iii. E.g. bradykinin – important circulatory effects including vasodilation and ↑ vessel permeability
3. **Hormones which have their site of action at the kidneys**
   a. ADH: ↑H2O loss in CCD via aquaporins
   b. Aldosterone: acts on distal tubule and CCD to exchange H and K from Na and H2O
   c. Calcitriol
   d. PTH" ↑Ca2+ reabsorption from distal tubule
   e. ANP: Produced by RA in response to ↑blood vol → causes ↑ secretion of Na from kidney

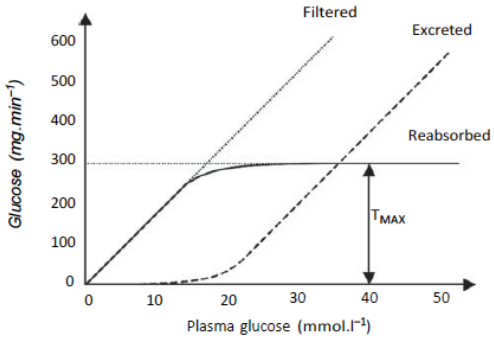
Describe the role of the kidney in the handling of glucose, nitrogenous products and drugs

Renal handling of glucose

- Normal plasma glucose 5mmol/L

Renal handling of glucose

- Glucose freely filtered at glomerulus
- Usually completely reabsorbed by PCT via:
  - Step 1: secondary active transport (SGLT-1 (proximally) or 2 (distally))
    - Na/K ATPase in BL membrane creates EC gradient for Na → Na moves down conc gradient into tubular cell → drives SGLT2 to carry Na + glucose in
  - Step 2. Facilitated diffusion
    - glucose then transferred from cell to interstitial fluid via GLUT 2 uniporter
- amount absorbed depends on amount filtered up to a transport maximum
  - Tubular reabsorption exhibits saturable kinetics
  - Tmax (max rate of tubular absorption) = 300-375mg/min
  - tubular cells exhibit heterogeneity in Tmax values
  - *Renal threshold* = plasma level of glucose at which significant amounts begin to appear in the urine
    - At normal GFR (125ml/L) threshold = plasma glucose 10-12mmol/L (2mmol/min filtered glucose load)
    - Predicted threshold = 16mmol/L
    - Actual threshold < predicted 2o "splay"
      - Heterogeneity in glucose reabsorption mechanisms between nephrons
      - Maximal enzyme activity occurs only after filtered glucose load > tmax



Glycosuria

- Carrier mechanism overloaded → filtered load > threshold → glycosuria
- Physiological consequences of glycosuria
  - Osmotic diuresis/ loss of fluid
    - High solute load prevents H2O reabsorption in LoH + distal tubules
  - Dissipate medullary interstitial gradient
    - prevent development + maintenance of medullary concentration gradient in LoH → ↓urine concentrating capacity
  - Loss of electrolytes esp. K
    - K secretion ∝ flow → ↑flow in distal tubule → ↓tubular [K+] = ↑K secretion down conc gradient in distal tubules + CD
    - Aldosterone released via RAAS in response to ↓intravascular vol → ↑Na absorption + K secretion
  - Loss of metabolic substrate
  - ↑risk UTI

Renal handling of urea

Nitrogenous products: Urea

- = the major nitrogenous waste product requiring excretion in the body
- produced in the liver as a waste product of the digestion of protein
  - Protein → broken down to constituent amino acids → separated into nitrogen moiety (ammonium) + CHO moiety
  - CHO moiety → goes on to further metabolic processing
  - Ammonium cannot be further oxidised = waste product + toxic → enters urea cycle → converts ammonium to urea + glutamine
  - high protein diet → excessive amounts of amino acids → ↑urea production + requirement for renal excretion

Renal handling of urea

- Urea is small (MW 60Da), water soluble, and freely filtered
- Highly polar and therefore does not permeate lipid bilayers → uniporters transport urea in the kidney

Transport

- 1. Freely filtered → therefore filtrate at glomerulus contains [urea] = [plasma]
- 2. Reabsorption
  - PT: H2O + solute reabsorbed in PT → luminal [urea]↑s → creates concentration gradient → urea diffuses from lumen to interstitium + peritubular capillaries via paracellular route = 50% reabsorbed
  - CD: variable fraction of water reabsorbed depending on hydration status → ↑luminal [urea]
  - Reabsorption range is constant irrespective of $[urea]_{plasma}$, i.e. there is no effective Tmax
- 3. Active secretion
  - LoH: epithelial membranes of *thin* regions of LoH express urea uniporters → urea secreted into tubule

Overall:

- urea is reabsorbed proximally and recycled between collecting ducts + LoH → resulting in net excretion of ½ filtered load
- Urea excretion can be calculated by:
  - %CO to kidneys = 25%
  - Filtration fraction: GFR / RBF

Renal drug clearance

- Renal drug clearance = urine [drug] x V / plasma [drug]

Involves 3 distinct processes:

- Glomerular filtration
  - Physiological factors:
    - Starlings forces

$$\text{Filtration pressure} \propto (P_G - P_{BC}) - (\pi_G - \pi_{BC})$$

Where P_G = Glomerular hydrostatic pressure (60mmHg)

P_{BC} = Bowman's Capsule hydrostatic pressure (18mmHg)

π_G = Glomerular oncotic pressure (32mmHg)

π_{BC} = Bowman's Capsule oncotic pressure (Negligable)

      - Filtration ↓s
        - Shock → ↓glomerular pressure
        - Obstruction → ↑bowmans capsule hydrostatic pressure
        - Hypoproteinaemia → hepatic failure, nephrotic syndrome
    - Ficks law
      - $\frac{1}{\sqrt{MW}} \times \frac{\Delta[drug].SA}{h}$
      - Filtration ↑s with ↓MW and ↑concentration gradient
      - Filtration ↓s with ↑GBM thickness (glomerulosclerosis, deposition) and loss of glomerular surface area
  - Drug factors
    - Size
    - Charge
    - Protein binding
- Active tubular secretion
  - Due to specific transporters
- Tubular reabsorption

Reabsorption of organic nutrients

- These include:
  - Glucose
  - Amino acids
  - Krebs cycle intermediates
  - Water soluble vitamins
  - Lactate, acetate, B-hydroxybutyrate
- Main site is prox tubule

Describe the principles of measurement of glomerular filtration rate and renal blood flow

Measurement of GFR

Describe the concept of renal clearance and its use to estimate flomerular filtration rate: PAST QUESTION

- GFR = amount of ultrafiltrate produced by the kidney per unit time

- GFR = 125ml/min = 180L/day
- measured indirectly by measuring renal clearance of certain substances

Clearance

- Renal clearance = vol of plasma completely cleared of a given substance by the kidneys per unit time (ml/min)
- Involves: glomerular filtration, secretion, reabsorption, and rarely tubular metabolism
- **Renal clearance = Vx[U]/[P]**
  - V = volume of urine or urine flow rate in ml/min
  - [U] = urinary concentration of substance in mg/ml
  - [P] = plasma concentration of substance in mg/ml

Estimating GFR:

- GFR = renal clearance of a substance if it is:
  - Freely filtered at glomerulus
  - Not secreted
  - Not reabsorbed
  - Not synthesized
  - Not metabolised
- The amount excreted in the urine = amount filtered
  - I.e. [plasma] x GFR = [urine] x urine vol
  - Rearrange: **GFR = urine vol x [urine] / [plasma]**

Substances used to estimate GFR

- Criteria
  - easily measured in urine + plasma
  - non-toxic
  - easily administered
- **Inulin**
  - Protein; polymer of fructose
  - MW 5800 Da→ freely filtered
  - Not reabsorbed, secreted, metabolised, or synthesized by the kidney
  - Therefore clearance of inulin = GFR
  - Requires continuous infusion for several hours to achieve steady state
- **Creatinine**
  - used to approximate GFR as is more practical
  - Released at a steady state from skeletal muscle cells (phosphocreatine)
  - Freely filtered + not reabsorbed.
  - *Small amount secreted → overestimates GFR by small amount
  - Cockcroft Gault formula used

Measurement of renal blood flow:

Measurement of renal blood flow:

- **PAH** is used
- At low concentrations: completely filtered + secreted in prox convoluted tubules
- Therefore no PAH remains in venous outflow
- The amount appearing in the urine therefore equals the amount entering the kidney
- Therefore clearance of PAH = RPF
- NB: PAH gives you renal *plasma* flow and not blood flow.
  - Renal blood flow is a function of renal plasma flow and the HCt.
  - Blood is composed of 45% blood cells and 55% plasma.

Therefore RBF = RPF/ (1-Hct)

Would it be sensible to use urea or glucose to measure GFR?

- No
- Neither urea or glucose would give accurate results
- Urea is reabsorbed in PT + variable amounts are reabsorbed in medullary collecting ducts (~50% reabsorbed) → underestimate GFR
- Glucose is freely filtered but in health is totally reabsorbed in proximal convoluted tubule → it would be impossible to measure GFR using glucose in health as value = 0

Other notes

- Although Cr clearance is a good estimator of GFR, the plasma creatinine is often used
  - Cr is not completely accurate because:
    - Some Cr is secreted by the tubules
    - [Cr]plasma at normal GFR varies between individuals
    - Cr production may not remain constant

Other notes

- RBF and Cr clearance are inversely correlated with age
- Cr clearance can be predicted using Cockroft Galt formula
  - CrClearance (ml/min) = (140 – age x wt) / (72 x serum Cr) and multiply by 85% for women
- Elderly pts have ↓Cr clearance

Describe the physiological effects and clinical assessment of renal dysfunction

Describe the changes that occur in the urine and the plasma with renal dysfunction: PAST QUESTION

Physiological effects of renal dysfunction

Renal dysfunction = abnormal function at any part of nephron → ↓GFR

- Functions of the kidney:

- Excretion of metabolic waste + drugs
- Regulation of water + electrolyte balance
- Regulation of plasma osmolality
- Regulation of acid base balance
- Regulation of BP
- Endocrine function
- Gluconeogenesis

Therefore renal dysfunction can lead to:

- **impaired excretion of waste products**
  - ↓GFR → accumulation of waste products:
    - ↑Cr: after >50% loss of nephron function; Cr freely filteres, minimally absorbed + secreted
    - ↑urea: uraemic symptoms when <5% functional nephrons; ↑plasma osmolality (NB doesn't activate ADH response as freely crosses CM)
    - accumulation of acids → raised anion gap metabolic acidosis
    - accumulation of renally excreted drugs/ metabolites (e.g. active morphine metabolites)
- **impaired regulation of water + electrolyte balance**
  - ↑K; K eliminated via secretion into CD; ↓GFR → ↓fluid delivery → ↓conc gradient across CD → ↓secretion
  - Na+: generally within normal range
- **Impaired regulation of plasma osmolality**
  - ↓filtration of glucose
- **impaired endocrine function**
  - e.g. renin, EPO, vitD2
  - ↓Ca2+ / ↑PO4 / ↑PTH / ↓vitD / ↓EPO
- **impaired acid base balance**
  - varying HCO3 and H+ excretion → ↑H+

Clinical assessment of renal dysfunction

- Classification
  - Prerenal: ie renal hypoperfusion e.g. hypovolaemia
  - Intrarenal: ie renal parenchyma
  - Postrenal: e.g. urinary tract obstruction
- **Plasma changes**
  - **↑Urea + ↑Cr:**
    - Cr: freely filtered; minimally secreted; not synthesised/reabsorbed; ↑non-linearly as renal failure progresses; often asymptomatic until GFR <10ml/min
    - Urea: can be ↑by other variables
  - **Electrolytes**
    - K: dependent on distal tubular excretion; normal maintained within normal limits until RF advanced
    - Na: typically normal – achieved in oliguric pts by ↑fractional excretion of Na + dietary restriction fo Na + H2O
    - Hypocalcaemia/ hyperphosphatamemia: ↓functioning nephrons → ↓hydroxylation of cholecalciferol to calcitriol in PCT → ↓serum Ca2+ ↓PO4 excretion
  - **Other**
    - Osmolality: ↑ as ↑serum urea: osmolality = 2xNa + urea + BSL
    - ↑PTH: ↓Ca2+ ↑PO4 → ↑PTH release by pituitary → 2o hyperparathyroidism
    - acidosis: raised anion gap metabolic acidosis 2o inability to excrete acid in tubules
    - hypoalbuminaemia: peritoneal dialysis
    - ↓EPO → anaemia
- Changes in urine
  - Volume: early inability to concentrate urine → later, inability to produce dilute urine
  - Severe renal dysfunction →
    - oliguria (<500ml/day)
    - anuria (<100ml/day)
    - risk of APO, fluid overload
  - microscopy: dysmorphic RBC, red cell casts (GN), granular casts (ATN)
  - proteinuria

Explain the renal responses to hypovolaemia

Explain the physiological processes that cause oliguria in response to hypovolaemic shock: PAST QUESTION

Definitions:

- Hypovolaemia = ↓circulating blood vol
- Hypovolaemic shock = ↓circulating blood vol + CO inadequate to maintain tissue perfusion e.g. trauma, haemorrhage, burns

Mechanism

- hypovolaemic shock → renal hypoperfusion (↓RBF) → ↓GFR → solute + water retention → restoration of intravascular volume
- oliguria = physiological compensatory mechanism to hypovolaemic shock; aim = retain H2O + Na
- achieved by number of sensors + effectors

Sensors

1. **Osmoreceptors**
   - Threshold 1-2% change
   - Specialised cells in hypothalamus which respond to ΔECF tonicity
2. **High pressure baroreceptors**
   - Carotid sinus + aortic arch
   - Monitor arterial BP + ↑SNS stimulation inr response to ↓MAP → RAAS
3. **Volume receptors**
   - Threshold 7-10%
   - Low pressure baroreceptors (stretch receptors) in walls of large veins + RA
   - ↑ADH secretion from post pit + ↑ANP
4. **Intra-renal baroreceptors**
   - ↓MAP → ↓renal afferent arteriole pressure detected → ↑renin secretion from JGA + ↑ATII + ↑aldosterone

	Production	Stimulus	Site of action	Effect
ADH	Nonapeptide from post pit	Hypovolaemia Hypotension ↑tonicity ATII Stress	Cortical + medullary CD Central	- **↑H2O reabsorption:** bind V2 Rs on BL membrane of principal cells in CD → ↑cAMP → insert aquaporins in membrane - **↑urea reabsorption** → ↑ADH-urea transporters → ↑osmotic gradient tubular fluid vs medulla - **vasoconstriction**: V1 Rs → ↑afterload - **Form concentrated urine** - **Thirst**
RAAS	Renin released from JGA	SNS stimulation ↓intrarenal pressure	ATII: eff > aff PCT Adrenal Hypothalamus Aldosterone: DCT + CD	- Renin: angiotensinogen → ATI → lungs (ACE) → ATII → adrenals → ↑aldosterone **ATII**: - **↓GFR** ○ mesangial cell constriction → ↓glom SA → ↓Kf → ↓GFR ○ afferent > efferent constriction → ↓GFR - **Vasoconstriction** ○ **peripheral** : via AT1R, GPCR Gq: ↑MAP ○ **constricts peritubular capillaries:** → ↓capillary pressure → ↓fluid reabsorption - **Tubular absorption** ○ **Direct effect: ↑Na/H2O reabsorption** CD ○ Indirect effect: ↑aldosterone ○ ↑K excretion from CD - **central effect** ○ **Stimulate ADH release** ○ **Thirst** - **SNS stimulation** - **-ve feedback on renin production** **Aldosterone**: - **↑NaCl/H2O reabsorption** in DCT + CD via.. - **upregulate + activate basolateral Na-KATPase** → via MR in principal cells → conc gradient for Na+ reabsorption - **upregulates apical ENaC** → ↑permeability to na+ → ↑reabsorption - **↑K excretion**
ANP	RA	Stretch (↑CVP)	Afferent + efferent	- dilation afferent arteriole/ constriction efferent arteriole → ↑GFR, ↑H2O, solute filtered.
SYNS		↓MAP	Heart Vessels	- ↑HR, ↑contractility, ↓venous capacitance → **↑CO, ↑VR, ↑SVR, ↑MAP** - **vasoconstriction**: constrict afferent + efferent arterioles (α1 effect) - **↑renin release (β1 effect)** → ↑RAAS → ↑salt + water reabsorption
ACTH	Post pit	hypovolaemia shock		- stimulates cortisol release → effect on catecholamines → maintains MAP - stimulates aldosterone release

Mechanism of oliguria

- Oliuria = UO <0.5mg/kg/hr or <400-500ml/day
- Overall effect: hypovolaemic shock → ↓RBF + ↓GFR + ↑Na + H2O reabsorption → oliguria
- Oliguria occurs secondary to 2 main effects:
  1. **↓RBF + ↓GFR**
     - ↓Kf by ↓filtration area by contaction of mesangial cells from SNS + ATII
     - ↓hydrostatic pressure in glom cap (PGC) by:
       - ↓RBF (autoregulated via myogenic + tubuloglomerular feedback)
       - afferent + efferent arteriolar tone
     - ↑glom cap oncotic pressure by:
       - ↓RBF and ↑filtration fraction
  2. **associated ↑Na + water reabsorption via:**
     - SNS + ATII + aldosterone
     - ↑H2O reabsorption: ADH → aquaporins via V2 receptors on basolateral membrane of principle cells CDs

NB can progress to acute renal failure

Explain the effects of anaesthesia on renal function

Outline the physiological changes that may explain why an otherwise well patient may have a reduced urinary output intraoperatively: PAST QUESTION

General

- Urinary vol + concentration are determined by GFR + reabsorption of that filtrate
- Hypothalamus acts as coordinator to regulate urinary output
- RBF

- Normal = 1250ml/min (25% CO)
- ↑blood flow required for production of large amounts renal filtrate for urinary excertion of waste products
- RBF = RPP / RVR

- GFR
  - Determined by sum of opposing hydrostatic + oncotic forces across glomerular capillary membrane
  - GFR = Kf [PGC-PB] + [πB- πGC])

Sensors – physiological response to surgery

- Osmoreceptors
  - Threshold 1-2% change
  - Specialised cells in hypothalamus which respond to ΔECF tonicity
  - Fasting state associated with surgery may ↑plasma osmolarity → activate osmoreceptors → ↑ADH
- High pressure baroreceptors
  - Carotid sinus + aortic arch
  - Monitor arterial BP + ↑SNS stimulation inr epsonse to ↓MAP
- Volume receptors
  - Threshold 7-10%
  - Low pressure baroreceptors (stretch receptors) in walls of large veins + RA
  - ↑ADH secretion from post pit + ↑ANP
- Intra-renal baroreceptors
  - ↓renal afferent arteriole pressure detected → ↑renin secretion from JGA + ↑ATII + ↑aldosterone

Effectors: factors → ↓UO intraoperatively

- surgery = stressful condition → secretion of stress hormones + ↓BP (hypovolaemia, anaesthetic agent)
- intraoperatively a ↓vol of ↑concentrated urine is produced due to:
  - ↓GFR
    - ↓Kf by ↓filtration area by contaction of mesangial cells from SNS + ATII
    - ↓hydrostatic pressure in glom cap (PGC) by:
      - ↓RBF (autoregulated via myogenic + tubuloglomerular feedback)
      - afferent + efferent arteriolar tone
    - ↑glom cap oncotic pressure by:
      - ↓RBF and ↑filtration fraction
  - ↑Na reabsorption → H2O reabsorption via:
    - SNS + ATII + aldosterone
  - ↑H2O reabsorption
    - ADH action → aquaporins via V2 receptors on basolateral membrane of principle cells CDs

Fluid and electrolytes

Describe the function, distribution and physiological importance of sodium, potassium, magnesium, calcium and phosphate ions

	Function	Distribution	Regulation	Physiological importance
Na+	1. Regulation of ECF vol: 2. Osmolality: ADH + thirst 3. RMP 4. Acid base balance (Na-H exchange pumps in kidney stimulated in acidosis)	Major extracellular cation Total body Na = 60mmol/kg ECF 140mmol/L (50%) ICF 12-20mmol/L (5%) Bone 45%	Na lost in sweat, GIT, urine *Renal handling of Na+* - Freely filtered at renal corpuscle: 180L/day x 140mmol/L = 25 000mmol/day - Undergoes tubular reabsorption (>99%) ○ Dependent on basolat membrane Na/K/ATPase pump (sets up Na gradient) ○ Final [Na+] leaving CD = dependent on ADH *Sites of reabsorption* - 65% in PCT via: ○ basolat: Na/K ATPase; apical Na/H antiporter ○ Na/glucose symporter (SGLT2) ○ Na/PO4 + Na amino acids co-transporters (luminal) ○ Na/HCO3 co-transporter (basolateral) - 25% in AscLoH via: ○ Thin AscLoH: paracellular ○ Thick AscLoH: paracellular; Na/K/2Cl symporter; Na/H antiporter - 5% reabsorbed in DCT ○ Na/Cl cotransporter ○ Na/K/ATPase pumps principle cells - 5% CD ○ Na/H pumps CT ○ ENac *Renal regulation of Na dependent on 2 factors:* **1. ΔGFR** - tubuloglomerular feedback: ↑Na/Cl delivery to macula densa - RAAS - SYNS **2. Rate of Na reabsorption** - ↑by: RAAS (aldosterone **), SYS ○ **Aldosterone** ↑s Na reabsorption by ↑ the number or activity of pumps in DCT/CT - ↓by: ANP, ↑arterial pressure via pressure natriuresis + diuresis - maintained by: glomerulotubular balance: ΔGFR → proportional Δreabsorption of Na in PCT	
K+	1. Control of intracellular vol: intracellular tonicity; Na/K/ATPase pump in CM 2. Membrane potentials: AP; RMP (determined by ratio of ICF:ECF K+ as per Nerst equation) 3. Intracellular pH regulation 4. DNA + protein synthesis 5. Enzyme function 6. Cardiac + neuromuscular activity	Major intracellular cation Total body K = 40-45mmol/kg - 90% ICF: [K] 150mmol/K - 2% ECF [K] 5mmol/L - 8% bone Normal plasma [K]: 3.5-5.3mmol/L	**1. Intake**: variable; completely absorbed upper GIT **2. Sequestration** - insulin + B2 agonist → ↑Na/K ATPase → K into cells - acidosis: K shifted extracellularly - cell lysis → K released - aldosterone → ↑K uptake into cells **3. Elimination (kidneys)** - K filtration (fixed) ○ K filtration: ECF [K] = 4mmol/L and GFR = 180L/day → 720mmol filtered/day ○ ECF [K] 5mmol/L; GFR 125ml/min → ~700mmol filtered/ day ○ Constant as GFR autoregulated via: tubuloglom feedback + myogenic mechanism - K reabsorption (fixed) ○ PT: 60-80% filtered K via paracellular diffusion via luminal K+ channels ○ AscLoH: 10-20% via passive paracellular + Na/K/Cl-symporter ○ CD: type A intercalated cells; only during ↓↓[K+] via luminal H/K ATPase - *** K secretion (variable → **regulatory step**) ○ CD: via principal cells; uptake of K via basolateral Na/K ATPase → K passively	Hyperkalaemia - less –ve RMP via Nerst → instability - weakness, paralysis, paraesthesia - ECG: tented T; prolonged PR; widened QRS; VF; asystole Hypokalaemia - more –ve RMP - K<2.5: weakness, cramps, rhabdomyolysis, myoglobinuria - Arrhythmias: premature atrial and ventricular beats, sinus brady, paroxysmal atrial /

			diffuses into tubular fluid via apical K channels **Control of K excretion** **1. [K+] perfusing kidneys** - ↑ECF [K+] → directly stimulates basolateral Na/K ATPase → ↑secretion **2. Aldosterone** - ↑[K+] → ↑aldosterone release → ↑production basolateral Na/K ATPase + production of luminal K channels → ↑K secretion + ↑permeablility to K **3. Distal tubular flow rate** - ↑flow rate (↑vol, ↑filtered Na, diuretics) → ↑K secretion - ↑reabsorption of Na into principle cells → ↑basolat Na/K ATPase activity → ↑K secretion - ↑fluid delivery e.g. diuretics → ↑flow → ↑secretion **4. Acidosis** - ↓K secretion via ↓activity of Na/K ATPase → ↓K uptake into principal cells	junctional tachy - ECG: ST depression, flat T wave, U waves
Cl-			reabsorption is dependent on Na reabsorption therefore tubular locations that reabsorb Cl and % of filtered Cl reabsorbed is similar to Na - PT: 65% - Descending thin LoH: - - Ascending LoH: 25% - DCT: 5% - CD: 5%	
Mg	1. Essential for most cellular functions 2. Cofactor in metabolism / enzymes 3. Role in muscle excitability 4. Modulate NT release 5. CVS: vasodilation, inhibit catecholamine release 6. Resp: bronchodilator 7. Biosynthesis DNA + RNA 8. Ca2+ antagonist	Major intracellular cation 99% ICF + bone Total body content 1000mmols 1% ECF (10mmols) Normal range: 0.8-1.2mmol/L	**Absorption** - daily requirement: 0.04mmol/day - dietery intake: 10-20mmol/day → 3-6mmol/d absorbed aross GIT in SI **Renal excretion** - freely filtered - Majority reabsorbed in PT - 3-5% excreted in urine control mechanisms - PTH + Vit D → ↑GI absorption - Follows Ca2+ flux in bone - Follows K flux across cells - Excreted by GFR → ↑by diuretics - Lost in diarrhoea	HypoMg - ↑risk arrhythmias HyperMg - >4mmol/L - N+V, drowsiness → neuromuscular depression + CVS - Heart block, asystole - ECG: wide QRS, CHB, systole
Ca2+	1. Neuromuscular transmission + nerve function 2. Membrane excitation 3. Pacemaker potential 4. EC coupling + muscle contraction: binds to troponinC, displacing tropomyosin, and exposing binding site for myosin on actin 5. Release of hormones and NTs 6. Enzyme activation 7. Coagulation: activate FVII, VIII, V 8. Bone structure 9. Intracellular 2nd messenger	Total Ca2+ 400mmol/kg 99% bone 1% ICF 0.3% ECF: plasma: - 40% protein bound (albumin) - 10% chelated to serum anions; - 50% free ionised Total Ca2+: 2.45-2.55mmol/L Ionized Ca2+: 1-1.5mmol/L	**Absorption** - daily intake: 1000mg → 10% absorption - GIT secretes up to 600mg/d → reabsorbed - 1. Short term = renal reabsorption via PTH + calcitriol - large amount filtered by the kidneys; 98-99% reabsorbed - PT: 60% reabsorbed under control of PTH - Remainder reabsorbed in ascLoH and DT 2. Long term = osteoclast activity via PTH, calcitriol, calcitonin **PTH** - produced in chief cells of parathyroid - pre-hormone → cleaved to prohormone → hormone (ER + golgi) - ↑synthesis/ release in response to ↓[Ca2+] - actions ○ ↑Ca2+ reabsorption DCT/CD ○ ↓PO4 reabsorption PCT ○ ↑activation of vit D to calcitriol ○ ↑bone resorption/ ↓bone formation → ↑Ca2+ release from bone	Hypercalcaemia: - <3mmol/L: asymptomatic or non specific sx - 3-3.5mmol/L: polyuria, polydipsia, dehydration, anorexia, N+V, weakness - CVS: short QT, ↓HR, HTN Hypocalcaemia - Mild to seizures, heart failure, tetany

			Calcitonin - secreted from parafollicular cells of thyroid - stimulated by ↑[Ca2+] - actions ○ inhibit osteoblast activity (↓bone reabsorption) ○ ↑Ca/PO4 excretion ○ ↓calcitriol synthesis ○ ↓jejunal absorption of dietary Ca2+ **Vit D** - cholecalciferol (vit D3) produced in skin following exposure to UV light - hydroxylated in liver → 25-hydroxycholecalciferol → hydroxylated in prox nephron to 1,25-dihydroxycholecalciferol (calcitriol) (hydroxylase activity dependent on PTH) - Actions ○ ↑Ca2+ absorption in small intestine ○ ↑bone reabsorption ○ ↑Ca^{2+} + PO4 reabsorption from PCT	
PO4	1. Oxidative phosphorylation of CHO, fat, protein metabolism 2. Structural component: nucleic acids, phospholipids, CM 3. 2nd messenger systems: cAMP, IP3 4. buffer in acid/ base	Mostly intracellular Bone 85% Normal: 0.8-1.3mmol/L	Renal excretion = major homeostatic regulator - 5-10% protein bound → 90% filterable at glomerulus - Nil secreted - Reabsorption ○ PCT: 80% reabsorbed in cotransport with Na+ ○ CD: 10% reabsorbed - 10% excreted ○ ↑loss with ↑Na loss and with 1o hyperparathyroidism Factors affecting tubular reabsorption: - PTH: ↓ - Glucagon: ↓ - Dietary phosphate: ↓ - 1,25-(OH)2D3 (calcitriol) ↑ - insulin: ↑	Hyperphosphataemia - ↑binding Ca2+ → hypocalcaemia Hypophosphataemia - muscle weakness -

NB: calcitriol = 1,25, dihydroxycholecalciferol

	Calcium gluconate	**Calcium chloride**
Chemical structure	2 glutamate ions 1 Ca^{2+} ions	$CaCl_2$
Dose	10ml of 10%	10ml of 10%
Potency	2.2mmol in 10ml	6.8mmol in 10ml
pH	6.0-8.2	5.5-7.5
Difference in adverse effects	Somewhat irritant to veins	Very irritable to veins
Administration	Can be safely given through peripheral IV cannulae	Best through CVC Can use in PIVC in resuscitation

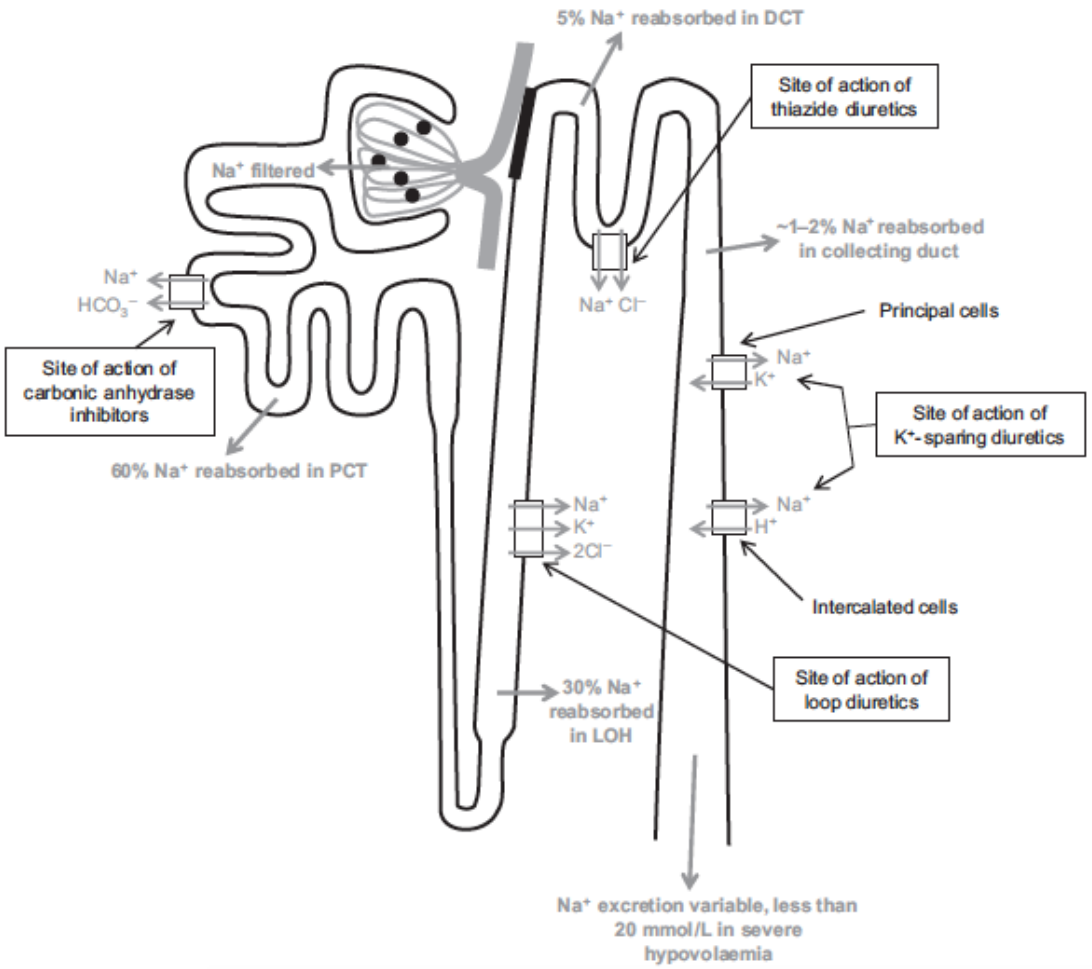


Figure 65.4 Na^+ handling by the kidney and the effect of diuretics.

Describe the mechanisms involved in the maintenance of fluid and electrolyte balance

Regulation of total body water

TBW = 60% body weight: 42L 70kg male
- ICF = 2/3 TBW (28L)
- ECF = 1/3 TBW (14L); Plasma = ¼ ECF (3L)

Role of kidneys
- Kidneys play important role in regulating: 1) volume 2) osmolality 3) distribution of body water (ICF vs. ECF)
- Control of Na^+ + water excretion serves to maintain: 1) body fluid vol 2) osmolality 3) arterial pressure
- Achieves this by:
  - Varying urine vol (500ml - 23L)
  - Varying urine osmolality (30-1400mOsmol/L)

Renal handling of body water
- RBF = 1440L/day (~20% CO)
- Glomerular filtration = 180L/day
- Reabsorption
  - PT: 60-70% H2O reabsorbed with electrolytes
  - Descending limb LoH: (10%): H2O reabsorbed via countercurrent mechanism
  - Ascending limb LoH + DCT: impermeable to water; 0% reabsorbed
  - DCT: 0% reabsorbed
  - CD: 2-14% H2O reabsorbed; variable depending on [ADH] → main location where vol + osmolality of urine regulated

3 component system

1. **Sensors**
   - **Osmoreceptors**
     - Sensed by hypothalamic osmoreceptors
     - Threshold 1-2% Δosmolality 285mOsm
     - Highly sensitive
     - ↑osmolality → ↑ADH secretion from posterior pituitary and vice versa
   - **Low pressure (volume) baroreceptors:**
     - RA + great veins
     - Detect Δintravascular vol
     - Threshold 7-10% Δblood vol
     - Potent (overrides ADH response)
     - ↓ECF vol → ↑SNS stimulation + RAAS + ANP + ADH (and vice versa)
   - **High pressure baroreceptors:**
     - aortic arch + carotid sinus
     - only sig when ΔECF vol large enough to affect MAP
     - regulate SNS stimulation
     - ↑vol → SNS stimulation (vasoconstriction) + ↑renin release
   - **Intrarenal baroreceptors:**
     - Glomerulotubular balance: ΔGFR induce proportional Δreabsorption of Na in PCT so that fraction reabsorbed remains relatively constant
     - Tubuloglomerular feedback: ↑NaCl delivery sensed by macula densa → a arteriole constriction, ↓GFR, ↓Na + H2O excretion
     - ↓vol → ↑renin → ↑ATII → ↑aldosterone
2. **Controller –** Hypothalamus
3. **Effectors**
   - *How do the kidneys regulate water handling?*
   - **1. Regulate intake**
     - ↓vol → baroreceptors → ↑renin → ↑ATII → thirst
   - **2. Regulate filtration**
     - ↑GFR → ↑salt + water excretion
     - GFR autoregulated via
       - Myogenic mechanism: ↑RPP → afferent arteriole stretch → reflex contraction → ↓RBP → ↓GFR
       - Tubuloglomerular feedback: ↑GFR → ↑filtered NaCl → sensed by macula densa → ↑aldosterone → ↓GFR
   - **3. Regulate reabsorption/ excretion**
     - ***Reabsorption of water. 2 ways:
       - **1. Pure water reabsorption:** through aquaporins in CD**;** mediated by ADH
       - **2. Osmosis** (i.e. in association with solute movement)**:** mediated by ATII, aldosterone, ANP

Determinants of above:

	Production	Stimulus	Site of action	Effect	
ADH	Nonapeptide from post pit	Hypovolaemia Hypotension ↑tonicity ATII Stress	Cortical + medullary CD Central	- - - - -	**↑H2O reabsorption:** bind V2 Rs on BL membrane of principal cells in CD → ↑cAMP → insert aquaporins in membrane **↑urea reabsorption** → ↑ADH-urea transporters → ↑osmotic gradient tubular fluid vs medulla **vasoconstriction**: V1 Rs → ↑afterload **Form concentrated urine** **Thirst**
RAAS	Renin released from JGA	SNS stimulation ↓intrarenal pressure	ATII: eff > aff PCT Adrenal Hypothalamus Aldosterone: DCT + CD	- **ATII:** - - -	Renin: angiotensinogen → ATI → lungs (ACE) → ATII → adrenals → ↑aldosterone **↓GFR** ○ mesangial cell constriction → ↓glom SA → ↓Kf → ↓GFR ○ afferent > efferent constriction → ↓GFR **Vasoconstriction** ○ **peripheral** : via AT1R, GPCR Gq: ↑MAP ○ **constricts peritubular capillaries:** → ↓capillary pressure → ↓fluid reabsorption **Tubular absorption**

				○ **Direct effect: ↑Na/H2O reabsorption** CD ○ Indirect effect: ↑aldosterone ○ ↑K excretion from CD - **central effect** ○ **Stimulate ADH release** ○ **Thirst** - **SNS stimulation** - **-ve feedback on renin production**
				Aldosterone: - **↑NaCl/H2O reabsorption** in DCT + CD via.. - **upregulate + activate basolateral Na-KATPase** → via MR in principal cells → conc gradient for Na+ reabsorption - **upregulates apical ENaC** → ↑permeability to na+ → ↑reabsorption - **↑K excretion**
ANP	RA	Stretch (↑CVP)	Afferent + efferent	- dilation afferent arteriole/ constriction efferent arteriole → ↑GFR, ↑H2O, solute filtered.
SYNS			Heart Vessels	- ↑HR, ↑contractility, ↓venous capacitance → **↑CO, ↑VR, ↑SVR, ↑MAP** - **vasoconstriction**: constrict afferent + efferent arterioles (α1 effect) - **↑renin release (β1 effect)** → ↑RAAS → ↑salt + water reabsorption

Determinants and regulation of ECF volume

ECF:
- portion of total body water outside body cells i.e intravascular, interstitial, transcellular
- ECF = 45% TBW = 19L in 70kg man → 1/3 within bone + CT → functional ECF vol 30% TBW = 13L

Determinants of ECF vol
- Principle determinant of ECF vol = total amount of osmotically active solutes in ECF
  - Osmolality = number of osmoles per *kg* of solvent = 280-295mosm/L
  - **ECF osmolality (mmol/lg H2O) = 2[Na2] + 2[K+] + [glucose] + [urea]**
- Tonicity = effective osmolality of a solution; measure of only those particles which are capable of exerting an osmotic force across the CM
  - Glucose (+ insulin) + urea freely cross CM = ineffective osmoles → do not contribute to ECF tonicity
  - **ECF tonicity (mmol/kg H2O) = 2[Na] + 2[K+]**
  - Na + Cl account for >90% ECF tonicity
  - As ΔCl are largely 2° ΔNa+ → the amount of Na^+ in ECF (+ consequent ΔH2O to maintain osmolality) = main determinant of ECF vol

Regulation of ECF vol
3 component system:
1. **Sensors**
   - **Osmoreceptors**
     - Sensed by hypothalamic osmoreceptors
     - Threshold 1-2% Δosmolality 285mOsm
     - Highly sensitive
     - ↑osmolality → ↓inhibition of post pit → ↑ADH secretion from posterior pituitary and vice versa
   - **Low pressure (volume) baroreceptors:**
     - RA + great veins
     - Detect Δintravascular vol
     - Threshold 7-10% Δblood vol
     - Potent (overrides ADH response)
     - ↓ECF vol → ↑SNS stimulation + RAAS + ANP + ADH (and vice versa)
   - **High pressure baroreceptors:**
     - aortic arch + carotid sinus
     - only sig when ΔECF vol large enough to affect MAP
     - regulate SNS stimulation
     - ↑vol → SNS stimulation (vasoconstriction) + ↑renin release
   - **Intrarenal baroreceptors:**
     - Glomerulotubular balance: ΔGFR induce ∝ Δreabsorption of Na in PCT so that fraction reabsorbed remains relatively constant
     - Tubuloglomerular feedback: ↑NaCl delivery sensed by macula densa → a arteriole constriction, ↓GFR, ↓Na + H2O excretion
     - ↓Na in ECF → ↓ECF vol → ↓stretch afferent arteriole → ↓stretch intrarenal baroreceptors → ↑renin → ↑ATII → ↑aldosterone
2. **Controller**: hypothalamus
3. **Effectors**: thirst, ADH, RAAS, ANP, intrarenal

	Producion	**Stimulus**	**Site of action**	**Effect**
ADH	Nonapeptide from post pit	Hypovolaemia Hypotension ↑tonicity ATII Stress	Cortical + medullary CD (principle cells) Central	- **↑H2O reabsorption:** bind V2 Rs on BL membrane of principal cells in CD → ↑cAMP → insert aquaporins in membrane - **↑urea reabsorption** → ↑ADH-urea transporters → ↑osmotic gradient tubular fluid vs medulla → ↑H2O reabsorption - **vasoconstriction**: V1 Rs → ↑afterload - **Form concentrated urine** - **Thirst**
RAAS	Renin released from JGA	SNS stimulation ↓intrarenal pressure ↓ECF vol	ATII: eff > aff PCT Adrenal Hypothalamus Aldosterone: DCT + CD	- Renin: angiotensinogen → ATI → lungs (ACE) → ATII → adrenals → ↑aldosterone **ATII**: - **↓GFR** ○ mesangial cell constriction → ↓glom SA → ↓Kf → ↓GFR ○ afferent > efferent constriction → ↓GFR - **Vasoconstriction** ○ **peripheral** : via AT1R, GPCR Gq: ↑MAP ○ **constricts peritubular capillaries:** → ↓capillary pressure → ↓fluid reabsorption - **Tubular absorption**

				○ **Direct effect: ↑Na/H2O reabsorption** CD ○ Indirect effect: ↑aldosterone ○ ↑K excretion from CD - **central effect** ○ **Stimulate ADH release** ○ **Thirst** - **SNS stimulation** - **-ve feedback on renin production** **Aldosterone**: - **↑NaCl/H2O reabsorption** in DCT + CD via.. - **upregulate + activate basolateral Na-KATPase** → via MR in principal cells → conc gradient for Na+ reabsorption - **upregulates apical ENaC** → ↑permeability to na+ → ↑reabsorption - **↑K excretion**
ANP	RA	Stretch (↑CVP)	Afferent + efferent	- ↑intravascular vol → ↑stretch RA → release ANP - dilation afferent arteriole/ constriction efferent arteriole → ↑GFR, ↑H2O, solute filtered.
SYNS			Heart Vessels	- ↑HR, ↑contractility, ↓venous capacitance → **↑CO, ↑VR, ↑SVR, ↑MAP** - **vasoconstriction**: constrict afferent + efferent arterioles (α1 effect) - **↑renin release (β1 effect)** → ↑RAAS → ↑salt + water reabsorption

NB: body canot control vol of ECF by moving water directly
- Na = main osmotically active solute in ECF
- Distribution of TBW between ECF + ICF is determined by [Na+] in ECF → therefore indirectly by system that controls ECF [Na+]
- Extracellular [Na+] = balance of intake, extra renal Na loss, and renal excretion

Describe how the body detects and response to a water deficit: PAST QUESTION

TBW = 60% total body weight
- ICF 55%
- ECF 45%
- Water deficit will affect both compartments
- Regulation of TBW = 3 compartment control system: sensors, central integrator, effectors
- Water deficit = ↓TBW; could be hyper, iso, or hypo-osmotic depending on underlying cause
- pure water deficit → ↑body fluid osmolality

Detecting water deficit + response
- Osmoreceptors
- Low pressure baroreceptors (volume)
- High pressure baroreceptors
- Intrarenal mechanisms

→ *Answer as above*

Outline the constituents and functions of plasma

Discuss the physiological roles of plasma proteins: PAST QUESTION

Plasma
- fluid medium of the intravascular compartment which transports substances between body tissues
- exist in equilibrium with tissue proteins as exchangeable pool

***Plasma proteins*:**
- 1o produced in liver, some production in other cells (macrophages, bone, plasma cells)
- globular molecules; total plasma protein concentration ranges 60-80g/L
- implications of starvation + ↓plasma protein concentration
- plasma proteins exist in equilibrium with tissue proteins as an exchangeable pool

Major classes of plasma proteins
- albumin: MV 70 000; 45g/L
- globulins: MW 150 000; 25g/L → subgroups α1, α2, β, y
- fibrinogen: MW 340 000; 3g/L

Physiological roles
1. **Proteolytic (complement, kinins, coagulation, fibrinolysis)**
   - Coagulation system: ATII, protein C (clot inhibition), fibrinogen (haemostasis), FII, IV, IX, X, prothrombin (α2 globulin)
   - Fibrinolytic system: protein C, protein S, plasminogen
2. **Role in acid/base**
   - 15% buffering capacity due to imidazole groups of histidine (pKa6.8)
3. **Oncotic pressure πc / capillary fluid dynamics**
   - Semi permeable memebrane: large MW = impermeable to CM
   - starlings forces: K[(Pc + πi) - (Pi+πc)]
   - plasma proteins ~25mmHg to plasma oncotic pressure
   - retains intravascular vol; prevent oedema
4. **Trasport carrier functions**
   - Bind substances (e.g. hormones, drugs) + transport
   - Renders bound ligand water soluble + prevents metabolis
5. **Enzyme systems**
6. **Immune response:**

- Complement system
- y globulins: eg IgG, IgM
- cytokines

7. **Metabolism**
   - provides amino acids to tissues for synthesis or catabolism

Detail:

- albumin: MV 70 000; 45g/L
  - main plasma protein
  - roles: oncotic pressure, acid base buffer, transport (CO_2, FFA, Br, Ca^{2+}, cortisol, thyroxine, copper), drug carrier, metabolism
- globulins: MW 150 000; 25g/L → subgroups α1, α2, β, y
  - α1-globulins: α1 antitrypsin; α1 acid glycoprotein (carrier of basic drugs)
  - α2-globulins: prothrombin → coagulation; haptoglobin → scavengers + sequesters free Hb
  - β-globulins: transferrin → iron carriage
  - y- globulins: immunoglobulins (IgG, IgM, IgA, IgE, IgD) → immune functions (humoral + cellular)
- fibrinogen: MW 340 000; 3g/L
  - coagulation
  - activation → fibrin → crosslink to form fibrin meshwork → stabilises platelet plug

Define osmotic pressure and explain the factors that determine it

osmotic pressure:

- pressure required to prevent movement of solvent molecules by osmosis across a semipermeable membrane
- i.e. measure of the osmotic tendency for water to cross the membrane
- calculated using a derivation of the ideal gas law - van't Hoff equation:
  - osmotic pressure = n x (c/M) x RT
    - where: n is no. of particles into which the substance dissociates (n = 1 for plasma proteins)
    - c = concentration in g/l
    - M = MW
    - C/M = molar concentration (mol/l)
    - R is universal gas constant = 0.082
    - T is absolute temperature (K)
  - This equation expresses relationship between solute

Describe the regulation of osmolality

Define osmolality

- Osmolality is the number of osmoles of solute per kg of solvent
- The normal osmolality of ECF (and therefore plasma) is 285-290mOsmol/kg

Osmolality vs. osmolarity

- osmolarity is the number of osmoles of solute per LITRE of solution; altered by temperature changes because of the expansion of the solution
- osmolality is the nmber of osmoles of solute per KG of solvent; independent of temperature

Measurement and regulation of osmolality

- Osmolality measured by osmometer; uses colligative properties of a fluid to calculate osmolality. This is done 2 ways:
  - Freezing point depression
  - Vapour point depression
- Osmolarity may be estimated using the formula: osmolarity = 2(na+) + BSL + urea
- Osmolar gap = difference between measured osmolality and estimated osmolarity and is usually <10
  - Gap is ↑ if there are alcohols, sugars, or contrast mediums
  - Hyperosmolar states exist where there is ↑ urea, hyperglycaemia, or hypernatraemia
- Osmolality is regulated by the body by the omol receptors in the hypothalamus which sense changes of 1-2% and ↑ or ↓ADH secretion *(See above)*
- Cellualr level: cells manage changes by ↑ the influx of solute and/or producing indogenic solutes which have minimal effect on metabolism

Write short notes on osmoreceptors: PAST QUESTION

Location

- anterior hypothalamus circumventricular organs which lie outside the BBB

Action

- respond to changes in ECF tonicity
- indirectly monitoring water balance
- linked to control sstem
- in response to ↑tonicity caused by water deficit → ↑ADH (from supraoptic and paracenicualr nuclei) + ↑thirst (trigger thirst centre in lateral hypothalamus)

Sensitivity

- respond to Δ1-2% ↑tonicity i.e. very sensitive
- low pressure baroreceptors (volume receptors) are less sensitive bt more potent than osmoreceptors
- reponse is rate dependent: rapid ↑plasma osmolality → much higher [ADH] initially than if plasma osmolality slowly risen

Outline the significance of oncotic pressure, colloid osmotic pressure and reflection coefficients

Osmosis

- Movement of solvent across a semipermeable membrane until the concentration of solution on both sides is equal

Colloid osmotic pressure

- Also called **oncotic pressure**
- The component of total osmolality that is due to **colloids** MW>30 000
- Colloids
  - large molecular weight non permeable particles
  - in plasma, proteins are major colloid present and are responsible for the majority of the oncotic pressure of plasma

- e.g. albumin, globulin, fibrinogen
- Plasma oncotic pressure = ~25-30mmHg = 0.5% total plasma osmotic pressure
  - Although low, this value is extremely important because of its role in capillary fluid dynamics (Starlings hypothesis)
  - Capillary membrane is impermeable to proteins, but permeable to most other substances present in plasma
  - Therefore plasma oncotic pressure is only force retaining water in capillaries (and therefore maininting circulating volume)
  - Albumin = major contributer to plasma oncotic pressure; 70% total value
- Oncotic pressure is measured with an oncometer: 2 chambers separated by semipermeable membrane permeable to water and solutes with MW <30 000. Pressure change in test chamber measured by sensitive pressure transducer to calculate oncotic pressure

Reflection coefficient

- Represents the capillary permeability to albumin, with 0 being freely permeable, and 1 being impermeable
- Normal: 0.6-0.9
- The more permeable = the less oncotic pressure the albumin exerts in the calculation of starling forces
- Filtration = capillary filtration coefficient (hydrostatic pressure difference) + reflection coefficient (colloid oncotic pressure difference)

Important definitions

- Molarity: number of moles of solute per kg of solvent – one mole of a substance = $6x10^{23}$ particles
- Osmosis: movement of solvent across a semipermeable membrane until concentration of solution on both sides is equal
- Osmotic pressure: pressure required to prevent movement of solvent molecules by osmosis across a semipermeable membrane
  - Osmotic activity of solute particles in an aqueous solution can be thought of as exerting an "osmotic pressure" = this is the potential to draw water into the solution
  - The osmotic pressure = a measure of the osmotic tendency for water to cross the membrane
- Oncotic pressure: (colloid osmotic pressure): component of total osmolality which is due to colloids MW>30 000
  - Albumin 75%
  - Globulin
  - Fibrinogen
- Osmol: defines the number of moles of a solute that contribute to the osmotic pressure of a solution. one osmol = $6x10^{23}$ particles regardless of the type of particle present
- Osmolality: number of osmoles of solute per kg of solvent; independent of temperature
- Osmolarity: number of osmoles of solute per litre of solvent and is dependent on temperature. Not the same as tonicity – osmolarity takes into account all of the solute concentrations, not just the ones that cant cross the semipermeable membrane

Tonicity: effective osmolality of a solution

- **Osmolality vs. tonicity**:
  - Osmolality measures the concentration of all the particles (solutes) present in the solution)
  - Tonicity is a measure of only those particles which are capable of exerting an osmotic force across the cell membrane.
    - Urea and glucose are 2 ineffective solutes: they can cross cell membranes and are ineffective at exerting an osmotic force across cell membranes
    - Na, Cl, Ca2+ do not cross cell membranes easily and are effective at exerting an osmotic force across a cell membrane
  - Tonicitiy is the effective osmolality of the solution and is that part of the total osmolality that is due to the effective osmoles.
  - Tonicitiy is what is important in determining fluid distribution across the cell membrane because it allows for those solutes which can cross the membrane

Colligative properties of a solution

- Properties of a solution that depend only on the particle concentration i.e. osmolality
- The number of particles per unit volume is important and not the type of particles
- Colligative properties are:
  - vapour pressure depression: vapour pressure is dependent on the vapour pressure of each chemical component and the mole fraction of that component in solution (Raoults law)
  - freeing point depression: freezing point ↓s in proportion to the molar concentration of the solutes
  - boiling point elevation: boiling point ↑s in proportion to the molar concentration of the solutes

Compare the advantages and disadvantages of synthetic colloids and SPPS (Stable plasma protein solution) in volume replacement: PAST QUESTION

Colloids

- solutions containing larger molecules (>30 000Da) that are dispersed throughout a solvent rather than forming a true solution
- particles arrange as groups of molcules + do not readily pass through a semi permeable memebrane
- 2 main groups:
  - synthetic: gelatins (gelofusin, haemaccel), starches (hetastarch), dextrans, hyman
  - blood product derived: SPPS, human albumin solution

	Details	**Pros**	**Cons**
Gelatins: gelofusin, haemaccel	Contain chemically modified polypeptides – bovine collagen MW 35 000 Da	Cheap Good initial plasma expanding properties	Effective plasma expansion time 2hrs Risk allergic reaction Anaphylaxis 1:13 000
Starches: HES	Amylopeptic (polymer of glucose) Hydroxylethyl groups substituted on the glucose molecules throughout the polymer More HES groups → longer starch takes to be metabolised Low MW HES: 70 000-130 000Da Medium MW: 2000 000 – 260 000Da High MW: >450 000	Good plasma expanding properties Long ½ life	Medium + high MW → ↓FVII + vWF → coagulopathies
Dextrans	Contain branched polysaccharides produced from lactic acid producing bacteria Classified according to average MW	Good plasma expanding properties Long half life	Associated with renal failure, coagulopathies, anaphylaxis – not commonly used
Human albumin	Contains 96% albumin derived from human plasma, serum, or placenta Sterilized by heat + ultrafiltration to prevent disease	Good plasma expanding properties Intravascular ½ life 24hrs	High cost Hypotension with rapid infusion due to perkallikrein – activates bradykinin

transmission	Side effects rare	Theoretical risk of disease transmission

Acid base

Definitions

- Bronsted-Lowry:
  - Acid = proton donor
  - Conjugate base = proton acceptor
  - HA + B ←→ BH+ + A-
- Acidosis: abnormal process or condition which would lead to an acidaemia if uncompensated
- Alkalosis: abnormal process or condition which would lead to an alkalaemia if uncompensated
- Acidaemia: plasma pH <7.35
- Alkalaemia: plasma pH >7.45
- Respiratory: disorder where primary disturbance is ΔPCO2
- Metabolic: disorder where primary disturbance is plasma [HCO3]
- Base excess: amount of strong acid (1 molar) required to be added to 1L of fully saturated blood at 37oC at PCO2 40mmHg to return the pH to 7.4. Normal BE = 0 +/- 2.0mmol/L
- HCO3
  - Standard HCO3: [HCO3] in fully saturated blood when pCO2 = 40mmHg at 37oC (a derived value). Normal = 24 +/- 2mmol/L
  - Plasma HCO3: actual HCO3 concentration in plasma; cannot be measured but is calculated from Henderson-Hasselbalch equation when pCO2 and pH are known.
  - NB when assessing ABGs
    - BE and standard HCO3 give the same info i.e. the non resp component to the acid base disturbance
    - The actual bicarb does not give any additional info as it has been derived from the pH and PaCO2
- Acid
  - Sources of acids
    - CO2: 12 500mmol/d;
      - principle acid product of metabolism is CO2 – equilavent to potential carbonic acid
      - Excreted by lungs and doesn't contribute to the net gain of plasma H+
    - Lactate: 1 500mmol/d
    - HSO4: 45mmol/d
    - H2PO4: 13mmol/d
    - Other acids: 12mmol/d
    - Organic acids in disease e.g. ketoacids
    - Alkalisin salts: K, lactate, acetate, citrate

Overview of acid base physiology: MAKEUP

General principles of acid base physiology

pH

- "power of hydrogen" → **measure of H+ ion activity in solution i.e. acidity**
- activity can be approximated by concentration → pH expressed as a function of [H+] ions: **$pH = -\log_{10}[H^+]$**
- normal body pH 7.35-7.45
  - acidaemia: pH <7.35
  - alkalaemia: pH >7.45
- maintenance of stable pH important for:
  - Enzyme function + body protein
  - Membrane excitability + energy production
  - State of ionisation of molecules → and therefore whether they are intra or extracellular

pKa

- **pKa = measure of the strength of an acid**
  - strong acid (and bases): completely dissociate in solution
  - weak acid (and bases): partially dissociate in solution; dissociated state (A-) and undissociated state (HA)
- Based on equation:
  - $HA \underset{k_2}{\overset{k_1}{\rightleftharpoons}} H^+ + A^-$
    - where K1 = rate constant for forward reaction
    - K2 = rate constant for backward reaction
    - When rate of forward = rate of backward → equilibrium
- equilibrium constant (Ka) $K_a = \frac{k_1}{k_2} = \frac{[H^+][A^-]}{[HA]}$
  - Ka: describes the strength of an acid by indicating how readily the acid gives up its H+
  - ↑Ka = ↑dissociation of HA → ↑[H]. Therefore ↓pKa = ↑acidity
  - ↓Ka = ↓dissociation of HA → ↓[H]. therefore ↑pKa = ↓acidity
- pKa
  - Ka transformed into pKa to produce an index → allow easy comparison of different substances
  - **$pKa = -\log_{10}Ka$**
  - pKa = pH at which the substance is 50% dissociated → the ↓pKa = ↑strength of acid
- Properties of pKa
  - Acid or base will be 50% ionised when pH of its solution = its pKa
  - **A**cids = more **i**onised **a**bove their pKa
  - **B**ases = more **i**onised **b**elow their pKa
  - An ↑pH of 1 > pKa →
    - Acid: 90% ionised
    - Base: 10% ionised

4 classes of acid base disorders:

Acid base disturbance classified by:

- pH disturbance – acidosis or alkalosis
  - normal arterial pH = 7.35-7.45 → corresponds to [H+] of 34-46nmol/L
  - Acidaemia = arterial pH <7.35
  - Alkalaemia = arterial pH >7.45
- aetiology – resp or metabolic

Resp acidosis
- ↓MV → pH <7.35 and PaCO2 > 45
- hypoventilation can be 2o to:
  ○ resp centre depression: opioids, OHS
  ○ neuromuscular disorders: GBS
  ○ chest wall disease: flail chest
  ○ airway disease: asthma, COPD
  ○ lyng parenchymal disease: ARDS
  ○ insufficient mechanical ventilation
- ↑CO2 production in MH
- insufflation of CO2 in laparoscopy
	Resp alkalosis
	- ↑RR → ↓PaCO2 + pH>7.45
	Causes
	- central: pain, anxiety, drugs
	- hypoxaemia: high altitude
	- activation of lung J receptors: PE
	- excessive mechanical ventilation

Metabolic acidosis
- ↑fixed acid → buffered by HCO3 → ↓HCO3
- [HCO3] <22 and pH <7.35
anion gap:
- Anion gap = sum of measured [cation] – sum of measured [anion]
- ([Na+] + [K+]) – ([Cl] + [HCO3])
- normal: 10-20mEq/L
- Unmeasured anions: e.g. albumin, sulphates, phosphates, plasma proteins
- ↑anion gap metabolic acidosis:
  ○ ↑Endogenous anions: lactic, fixed (AKI), ketoacids
  ○ ↑exogenous acids: salicylate, ethanol, methanol, ethylene glycol
- Normal anion gap metabolic acidosis
  ○ Hyperchloraemic acidosis
  ○ Chronic GI HCO3 loss or RTA
  ○ Hypoalbuminaemia associated with ↓anion gap
	Metabolic alkalosis
	- HCO3 >26mmol/L
	Causes:
	- ↑exogenous alkali: NaHCO3, massive transfusion
	- ↓endogenous acid: severe vomiting, NG drainage, diuretics

Systemic consequences of acid base disturbance

Molecular level:

- Ionisation of moelcules: alter ability to cross cell membranes; affect shape and function
- Enzyme function: denatured + function impaired
- RMP:
  - Permeability of neuronal membrane ion channels → affects RMP
  - Membrane depolarisation towards threshold potential → spontaneous AP more likely
  - Membrane hyperpolarisation → AP more difficult

By system:

	Acidosis/ hypercapniea	Alkalosis/ hypocapnia
CNS	- Cerebral vasodilation 2o ↑pCO2 - CBF ∝ PaCO2 between 26-80mmHg; >80mmHg arterioles max vasodilated; further ↑PaCO2 → no further ↑in CBF	
CVS	- ↓inotropy: direct myocardial depressant - ↑SNS tone - ↓responsiveness to catecholamines pH<7.2 - arrhythmia: 2o SNS tone + electrolytes - vasodilation: 2o hypercapnoea	- ↑myocardial contractility by ↑responsiveness of myocardium to circulating catecholamines - ↑myocardial O2 demand - ↓myocardial O2 delivery - vasoconstriction of coronary circulation + OHDC to left
Resp	- ↑MV: peripheral (carotid bodies ↓pH) + central (↑PaCO2) chemoRs ↑vent - R shift OHDC - ↑pCO2 → bronchodilation; ↑PSY → bronchoconstriction; bronchoconstriction > bronchodilation	- OHDC shifted to L
Electrolytes	- ↑K by 0.6mmol/L for every 0.1 unit ↓pH 2o impaired Na/K ATPase - ↑ ionised Ca2+: H+ ions compete for same binding site on albumin as Ca2+ → displace Ca2+	- Hypocalcaemia → ↑Na permeability of neuronal cell membrane → RMP more unstable
MSK	- Chronic metabolic acidosis → consumes bone PO4 to buffer H ions → OP	-
Cellular function	- Enzyme denaturation + functional impairment - Molecular ionisation: Δionisation → Δmolecules ability to cross cell membrane or affect function - RMP: Δion permeability → alter RMP	-

Describe acid-base chemistry using the HendersonHasselbach equation and strong ion difference

Siggaard-Anderson approach

- Traditional approach focused on CO2 and HCO3
- Accepts Bronsted-Lowry definitions of acids and bases

Acid base disturbance looked at using 3 factors:

1. **Henderson hasselbach equation**
   - Based on dissocation equation for carbonic acid: CO2 + H2O ←→ H+ HCO3
   - [H+] expressed as a function of the ratio between pCO2 and serum HCO3 → quantified logarithmically as Henderson-Hasselbalch equation:
   - Henderson-hasselbach equation: **pH = pKa+log10[A-]/[HA]** **or** **pH = pKa+log10[HCO3] / pCO2**
     - Based on law of mass action
       - K = K1/K2
       - In solution: an acid dissociated into H+ ion + a base (A-): $HA \underset{k^2}{\overset{k^1}{\rightleftharpoons}} H^+ + A^-$
       - Proportions of acid/ base are dependent on dissociation constants K1 (forward rxn) and K2 (backward rxn)
       - **[H+] = K[HA]/[A-]** → [H+] = K x pCO2 / [HCO3] where [H+] depends on: dissociation constant; ratio of buffers A- and H
       - logarithmic conversion applied to above → Henderson Hasselbalch equation produced.
   - In the traditional approach, physiological acid-base state is regulated by:
     - H ions which determine the pH
     - HCO3: most important buffer in the system; regulated by the kidney
     - pCO2; regulated by the resp system
   - Flaw: other important buffers exist → HCO3 and pCO2 are therefore not independent
2. **Base excess**
   - Method of measuring metabolic component
   - resets sample to normal pCO2 → titrates to pH 7.4 using molar acid → number of mmol/L = base excess
   - i.e. Measure of how acidotic or alkalotic sample is without any contribution of CO2
3. **Anion gap**
   - Measure of [unmeasured anions] (e.g. plasma proteins)
   - Based on theory of electrical neutrality → ↑anion gap = unmeasured organis acid; normal anion gap = ↓HCO3 counteracted by ↑[Cl-]
   - ↑anion gap: ketoacidosis / etoh / DM / starvation/ HONK / lactic acidosis / uraemia/ methanol/ ethylene glycol / salicylate / paraldehyde
   - normal anion gap: diarrhoea / parenteral nutrition / carbonic anhydrase inhibitors / HCl / ileostomy / pancreatic fistula

Stewart approach:

- Mathematical explanation of acid base balance
- Defined acids = ions that shift dissociation equilibrium of water to ↑[H+] + ↓[OH-]

Governed by laws:

1. **Electroneutrality:**
   - sum of +vely charged ions must = sum of –vely charged ions
2. **Law of mass action**
   - Dictates dissociation equilibria of incompletely dissociated substances.
3. **Conservation of mass:**
   - Amount of a substance remains constant unless added, removed, generated, destroyed
   - The total concentration of an incompletely dissociated substance = sum of concentrations of its dissociated + undissociated forms

General principles of Stewarts approach

Classification of variables as independent or dependent:

- 3 **independent** parameters control acidity ([H+] in arterial or venous plasma
  - **SID:**
    - Difference between the completely dissociated cations and anions in plasma
    - Law of electrical neutrality means that: [Na+] + [K+] + [H+] = [Cl-] + [lactate] + [HCO3] + [A-] + [CO_3^{2-}]
    - Often simplified to Na, K, and Cl
      - **[SID] = [Na+] + [K+] – [Cl-]** = 40-45 (cations > anions)
    - Regulated by kidneys + GIT: via differential reabsorption of Na and Cl
    - SID changed by 2 methods: changes due to ↑ or ↓H2O and ↑ or ↓strong ions
      - 1. Concentration change
        - dehydration: concentrates alkalinity → ↑SID
        - overhydration: dilutes alkaline state → ↓SID
      - 2. Strong ion changes
        - ↑SID → alkalosis: dehydration (due to ↑Na+), Cl loss
        - ↓SID → acidosis: free water excess (↓Na+), NS, severe diarrhoea (loss K and Na), ↑unmeasured anions (lactic acidosis, ketoacids)
  - **Atot (total weak acid concentration):**
    - summarises the non-volatile weak or partially dissociated electrolytes/ acids as a theoretical single –ve charge anion
    - Weak acids = mainly plasma proteins (albumin, phosphate)
    - [Atotal] = 2.43 x [total protein]
  - **PCO2**
    - Regulated by resp system
- **Dependent** variables:
  - **pH**
  - **HCO3**
  - I.e. HCO3 and H+ ions represent the effects rather than the causes of acid base derangements
- Principle: Δ[H+] or pH occur not as a result of how much [H+] is added or removed, but as a consequence of water dissociation in response to Δ[SID], pCO2, weak acid.

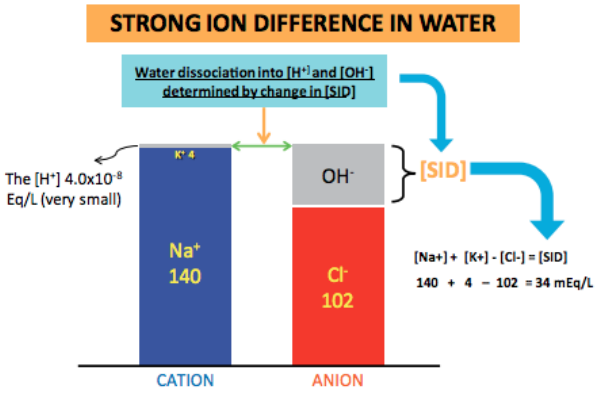
Strong ion gap

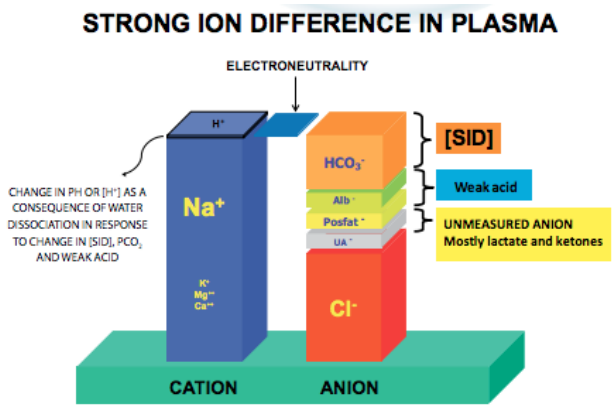
- Difference between apparent SID and effective SID → should be 0 (+ve value suggests possible organic acidosis due to endogenous acids or intake of exogenous acids)

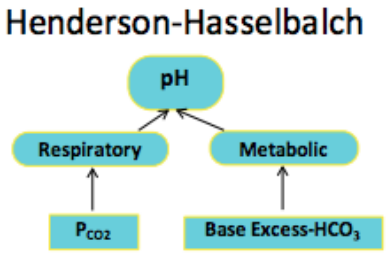
- SIG = anion gap – [A-]
- [A-] = 0.28 x (albumin) + 2.14 x (phosphate)

Causes of metabolic acidosis based on Stewart approach

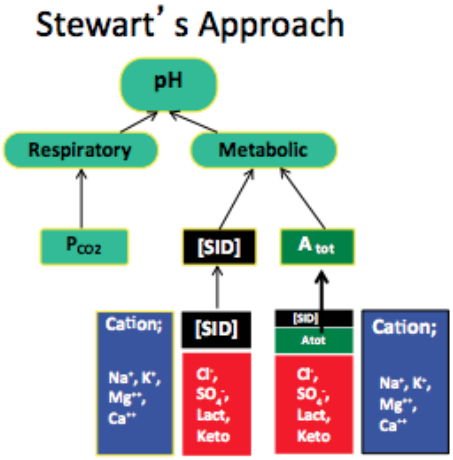
- Low SID and high SIG: ketoacidosis / alcoholic / diabetic / starvation / lactic acidosis / methanol / ethylene glycol / salycilate
- Low SID and low/ normal SIG: diarrhoea / parenteral nutrition / carbonic anhydrase inhiitors / renal tubular acidosis / ileostomy / ureterosigmoidostomy / pancreatic distula







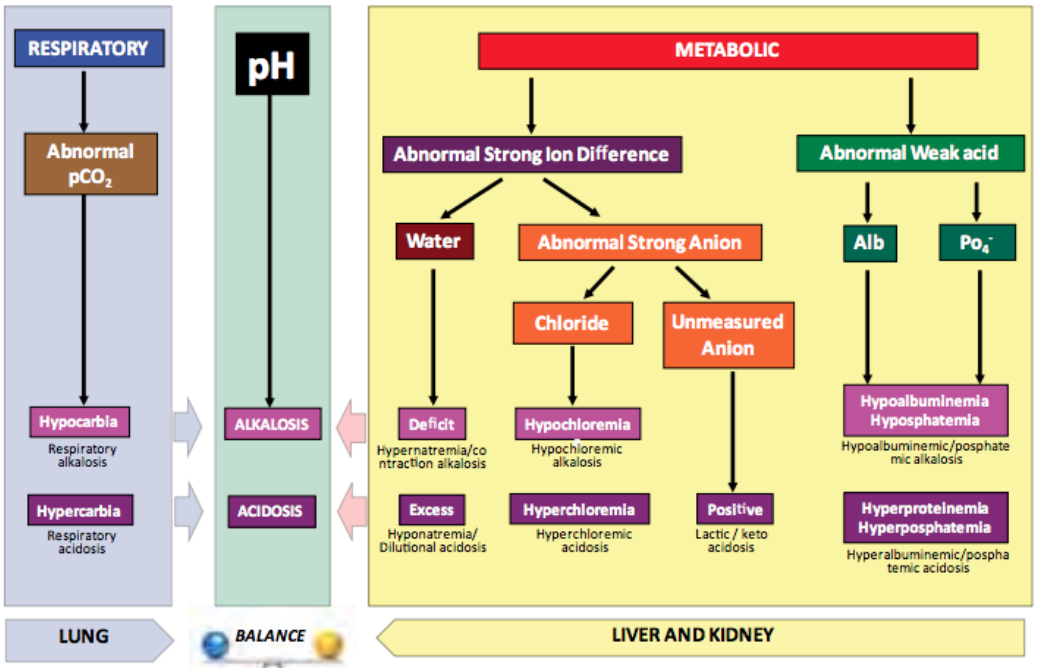
Determinants of plasma pH, as assessed by the H-H. Base excess and standard HCO3- determine the metabolic component of plasma pH



Determinants of plasma pH, at 37^{0}C, as assessed by the Strong Ion Difference [SID] model of Stewart. [SID$^+$] and [A_{tot}] determine the metabolic component of plasma pH

CLASSIFICATION OF PRIMARY ACID BASE DISTURBANCE

Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 2000 Dec;162(6):2246-51



Key equations: Stewart–Fencl–Story approach

The simplified Stewart model involves two equations:

$$BDE_{NaCl} = [Na^+] - [Cl^-] - 38 \quad (1)$$

where BDE_{NaCl} (mEq/L) is the base deficit excess for Na^+/Cl^-/free water.

$$BDE_{Alb} = 0.25 \times (42 - [albumin]) \quad (2)$$

where BDE_{Alb} (mEq/L) is the base deficit excess for albumin (in units of grams per litre).

- Can apply Henderson hasselbalch equation to bicarbonate buffer system
  - $CO2 + H2O \leftrightarrow H2CO3 \leftrightarrow H^+ + HCO3^-$
  - $pH = pKa + \log10[HCO3^-]/[H2CO3]$
  - pKa of HCO3/H2CO3 equilibrium = 6.1 and [H2CO3] can be related to solubility and PaCO2 → equation rewritten as:
    - $pH = 6.1 + \log10[HCO3^-]/0.23 \times PaCO2$
    - 0.23 = solubility factor
    - PaCO2 measured in kilopascals
    - Normal plasma pH predicted by inserting normal values for [HCO3] = 24mmol/L and PaCO2 = 5.3kPa
    - $pH = 6.1 \log 1024/0.23 \times 5.3 =$ **7.4**

Describe the regulation of acid/base balance

- Acid base balance = maintaining normal [H+] in body fluids
  - pH maintained between 7.35-7.45 = [H+] 34 - 46nmol/L
  - 3 mechanisms
    - Buffering: intracellular + extracellular
    - Respiratory regulation: excrete CO2
    - Renal regulation: reabsorb HCO3 + secrete H+ ions
- maintenance of stable pH important for:
  - Enzyme function + body protein
  - Membrane excitability + energy production
  - State of ionisation of molecules → and therefore whether they are intra or extracellula
- 2 main principles of acid base balance:
  - 1. Matching excretion of acid/base equivalents to their input, and
  - 2. Regulating the ratio of weak acids to their conjugate bases in buffer systems

Acid production divided into:

- volatile acids
  - CO2 + derivates
  - End product of cellular aerobic metabolism:
  - Generated at rate of 12 000mmol/day → removed by lungs at same rate of production = no net gain/ loss of H+
  - CO2 is not an acid, but when reacts with water it is converted to weak acid carbonic acid, H2CO3
  - $CO2 + H2O \leftrightarrow H2CO3 \leftrightarrow H^+ + HCO3-$
- fixed acids
  - phosphate, sulphate, lactate, ketones
  - from dietary intake ~100mmol/day in diets containing animal protein

- **kidney = only physiological way to excrete fixed acid**
- **The only way to excrete fixed acid = formation of new bibarbonate**
- NB the amount of acid excreted can be ↑↑↑ in disease states e.g. DKA

Regulation of acid base balance

- Buffer
  - ICF: HCO3/ CO2; Hb
  - ICF: Proteins; Phosphate
- Respiratory regulation
- Renal regulation
  - Reabsorption of HCO3
  - Excretion of fixed acids: secreted H bound to H2PO4; NH4 formation

Buffer

- Buffer = weak acids + conjugate base (or weak base + conjugate acid)
- **Buffer resists a change in pH** → by releasing or absorbing H+ in response to addition of stronger base or acid
- ECF + ICF buffering systems

Main extracellular buffering systems include:

1. **bicarbonate (HCO3 / CO2)**
   - most important in ECF due:
     - abundance of HCO3 (24mmol/L) in plasma
     - Open system: CO2 (in equilibrium with H2CO3) can be eliminated via lungs
     - Kidneys able to regulate HCO3
   - Components related by the Henderson-Hasselbalch equation:
     - pH = pKa + log10([HCO3]/0.03 xpCO2)
   - $H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$ (*catalysed by CA*)
     - CO2 + H2O expired by lungs
   - pKa 6.1 → close to baseline plasma pH 7.4
2. **Haemoglobin (Hb/H^+Hb)**
   - Hb present in large quantities within RBC (140g/L)
   - Large number (38) of histidine groups → serve as effective buffer
   - deoxyHb better buffer for acid cf oxyhb due to conformational change and pKa

Main intracellular buffer systems include:

1. **Proteins (P^-/HP)**
   - Amino acid side chains: buffer acids (via amine side chains) and alkalis (carboxyl side chains)
   - Lower conc than Hb + less histidine groups → less important buffer system
2. **Phosphate (HPO_4^{2-} / $H_2PO_4^-$)**
   - despite pKa (6.8) close to baseline plasma pH – not available in large quantities → therefore less important

Long term buffer (days to weeks)

- H+ may also be very slowly buffered by bone – via exchange for Na + Ca2+ ions

Respiratory regulation

Respiratory compensation (hours to days)

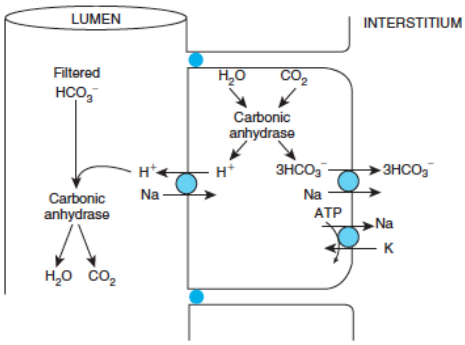
- Does not directly excrete H, but CO2 (i.e. open system) → ↑buffering capacity of HCO3 system
- Regulated by central (80%) + peripheral (20%) chemoreceptors
  - PaCO2 inversely related to minute ventilation
  - metabolic acidosis → H+ binds HCO3 → ↑PaCO2 → diffuses into CSF → intracerebral acidosis → sensed by medullary resp centre → ↑MV → ↓PaCO2 → ↑plasma pH (resp compensation)
  - Ventilation ↑by 2L/min for every 1mmHg ↑pCO2
  - pH = 6.1 + log [HCO3] / 0.03PaCO2
- maximal expected resp compensation: **PaCO2 = 1.5 x [HCO3] + 8 +/- 2**
- **Note: resp compensation is unable to produce net elimination of fixed acids as every CO2 eliminated by lungs is equivalent to removal of both H+ and HCO3**

Renal correction (days to weeks)

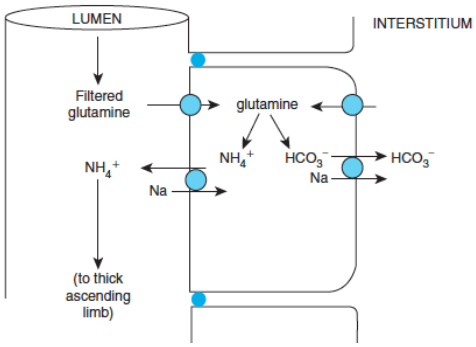
- Takes days to weeks
- Alters plasma [HCO3] to restore [HCO3]/PaCO2 ratio
- 2 mechanisms:
  - reabsorption of HCO3
  - elimination of fixed acids: secreted H buffered by phosphate; NH4 formation/ ammoniagenesis

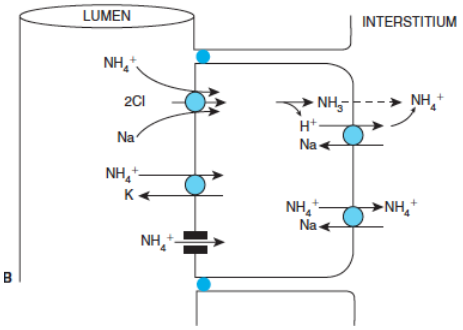
1. Reabsorption of HCO3

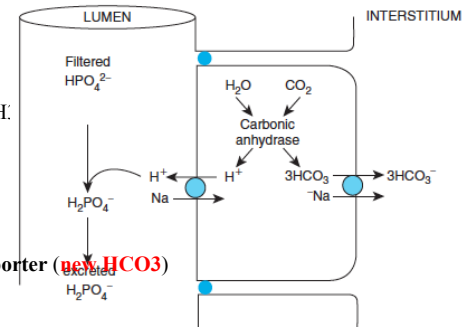
- HCO3 freely filtered; 4320mmol/day: plasma [HCO3] 24mmol/L x GFR 180L/day
- **PT**:
  - 80% reabsorbed, irrespective of plasma pH
  - **Basically**: PT: ↓pH → ↑Na/H antiporter activity → ↑H secretion → ↑reabsorption of H
  - **Mechanism**: *HCO3 cannot directly cross apical membrane of tubules*
    - **Na/H antiporter**: H into tubule / Na reabsorbed into PT → Na gradient
    - Filtered HCO3 + H+ → *CA* → H2O + CO2
    - CO2 lipid soluble → diffuses along conc gradient into cell
    - In PT cell: reverse reaction occurs: CO2 + H2O → *CA* → HCO3 + H+
    - **Na/HCO3** co-transporter: HCO3 + Na reabsorbed into blood
  - Net effect: reabsorption 1 molecule HCO3 1 molecule Na from lumen into blood
  - NB: no net elimination of H+ by this method –purpose of H+ secretion = facilitate reabs
- **DCT/ CD**
  - In α-intercalated cells: ↑**H-ATPase** → ↑H secretion → ↑reabsorption of HCO3 (control
- 4 major factors which control HCO3 reabsorption are:
  - Luminal HCO3 concentration
  - Luminal flow rate
  - Arterial pCO2
  - ATII



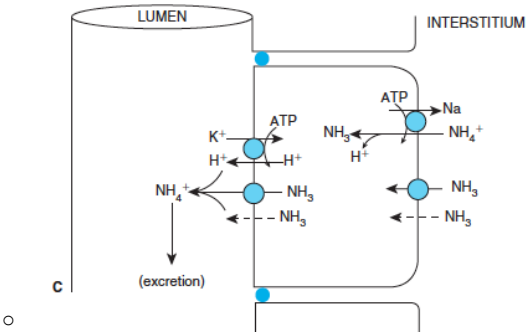
2. Elimination of fixed acids (H+ bound to titratable acid)

- **NB: kidney = only physiological way to excrete fixed acid**
- **NB: the only way to excrete fixed acid = formation of new bibarbonate**
- **Secreted H+ being buffered by phosphate**
  - After all HCO3 ions reabsorbed, secreted H bound to titratable acids (e.g. HPO_4^{2-}) esp. in DT/ CD
  - In cell: H2O + CO2 → H+ + 3HCO
    - **H/Na antiporter**: H secreted; Na reabsorbed
      - HPO42- combines with secreted H+ → H2PO4 → excreted
    - **HCO3/Na cotransporter**: HCO3 + Na reabsorbed
- **NH4 formation**
  - **Basically**: when all titratable acids are exhausted in tubules → H+ is bound to tubular NH3
  - **Mechanism**:
    - Liver: glutamine synthesised from NH4 and HCO3
    - PT:
      - glutamine converted back to NH4 and HCO3
      - **NH4 secreted** into tubule via **Na/NH4 antiporter**
      - Na + **HCO3 reabsorbed** into interstitium via **Na/HCO3 cotransporter** (**new HCO3**)
        - 

    - Thick ascLoH
      - Most NH4 involved in cycling within medullary interstitium
      - 80% tubular **NH4 reabsorbed** from lumen via **Na/K/2Cl** (passes through K site)
      - NH4 reabsorbed into interstitium **via: Na/NH4 exchanger** + NH3 diffusion
        - 



- CD
  - Secretion via parallel transport of NH3 and H ions → NH3 + H → NH4 → excreted



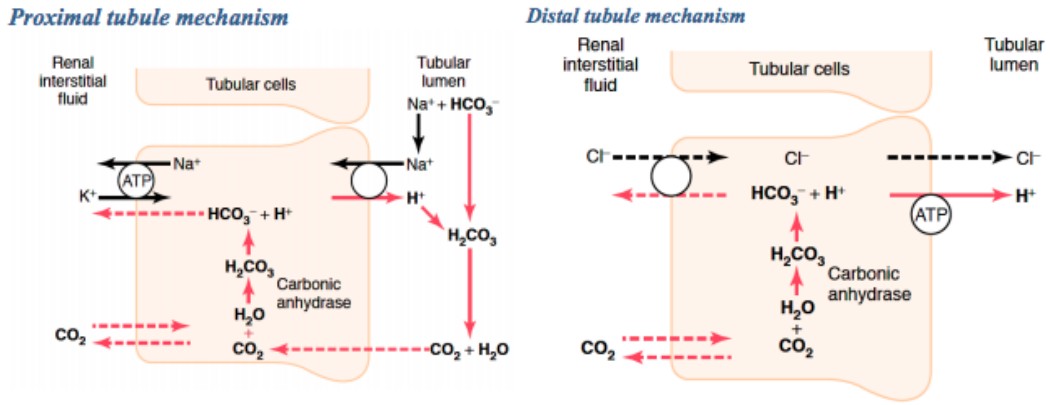
NB: the fate of secreted H+ depends on whether it combines with HCO3 or urinary buffer. Which of these 2 processes occurs is determined by:
- mass of each buffer present
- independent pKa of conjugate pairs
- luminal pH

*Role of the kidneys in **excretion** of acid: PAST QUESTION (high fail rate)*

Acid production divided into:
- volatile acids
  - CO2 + derivates
  - End product of cellular aerobic metabolism:
  - Generated at rate of 12 000mmol/day → removed by lungs at same rate of production = no net gain/ loss of H+
  - CO2 is not an acid, but when reacts with water it is converted to weak acid carbonic acid, H2CO3
  - CO2 + H2O ←→ H2CO3 ←→ H+ + HCO3-
- fixed acids
  - phosphate, sulphate, lactate, ketones
  - from dietary intake ~100mmol/day in diets containing animal protein
  - **kidney = only physiological way to excrete fixed acid**
  - **The only way to excrete fixed acid = formation of new bibarbonate**
  - NB the amount of acid excreted can be ↑↑↑ in disease states e.g. DKA

*Kidneys **excrete** fixed acids in 2 ways:*
- Secreted H+ being buffered by phosphate
- NH4 formation

1. Secreted H+ being buffered by phosphate
- very small amount of H+ filtered by kidneys each day
- plasma [H] = 40nmol/L; GFR 180L/day therefore 7.2micromol/day
- H+ actively secreted via either PT or DCT
  - After all or most filtered HCO3 is reabsorbed → secreted H combines with phosphate + other organic buffers
  - PT
    - **Na/H antiporter** (major) + **H/ATPase** (minor)
    - Almost all H secreted binds to HCO3 → reabsorption of bicarbonate → no net H excretion
    -
  - DCT
    - H actively secreted by type A intercalated cells by **H-ATPase**
    - Secreted H → reabsorption of HCO3 or buffered by phosphate or excreted as NH4
    - **Excretion as H2PO4 → generate new HCO3 → net excretion of fixed acid**



2. NH4 formation
- aa metabolism → NH4 + HCO3
- renal excretion of NH4 → net gain of new HCO4 = excretion of fixed aacid
- NH4 mainly produced within PCT from glutamine
  - Glutamine → glutamate + ammonium → α-ketoglutarate → 2HCO3
  - Stimulated by acidosis – kidney takes days to reach ↑levels of excretion
  - Daily obligatory excretion of 50-100mmol acid
  - Not a component of titratable acidity: as pKa of NH3-NH4 reaction is 9.2, it cannot be back titrated with alkali to 7.4
- Ammonium undergoes complicated cycling within kidney
  - NH4 **produced** in PCT from glutamine

- 75% NH4 **reabsorbed** in thick ascending limb LoH
- NH4 enters medullary interstitium → high concentration
- NH4 **secreted** into DCT depending on acid load

**** most important point: H+ ions lost in the urine as dihydrogen phosphate or ammonium = generation of new HCO3**

Homeostatic control of tubular aci excretion

- glomerulotubular balance
  - H+ secretion and HCO3 reabsorption varies directly with GFR
  - ↑GFR → ↑HCO3 reabsorption → prevents large changes of acid/base balance with ΔGFR
- PaCO2 and renal intracellular pH
  - Single most important determinant of renal H+ secretion = PaCO2
  - Renal tubular cells respond directly to the pCO2 of perfusing blood
  - CO2 → ↑intracellular [H+] by mass action → ↑ rate of H secretion and ↑number of luminal H pumps
  - Intracellular pH is more dependent on PaCO2 than arterial pH due to the low membrane permeability to H+ and HCO3-

******* Examiners comments:**

Note:

- reabsorption of filtered HCO3 is NOT associated with excretion of H+, rather with ***secretion*** of H+ with combines with filtered HCO3.
- The ONLY way to excrete acid is by formation of NEW bicarbonate. This can be done in 2 main ways:
  - Formation of NH4 in the PCT
  - Secreted H+ being buffered by PO4
- Excretion of free acid is minimal; even at minimum urine pH 4.4 → kidney does not excrete acid simply by secretion from intercalated cells in distal nephron. The amount of H ion containined in even the most acidic urine is tiny

Discuss how the body handles a metabolic acidosis: PAST QUESTION

Background

- metabolic acidosis = abnormal primary process or condition leading to an ↑ in fixed acids in the blood
- body responds via:
  - buffering: short + long term
  - compensation: via altered ventilation
  - correction: via renal excretion

Buffering

- body able to rapidly resist large Δplasma pH via number of ECF + ICF buffering systems

Main extracellular buffering systems include:

1. **bicarbonate (HCO3 / CO2)**
   - most important in ECF due:
     - abundance of HCO3 (24mmol/L) in plasma
     - Open system: CO2 (in equilibrium with H2CO3) can be eliminated via lungs
     - Kidneys able to regulate HCO3
   - $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$ (*catalysed by CA*)
   - pKa 6.1 → close to baseline plasma pH 7.4
2. **Haemoglobin (Hb/H^+Hb)**
   - Hb present in large quantities within RBC (140g/L)
   - Large number (38) of histidine groups → serve as effective buffer
   - deoxyHb better buffer for acid cf oxyhb due to conformational change and pKa

Main intracellular buffer systems include:

1. **Proteins (P^-/HP)**
   - Amino acid side chains: buffer acids (via amine side chains) and alkalis (carboxyl side chains)
   - Lower conc than Hb + less histidine groups → less important buffer system
2. **Phosphate (HPO_4^{2-} / $H2PO_4^-$)**
   - despite pKa (6.8) close to baseline plasma pH – not available in large quantities → therefore less important

Long term buffer (days to weeks)

- H+ may also be very slowly buffered by bone – via exchange for Na + Ca2+ ions

Respiratory compensation (hours to days)

- Does not directly excrete H, but CO2 (i.e. open system) → ↑buffering capacity of HCO3 system
- Regulated by central (80%) + peripheral (20%) chemoreceptors
  - metabolic acidosis → H+ binds HCO3 → ↑PaCO2 → diffuses into CSF → intracerebral acidosis → sensed by medullary resp centre → ↑MV → ↓PaCO2 → ↑plasma pH (resp compensation)
  - Ventilation ↑by 2L/min for every 1mmHg ↑pCO2
  - pH = 6.1 + log [HCO3] / 0.03PaCO2
- maximal expected resp compensation: **PaCO2 = 1.5 x [HCO3] + 8 +/- 2**
- **Note: resp compensation is unable to produce net elimination of fixed acids as every CO2 eliminated by lungs is equivalent to removal of both H+ and HCO3**

Renal correction (days to weeks)

- Alters plasma [HCO3] to restore [HCO3]/PaCO2 ratio
- Kidneys able to definitively correct metabolic acidosis by:
  1. **Reabsorption of HCO3**
     - PT: ↓pH → ↑Na/H antiporter activity → ↑H secretion → ↑reabsorption of HCO3
     - In α-intercalated cells of DT/ CD: ↑H-ATPase → ↑H secretion → ↑reabsorption of HCO3 (controlled by aldosterone)
  2. **Elimination of fixed acids (H+ bound to titratable acid)**
     - **NB: kidney = only physiological way to excrete fixed acid**
     - **NB: the only way to excrete fixed acid = formation of new bibarbonate**
     - i. **Secreted H+ being buffered by phosphate**
       - After all HCO3 ions reabsorbed, secreted H bound to titratable acids (e.g. HPO_4^{2-}) esp. in DT/ CD → excreted
     - ii. **NH4 formation**
       - When all titratable acids are exhausted in tubules → H+ is bound to tubular NH3 → excreted as NH4+

- NH4+ synthesised from glutamine deamination → also generating HCO3 which is absorbed

Discuss the role of haemoglobin as a buffer: PAST QUESTION

Hb = iron containing metalloprotein abundant in RBC + responsible for O2 transport

Buffer

- Buffer = a substance which resists a change in pH by absorbing or releasing H+ ions
- normally consists of a weak acid and its conjugate base, resisting pH change when a stronger acid or base is added
- buffer binds H+ ions reversibly to minimise the ΔpH
- generally: B + H+ ←→ HB+ (H buffer)

Factors required for effective buffering:

- effectiveness of buffer dependent on:
  - amount of buffer present
  - pH of carrier solution
  - pKa of buffer (pH at which 50% of the acid is dissociated)
  - whether it follows an "open" (physiological) or "closed" (chemical) system
- Major buffer systems in the body:
  - ECF: carbonic acid / HCO3 and Hb
  - ICF: protein + phosphate

Hb as a buffer

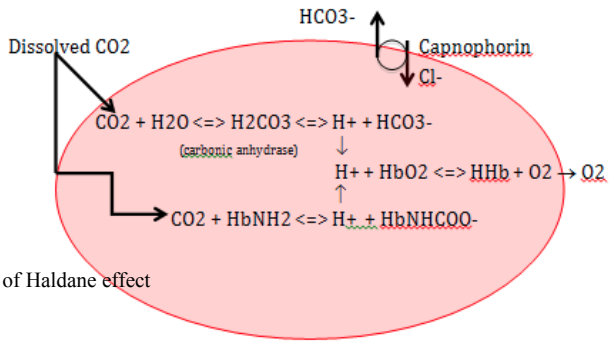
- Hb present in large quantities within RBC (~150g/L = 2x [plasma protein])
- Major role in buffering acid in ECF (1° non-HCO3 buffer of blood)
- 6x more effective as buffer than plasma proteins because:
  - [Hb] twice as much
  - each Hb molecule contains 3x more histidine residues than plasma proteins

Clinical importance

- Buffers H and CO2 formed from cellular metabolism
- Buffers H load from fixed acids ingestion, prior to renal excretion
- Assists CO2 carriage, esp. in venous blood (limits pH drop for venous blood)

Structure of Hb and relationship to function as buffer

1. **Structure of Hb**
   - Contains histidine residues (38) with imidazole side chain on 4 globin chains
     - Imidazole has pKa 6.8 → effective buffer at ICF physiological pH 6.8-7.1
   - Amino acid groups
     - CO2 and H2CO3 bind with amino acid groups → carbamino compounds (accounts for 15% CO2 transport)
     - Hb = effective buffer for CO2 due to: solubility of CO2; presence of carbonic anhydrase; capacity of Hb
2. **Hb = weak acid**
   - Hb buffers H+ and forms HCO3 within RBC
   - ↑Intracellular HCO3 → diffusion down conc gradient out of cell
   - presence of acid in ECF → maintenance of conc gradient + conti
3. **DeoxyHb**
   - Deoxy Hb = more effective buffer than oxyhb (Haldane effect)
   - deoxyHb (pKa 8.2) dissociates > oxyhb (pKa 6.6)



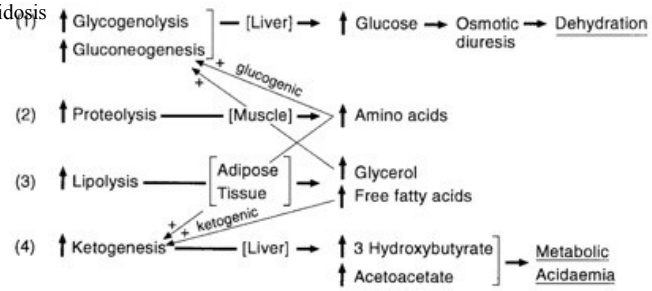
Reactions within RBC

- cellular metabolism producs CO2 → CO2 taken up by RBC → carried by H groups
- H2O + CO2 → *carbonic anhydrase* → H2CO3 ←→ H+ + HCO3
- Hb acts as a buffer for H+ (deoxy Hb bettern than oxyhb) → accounts for 30% of Haldane effect
- HCO3 in RBC exchanged for Cl via antiporter → Hamburger effect

Outline the physiological consequences of diabetic ketoacidosis: PAST QUESTION

Definitions

- DKA occurs mainly in insulin dependent diabetics with relative or absolute insulin deficiency
- Results in fluid + electrolyte abnormalities + raised anion gap metabolic acidosis
- Principle underlying cause = loss of insulin → inability of cells to transport + utilise glucose within cells → catabolic state
- Metabolic mechanisms activated:
  - Gluconeogenesis: FA + lactic acid metabolism →↑BSL
  - Glycogenolysis → ↑BSL
  - Hepatic ketone production (ketogenesis – incomplete FA metabolism)
  - Proteolysis → ↑aa
  - Lipolysis → ↑glycerol + ↑FFA



Effect of hyperglycaemia

- ↑BSL overwhelms renal tubular cell threshold for resorption of glucose → hyperosmolar urine + osmotic diuresis
- initial polyuria, polydipsia → intravascular vol depletion →
  - ↓vol, ↑osmolarity (~2%) → ↑ADH → thirst + oliguria
  - ↓vol (~10%) → ↓BP → RAAS → ↓UO
  - pseudo ↓Na (lipemic serum → spurious hyponatraemia)
  - late stage: hypovolaemic shock → lactic acidosis

effect of ↑ketoacids/ metabolic acidosis

- ketoacids (acetoacetate, β-hydroxybutyrate, acetone) → ↓pH
- Buffers: HCO3, Hb, proteins, phosphate + resp compensation (↑RR → kausmals respirations)
- CNS:
  - impaired consciousness
- Respiratory
  - Chemoreceptors (carotid body, medulla) detect ↓ECF pH → activate medullary resp centre to ↑MV → hypocarbia
  - R shift OHDC → ↑O2 delivery to tissues
- CVS
  - ↓pH = -ve inotrope (↓contractility)
  - depressed myocardial function + ↑arrhythmogenicity through ↑K+
  - Acidosis → direct ↓SVR (metabolic autoregulation), ↑PVR
  - SNS activation (baroreceptor effect): ↑HR, ↑PVR, ↓GFR (NB: impaired SNS response as ↓response to catecholamines when pH <7.2)
- Electrolyte
  - ↓HCO3
  - ECF ↑K due to H/K exchange (↓total body K due to hyperosmolar diuresis)
  - ↑Ca2+ due to H/Ca2+ exchange within bone
- If allowed to continue → coma + circulatory collapse

Explain how a metabolic acidosis develops in hypovolaemic shock: PAST QUESTION

Definitions

- metabolic acidosis = process which results in ↓pH through depletion of HCO3
- hypovolaemia shock occurs when there is ↓intra +/- extravascular volume → inadequate tissue perfusion to meet metabolic demand re provision of substrates + removal of waste

Formation of metabolic acidosis in hypovolaemic shock

- ↑metabolic acid production (type A lactic acidosis)
  - insufficient O delivered to tissues
  - ↑anaerobic metabolism through glycolysis → formation of lactic acid from pyruvate
    - energy inefficient process: 2ATP for each mol of glucose → formation large amounts lactic acid
    - hepatic hypoperfusion → lactic acid unable to enter Cori cycle to convert back to glucose

Effect on body

- Buffers: HCO3, Hb, proteins, phosphate + resp compensation
- CNS:
  - impaired consciousness
- Respiratory
  - Chemoreceptors (carotid body, medulla) detect ↓ECF pH → activate medullary resp centre to ↑MV → hypocarbia
  - R shift OHDC → ↑O2 delivery to tissues
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- Electrolyte
  - ↓HCO3
  - ECF ↑K due to H/K exchange (↓total body K due to hyperosmolar diuresis)
  - ↑Ca2+ due to H/Ca2+ exchange within bone

Describe the effects of intravenously administered sodium bicarbonate (8.4%) 100ml used in asystolic cardiac arrest in 70kg man: PAST QUESTION

NaHCO3 = hypertonic solution (2000mOsm/L); alkalinising effect on blood pH due to HCO3 load

- Effects via:
  - Hypertonicity: 200mOsm/kg osmotic load
  - High Na content
  - Alkaline: 100mmol HCO3 load
- Hypertonicity
  - High osmolar load → acutely precipitate osmotic diuresis by kidneys
  - Bicarb bolus → ↑1.4% in plasma osmolality → >1% change → stimulates central osmoreceptors → ADH release → fluid retention by kidneys
  - Water drawn out of cells → ↓cell size
  - Intravascular space expanded
- Alkaline load
  - Resp:
    - HCO3 will neutralise H+ → CO2 + H2O
    - CO2 may diffuse across cell membranes → H2CO3 → dissociate again → H + CO2
    - Process worsens intracellular acidosis
    - ↑CO2 diffusion → CSF acidosis → ↑Resp drive → ↑RR
    - HCO3 → ↑pH → L shift OHDC
  - CVS
    - Neutralisation of acidaemia → may ↑cardiac contractility
  - Renal
    - HCO3 neutralises H → inhibits H/K exchanger → ↑K influx → ↓extracellular [K]
    - May overshoot metabolic alkalosis

Limitations due to asystolic cardiac arrest

- absence of CO or chest compressions → alkalising effect limited to region of infusion
- without restoration of CO, renal effects negated by inadequate blood flow
- pH ↓ due to ongoing ischaemia → lactic acidosis

- can worsen acidosis if inadequate ventilation and elimination
- now discouraged

How does a fall in temperature influence blood gas solubility and acid-base value: PAST QUESTION

pH and temperature

- pH of blood is temperature dependent
- ↓temp → ↑pH
- for every ↓1oC → ↑0.015pH due to ↓ionic dissociation of water

Blood gas solubility

- as blood cools → CO2 ↑solubility → ↓pCO2 (as total CO2 remains unchanged)
- ionic dissociation of H2O ↓ → formation of ↓H+ and therefore contributing to ↑pH
- Henry's law: concentration of gas ∝ to partial pressure via solibilty coefficient at given temp i.e. concentration (gas) = partial pressure x solubility

Acid base values

- ABG analysers operate at 37°C
- pH and PaCO2 can be mathematically corrected to determine their actual values at patient temp
- alpha stat hypothesis
  - refers to degree of ionisation of imidazole groups remaining constant despite Δtemp whilst keeping CO2 stores constant (i.e. pH Δwith temp)
  - ↓temp → ↓pKa imidazole moieties on proteins
  - no change in overall CO2 stores
- pH stat hypothesis
  - refers to the theory that pH should remain constant despite changes in temperature
  - to overcome ↑solubility of CO2 → CO2 added to system to maintain constant pCO2 (40mmHg). There is overall ↑Co2 stores

Blood gas values

- alpha stat:
  - blood sample heated to 37 degrees can be interpreted aginast values for 37o regardless of what temp patient is
  - permits alkaline drift that normally occurs with hypothermia
  - targets normal pH and PaCO2 at 37oC and accepting that patients actual blood pH will be >7.45
- pH stat:
  - blood sample measured against normalised values at 37 degrees regardless of what temp the blood is.
  - No change in pH with temp change

Effect of bicarbonate administration: MAKEUP

- Only of benefit when:
  - CPR >10mins
  - When ↑min vent possible i.e. ventilated
  - AGAs → pH <7.0
  - VF associated with TCA or hyperkalaemia
- Potential problems associated with administration include:
  - Produces a paradoxical ICF acidosis
  - May produce an ECF alkalosis
    - Shifts the HbO2 curve to the left → ↓O2 availabilty at a cellular level
    - Shifts K into cells and may result in:
      - Hypokalaemic cardiotoxicity in K depleted patients
      - Tetany in renal failure or Ca2+ depletion
  - The solution is hyperosmolar → excessive Na+ load
  - CSF equilibrates slowly with [HCO3] – ventilation may be maintained despite ↑[HCO3], therefore vent may be maintained despite ↑[HCO3] resulting in resp alkalosis
  - When acidaemia due to organic acids, subsequent metabolism of such acids and regeneration of HCO3 will produce metabolic alkalosis

NB re acid base:

1. Balance principle

- Multiple routes for entry of acids or bases:
  - Processing of ingested food
  - Secretions of GIT
  - De novo generation of acids and bases from metabolism of stored fat and glycogen
- Kidneys = overall maintenance of H+ ion balance

2. Body fluids are buffered

- Often lag between input + output → allowing transient accumulation of acid or base
- Buffer system = 3 substances that have defined relations to each other according to the equilibrium constant: a weak acid, its conjugate base, and free protons

3. Input and output of acids alter HCO3 but not the PaCO2

- in CO2-HCO3 buffer system, the concentration of the weak acid (CO2) is essentially constant → because PaCO2 is regulated by resp system

4. Excretion of CO2 and HCO3 are independent of each other

Renal – other

Renal replacement therapy – Dialysis: MAKEUP

Dialysis = the separation of particles in a liquid based on their ability to pass through a membrane

Indications

- Failure of normal renal functions: i.e.
  - Acid

- Electrolyte derangement: particularly hyperkalaemia
- Intoxications
- Overload
- Uraemia

Physical mechanisms

- fluid + electrolytes can be removed by 4(??) different mechanisms
- Diffusion:
  - spontaneous movement of substances from a higher concentration to a lower concentration, where rate of movement is proportional to the concentration gradient as per Fick's Law
- Ultrafiltration:
  - Movement of water, as determined by Starlings Forces
  - When a solvent passes through a membrane, the process is called osmosis
  - The frictional forces between solutes and water molecules will pull dissolved substances along, a process known as bulk flow or solvent drag

Implementation

- haemodialysis:
  - Uses diffusion
  - Blood is pumped through an extracorporeal circuit that contains a dialyser
  - Dialysate flow is countercurrent, with maximizes the gradient for diffusion
  - Solutes move across a membrane between blood and dialysate as per Fick's Law
    - Concentration gradient between blood and dialysate: flow rate of blood and dialysate
    - Solubility of the solute: mass, charge, protein binding
    - Dialysis membrane permeability: thickness, porosity, surface area
- Haemofiltration
  - Uses ultrafiltration
  - Positive hydrostatic pressure in blood and a negative hydrostatic pressure in dialysate is generated → causing ultrafiltration and removal of solutes via solvent drag
  - Elimination via bulk flow is independent of solute concentration gradients across the membrane
  - Transport is dependent on starling forces
    - The transmembrane pressure generated: blood flow to the membrane; onxotic pressure gradient
    - Porosity of the membrane
  - Additionally, a high filtration fraction will cause excessive haemoconcentration, and clotting of the filter
  - The filtered fluid (ultrafiltrate) is discarded, and replaced with another fluid depending on the desired fluid balance

Differences

- RRT can be via:
  - Peritoneal dialysis
  - Intermittent haemodialysis
  - Continuous renal replacement therapy (CRRT)
    - CVVH
    - CVVHD
- IHD causes greater cardiovascular instability compared to CRRT as the fluid and electr
- Small molecules <500Da and electrolytes can be removed by filtration or dialysis
- Medium sized molecules 500-5000Da are best removed by filtration
- Proteins 5000-50 000Da are removed by filtration: this includes removal of inflammato
- Water is best removed by filtration

Drugs Removed on RRT	Drugs not removed on RRT
Barbiturates	Digoxin
Lithium	TCAs
Aspirin	Phenytoin
Sotalol/Atenolol	Other beta-blockers
Theophylline	Gliclazide
Ethylene Glycol	Benzodiazepines
Methanol	Warfarin
Aminoglycosides, metronidazole, carbapenems, cephalosporins, penicillins	Macrolides, quinolones

Pharmacokinetics of RRT

Affected by:

- Free drug in plasma: drugs with a small proportion of free drug in plasma are poorly rer
  - Highly protein bound substances
  - Drugs with VD >1L/kg
- Size: small molecules (<500Da) are more easily cleared by diffusive methods of RTT
- Dose/ flow rates: ↓flow rates will ↓clearance
- Membrane permeability
- Residual renal function
- Timing

Explain the physiological principles underlying the use of peritoneal dialysis in a patient with chronic renal failure with this dialysate solution: PAST QUESTION

- peritoneal dialysis occurs across a membrane (peritoneum) by exchange between dialysate and patients blood
- aim: achieve balance of - fluid, electorlytes, acid-base, excretion of toxins/ waste
- solvent = H2O (medium for solute transfer)
- solutes: Na/ K / Mg2+/ lactate / Cl / glucose / Ca2+

**** GLUCOSE: mmol/L x 18 = mg/dl → 2.5g per 100g H_2O = 25g / L = 2500mg /L ****

Dialysate	Plasma
Na^+ 132 mEq/L	Na^+ 145 mEq/L
Mg^+ 0.5 mEq/L	Mg^+ 1 mEq/L
K^+ 0 mEq/L	K^+ 4.5 mEq/L
Lactate 40 mEq/L	HCO_3^- 26 mEq/L
Cl^- 96 mEq/L	Cl^- 110 mEq/L
Glucose 2.5 g%	Glucose 0.1 g%
Ca^{2+} 3.5 mEq/L	Ca^{2+} 3.5 mEq/L

Principles

- **Factors governing solute movement:**
  - **Diffusion**
    - Movement of solutes from area of high to low concentration
    - Rate of diffusion = based on Fick's law:
      - Fick's law: rate of diffusion is proportional to: surface area x concentration gradient x membrane permeability / membrane thickness
      - Modified Fick's law: the rate of diffusion of a substance across a unit area of membrane is directly proportional to the tension gradient or the partial pressure gradient
    - Gibbs-Donnan effect
      - if a semi permeable membrane separates 2 solutions + at least 1 of those solutions contains a non-diffusible ion → the distribution of other ions across the membrane will be altered
      - The distribution of permeable charged ions will be influenced by both their valence + distribution of uncharged ions
  - **Solvent drag/ convection**

- Movement of solutes <5000Da acorss membrane that occurs with flow of solvent due to ultrafiltration

- **Factors governing solvent movement**
  - **Ultrafiltration**
    - Movement of water across a membrane based on Starlings forces where:
      - Net filtration pressure = Kf [(hydrostatic pressure in blood – hydrostatic pressure in dialysate) – (oncotic pressure in blood – oncotic pressure in dialysate)]
    - Glucose provides dialysate oncotic pressure
  - **Osmosis**
    - Movement of water (solvent) from area of high to low [water]
    - Determined by osmolarity of solution – estimated by: 2x[Na] + 0.55 [glucose] + 0.36 [BUN]
    - Governed by van't Hoff equation
      - Osmotic pressure = nRT
      - Osmotic pressure = osmolality x ideal gas constant x temperature
- **Buffer for acidosis**
  - Lactate → metabolised in liver, consuming H+ → effectively produces HCO3

Explain the principles of haemodialysis: PAST QUESTION

Princples involved in haemodialysis

- **Factors governing solute movement:**
  - **Diffusion**
    - Movement of solutes from area of high to low concentration
    - Rate of diffusion = governed by Fick's law:
      - $$D = \frac{sol}{\sqrt{MW}} \times \frac{surf\ area}{thickness} \times \Delta conc$$
      - Fick's law: rate of diffusion is proportional to: surface area x concentration gradient x membrane permeability / membrane thickness
      - Modified Fick's law: the rate of diffusion of a substance across a unit area of membrane is directly proportional to the tension gradient or the partial pressure gradient
    - Gibbs-Donnan effect
      - if a semi permeable membrane separates 2 solutions + at least 1 of those solutions contains a non-diffusible ion → the distribution of other ions across the membrane will be altered
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- **Factors governing solvent movement**
  - **Ultrafiltration**
    - occurs when hydrostatic pressure forces a liquid against a semipermeable membrane → suspended solids+ high MW molecules are retained (e.g. proteins, RBC), while H2O and low MW solutes pass through membrane
    - rate of filtration determined by sum of opposing hydrostatic + oncotic pressures (Starlings equation)
      - NFP = Kf [(**PB** – **PD**) – σ(**πB** – **πD**)
      - K = filtration coefficient; measure of how permeable membrane is to solute
      - σ = reflection coefficient; measure of how resdily the membrane maintains [protein]
  - **Osmosis**
    - Movement of water (solvent) from area of high to low [water]
    - Determined by osmolarity of solution – estimated by: 2x[Na] + 0.55 [glucose] + 0.36 [BUN]
    - Dialysate solution is hyperosmolar relative to blood → H2O drawn out of blood into dialysate solution
- **Counter current flow**
  - Maximises diffusive clearance of solutes by maintaining concentration gradient along length of membrane

List the hormones that regulate renal tubular reabsorption and describe their action + site of action: PAST QUESTION

Hormones with direct effect:

	Role	Synthesis	MoA

ATII	Preserves blood vol + pressure		- **↓GFR**
			  ○ mesangial cell constriction → ↓glom SA → ↓Kf → ↓GFR
			  ○ afferent > efferent constriction → ↓GFR
			- **Vasoconstriction**
			  ○ **peripheral** : via AT1R, GPCR Gq: ↑MAP
			  ○ **constricts peritubular capillaries:** → ↓capillary pressure → ↓fluid reabsorption
			- **Tubular absorption**
			  ○ **Direct effect: ↑Na/H2O reabsorption** CD
			  ○ Indirect effect: ↑aldosterone
			  ○ ↑K excretion from CD
			- **central effect**
			  ○ **Stimulate ADH release**
			  ○ **Thirst**
			- **SNS stimulation**
			- **-ve feedback on renin production**

Aldosterone	Preserves blood vol (Na+ reabsorption)
	Controls K and H secretion
		Steroid hormone
		Zona glomerulosa of adrenal cortex
		Release stimulated by ATII, ↑[K], ACTH
			- acts on CCD to ↑Na+ reabsorption + ↑K secretion by principal cells via:
			  ○ ↑Na^+ luminal channels
			  ○ ↑action of Na/K ATPase pumps on basolateral membrane
			- ↑H secretion via Type A intercalated cells in CD → ↑HCO3 reabsorption

ADH	Preserves blood vol	Synthesised in hypothalamus Released by post pit	- insertion of aquaporins via V2 Rs in medullary and cortical CDs → ↑H2O reabsorption - ↑Na reabsorption in CCD - ↑urea reabsorption in medullary CDs

ANP	↓blood vol	Released by atrial stretch (baro) Rs in response to ↑blood vol	- Dilates mesangial cells + afferent arterioles to ↑GFR and inhibits Na reabsorption in PT + CDs
PTH	Maintains Ca2+ + PO4 homeostasis	Parathyroid	- ↑Ca2+ luminal channels + ↑basolateral Ca2+/ATPase and Na/Ca2+ antiporter activity, ↑Ca2+ reabsorption in DCT - ↓PO4 reabsorption

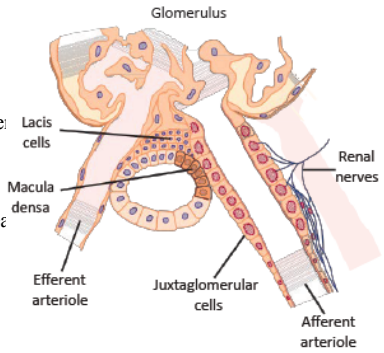
Hormones with indirect effects on reabsorption

- adenosine, histamine, NAd, thromboxane A2, leukotrienes, endothelin → constrict mesangial cells + afferent arterioles → ↓GFR
- Prostaglandins (NB not hormones): PGE2, PGI2, NO → dilate mesangial cells and afferent arterioels → ↑GFR

Describe the process of tubuloglomerular feedback: PAST QUESTION

Tubuloglomerular feedback

- Important component of autoregulation of GFR between MAP 75-170mmHg
  - –ve feedback loop to pressure natriuresis + diuresis
  - associated with JGA
- JGA
  - formed by thick AscLoH passing between afferent arteriol and efferent arteriole close to glomue
  - Monitors fluid flow through DCT + adjusts GFR accordingly (ΔRBF are secondary)
  - Contains:
    - Granular cells: produce + store renin; found in walls of afferent arteriole
    - Extraglomerular mesangial cells: contractile cells which control effective surface area
    - Macula densa: sensing unit; thick AscLoH; contain Na/K/2Cl symporter



Process

- Basically: ↑GFR → ↑Na and Cl at macula densa → stimulates adenosine production
- MoA:
  - ↑RPP → ↑glom cap pressure → ↑GFR → ↑rate of delivery of Na/Cl to macula densa
  - ↑[Na+] sensed by macula densa cells through Na/K/2CL cotransporter.
  - Intracellular movement of Na, K, Cl coupled to osmotic movement of H2O into macula densa cell → cellular swelling in proportion to GFR
  - Stimulates Na/H antiporter → depolarizes cell
  - ↑Ca2+ entry across basolateral membrane → Ca2+ releases ATP in close proximetry to mesangial cells
  - ATP breaks down to adenosine → stimulate P2 purinergic Rs on mesangial cells + afferent arteriole smooth muscle
  - Adenosine →
    - afferent arterioles vasoconstrict → ↑renal vascular resistance → ↓RB
    - glomerular mesangial cells contract → ↓surface area for filtration → ↓GFR
    - granular cells inhibited from secreting renin
  - NB adenosine released in proportion to degree of cell swelling
- When ↓RPP + ↓GFR → opposite effect with production of nitric oxide in place of adenosine → dilates smooth muscles

How is dilute and concentrated urine produced? MAKEUP

Dilute + concentrated urine:

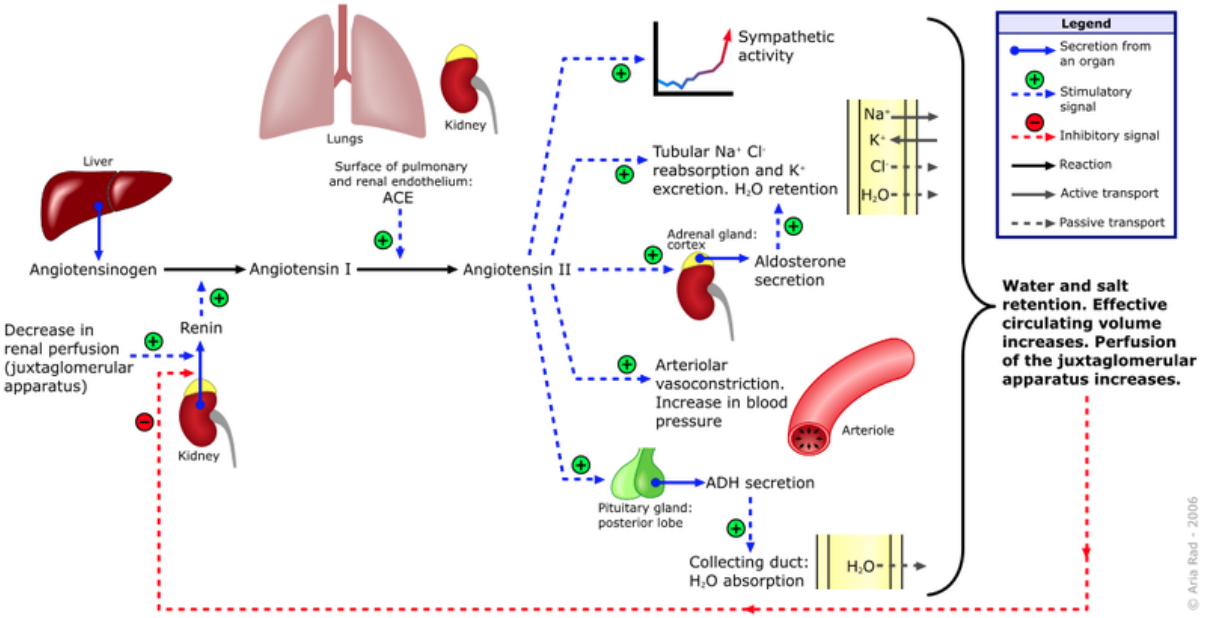
How is dilute urine produced?

- Kidneys can produce urine that is hypoosmotic, isosmotic, hyperosmotic
- Hypoosmotic urine:
  - Tubules (esp. thick AL LoH) reabsorb more solute than water → and the dilute fluid that remains in the lumen is excreted
  - 2 factors:
    - 1. DCT:
      - impermeable to H2O; permeable to NaCl
      - If states of excess H2O → urine diluted by reabsorption of ↑NaCl ions in DCT without reabsorption of water
    - 2. CD:
      - relatively impermeable to H2O – need ADH to open aqua pores or water channels
      - NaCl are still reabsorbed and leave the urine

How is concentrated urine produced?

- Hyperosmotic urine:
  - Reabsorption of water from lumen into hyperosmotic interstitium concentrates luminal fluid → leaving concentrated urine to be excreted
- Fluid deprivation:
  - 1. DCT
    - acts normally by reabsorbing NaCl; impermeable to H2O
    - therefore fluid leaving the DCT is dilute with osmolarity <100mOsmol/kg
  - 2. ADH
    - Released from hypothalamus when baroreceptors and osmoreceptors detect ↓ plasma volume or ↑ osmolality
    - ADH acts on CT within cortex and medulla → reabsorption of H2O
    - In medulla: ↑H2O can be reabsorbed because of the high interstitial fluid osmolality produced by the loop of Henle. This allows the production of small quanity of concentrated urine
  - Max urine osmolarity kidneys can produce is 1400mOsmol/kg
  - Urea accounts for ½ of the osmolality of this concentrated urine, and Na, Cl, K = remainder

Renin-angiotensin-aldosterone system



RENAL PHARMACOLOGY

Drugs used to treat hyperkalaemia: MAKEUP

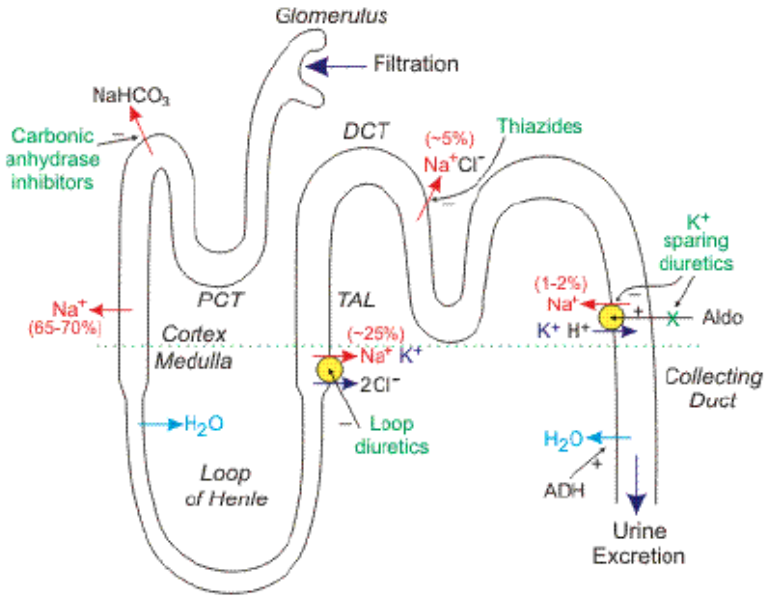
- 8.4% NaHCO3
  - acutely ↓plasma [K+] by moving K intracellularly and restoring transmembrane K gradient
  - short duration of effect
- Calcium:
  - 10ml 10% CaCl (6.8mmol) or 10% CaGluconate (2.2mmol); immediate onset; stabilises cardiac membrane by ↓threshold potential
- insulin/glucose
  - 10units IV + 50ml 50% dextrose
  - insulin receptor agonist → transcellular shift of K from extracellular to intracellular space via upregulation of Na/K ATPase → transient ↓ in serum [K+]
  - should ↓[K+] by 1-2mmol/l within 30 mins; effect can persist for 2-3 hours
- K exchange resin
  - K binder; exchanges 1mmol of K for 1mmol of Na for every gram of resin
  - 15-45g
  - onset 2 hours
  - prevents K reabsorptionin GIT (predominantly colon where K secretion occurs)
- Frusemide/ loop diuretics
  - Only effective if renal function intact
  - 40mg IV
  - onset 15mins
  - loop diuretic: inhibition of Na/K/2CL transporter in ascending LoH → ↓K reabsorption and ↑tubular flow rate → ↑collecting duct secretion of K due to ↑tubular flow rate
- Beta2 agonists e.g. salbutamol
  - 5mg via nebuliser; repeated
  - onset 30mins
  - B2 agonism → ↑intracellular [cAMP] → transcellular shift of K from extracellular to intracellular space → transient ↓serum [K+]
- K+ free fluid rehydration/ dilution
- Dialysis
  - Dialysis fluid adjusted to create large concentration gradient for K extraction via dialysis of filtration
- NB only loop diuretics + K exchange resins lower total body K content; the others induce an intracellular K shift which is not sustained and do not directly result in body elimination of K
- IV fluid rehydration lowers total body K if there is a resulting diuresis

Describe alterations to drug response due to renal disease

Outline a physiological basis of classifying diuretics related to their site of action

Site of action

- Glomerulus: osmotic (mannitol)
- PCT: Carbonic anhydrase inhibitors (acetazolamide)
- Loop: Loop diuretics (frusemide)
- DCT: Thiazide (hydrochlorothiazide)
- CD: Potassium sparing diuretics (spironolactone)



Describe the pharmacology of diuretics including mannitol, frusemide, thiazides, aldosterone antagonists and carbonic anhydrase inhibitors

	Osmotic diuretic e.g. mannitol	**Carbonic anhydrase inhibitor e.g. acetazolamide**	**Frusemide**	**Thiazide e.g. hydrochlorothiazide**	**Aldosterone antagonist**
Chem	Polyhydric alcohol	sulfonamide	Anthranilic acid (sulfonamide) derivative	Chemically related to sulfonamides	Synthetic steroid
Uses	↓ICP and vol CSF in presence of cerebral oedema or during neurosurgery diuresis Acute glaucoma Bowel prep	**weak diuretic** glaucoma mountain sickness respiratory alkalosis in ICU menieres disease familial periodic paralysis petit mal epilepsy	Oedema of cardiac, renal, hepatic origin Chronic renal failure (diuresis) HTN ↑ICP symptomatic hypercalcaemia	Moderate HTN LV failure symptom control Diabetes insipidus Renal tubular acidosis	CCF Cirrhosis with ascites + oedema Refractory oedema HTN Nephrotic syndrome with thiazides to conserve K Dx + rx Conns syndrome
Pres	10% and 20%mannitol in water; crystallization can occur at low temps	Tablets: 250mg Vials 500mg sodium salt of acetazolamide for reconstitution with water	CS; protected from light;10mg/ml Tablets 20/40/500mg Syrup		Tablets: 25/50/100mg Fixed dose combinations
Site	**Glomerulus**	**Proximal tubule**	**Loop of henle**	**Distal tubule**	**distal tubule**
Action	**Diuretic**: Low MW; freely filtered, not reabsorbed → **↑osmolality of filtrate** + tubular fluid → ↑water excretion **↓CSF pressure + vol** by: ↓rate of CSF formation + osmotic movement of ECF water across BBB into plasma	**Reversible non-competitive antagonism of carbonic anhydrase (CA)** in PCT CA catalysis: H + HCO3 → H2CO3 → CO2 + H2O **Normally**: Na reabsorbed in exchange for H ions in PT via Na/H exchanger. **Acetazolamide ↓availability of H ions → urinary loss Na + HCO3 + retention H^+**	**Inhibit Na/K/Cl symporter** in thick ascLoH → impairs counter current multiplier, ↓tonicity of medulla → ↓H2O reabsorption in CD Induces PG synthesis, ↑renal vasodilation and blood flow → ↑diuresis	Early segment of DCT: - **inhibits Na/Cl symporter** → ↓NaCl reabsorption → ↑Na, Cl, + H2Oexcretion Late DCT → - ↑Na load reaching DCT tubule → stimulates exchange with **K/H → ↑K secretion** ↓carbonic anhydrase activity → ↑HCO3 excretion (little clinical significance)	**competitive antaonist of aldosterone** at receptor site in DCT → **inhibits Na reabsorption + ↑K reabsorption** → promotes Na+ excretion + potentiates other diuretic agents
CNS	↓ICP; preservation of CBF (if intact autoreg) Doesn't cross intact BBB				Sedation; muscular weakness
CVS	↑CO ↑BP 5-10mmHg	Anticonvulsant ↓CSF pressure: ↓CSF production ↓IOP: ↓aqueous humur production	arteriolar vasodilation → ↓SVR; ↓preload pulmonary vasodilation	antihypertensive 2° ↓plasma volume + ↓SVR	↓BP: 2° alteration of ECF: ICF [Na] gradient or aldosterone antagonist effect on arteriolar smooth muscle
Resp		↑MV 2° metabolic acidosis ↑CO2			
Renal	**↑RBF**; ↓renin secretion washes out medullary interstitial gradient → ↓ability to produce concentrated urine	Alkaline urine → hyperchloraemic metabolic acidosis	**↑RBF** hypochloraemic alkalosis may precipitate hypocalcaemia due to ↑Ca2+ excretion	**↓RBF**; ↓GFR ↓uric acid excretion	diuresis with retention of K+ RBF + GFR unaffected free water clearance may ↑
Metabolic		hyperchloraemic metabolic acidosis	↑Na (net water loss); ↓K, ↓Mg2+ ↓Cl	↓K+, **↓Na**, ↓Mg2+ hypochloraemic alkalosis	↑K, ↓Na; hyperchloraemic acidosis
Other	↓Na; ↓Kl ↑urea	Inhibits gastric + pancreatic secretion	↑plasma cholesterol and TG	glycogenesis + insulin secretion + ↑glycogenolysis → ↑BSL	Anti-androgenic
Toxicity/ SE	Circulatory overload Rebound ↑ICP Irritant to tissues + veins Vacuolization	GI; haem disturbance Rash, renal stones, hypokalaemia	Deafness Interstitial nephritis in high doses	Arrhythmias 2o ↓K	Hyperkalaemia esp. in renal failure N+V
Route/ dose	ICP: 1g/kg over 15mins Diuretic: 0.5-1g/kg	PO/ IV: 250-1000mg daily	PO: 20-2000mg daily IV: 10-1000mg / IVI: <4mg/min		PO 100-400mg daily
Onset	Minutes Diuresis 1-3 hours post administration	PO: 1-2hr IV: 5-10min	IV: 5 mins PO: 30-60min	Diuresis: <90mins	Slow; 3-4 days for diuretic effect to become established
Duration	1-4hours	PO: 8-12hr IV: 4-5hr	IV: 2hrs PO: 4-6hrs	4-6hr	
A	17% absorption small bowel	bioavailability >95%	65% bioavailability	bioavailability variable (70%);	bioavailability 70%

					extensive 1st pass metabolism
D	Biphasic distribution to plasma and extracellular water VD 0.5L/kg	70-90% PB	95% protein bound (albumin) VD 0.1L/kg	40-70% PB VD: 4-8L/kg	90% PB to albumin in plasma
M	Not metabolised	Not metabolised	***** In kidney to glucuronide *****	Minimal	rapidly + extensive deacetylation + dethiolation in liver; some metabolites (e.g. canrenone) active
E	Unchanged in urine Clearance 7ml/min/kg Elimination ½ life 70mins	Unchanged in urine Clearance 2.5L/hr Elimination ½ life 2-6hours	80% in urine unchanged + glucuronidated 20% faeces clearance 2ml/min/kg elimination ½ life 45-90mins	Renal (95% unchanged) Elimination ½ life 6-15hr	Urine small biliary eliminiation ½ life 1-2hrs
Special points	Do not co-adminster with blood	CI in liver/ renal failure as will worsen metabolic acidosis Removed by haemodialysis	Frusi → ↑effects NDMR probs due to hypokalaemia Not removed by haemodialysis		↓responsiveness to coadministered pressor agents + ↑effects of CVS depressants ↑serum conc co-administered dig

Outline the effects of IV administration of 500mls of 20% mannitol and the potential problems associated with its us: PAST QUESTION

Mannitol = osmotic diuretic
- 20% solution = 200mg/ml → osmolality = 1100mosm/L
- Uses:
  - ↓CSF pressure/ vol: cerebral oedema, glaumcoma
  - perioperative diuresis in jaundiced patients (renoprotective)
  - initiate diuresis in transplanted kidneys/ prevention of post-ischaemic ATN
- Physicochemical properties
  - Low MW (182Da)
  - Freely filtered at glomerulus
  - Not absorbed
  - Charge polysaccharide – doesn't cross BBB
  - 4x plasma osmolality

Effects
- ↑ECF osmolality
- hyperosmotic; doesn't cross CM → draws water from ICF into intravascular space
- e.g. 70kg subject with TBW 42L (ICF 23L, ECF 19L) with osmolality 290mOsm/kg → ↑ECF by 2.1L → 25% of this will remain intravascular = ~500ml
  - Plasma osmolality: ↑>1% threshold of osmoreceptors: ↑osmolality sensed by osmoreceptors → ↑ADH + ↑thirst
  - Blood volume: ↑>10% threshold of vol receptors: ↑ANP from atrial stretch receptors → ↓RAAS → ↓Na reabsorption → ↑Na + H2O secretion
  - Osmotic diuretic: overall effect = natriuresis + excretion of excess water

Potential problems
- Volume depletion, hypernatraemia: → freely filterable + not reabsorbed → osmotic diuretic
- Volume expansion, hyponatraemia: occurs with underlying renal failure or ↑↑doses; ↑plasma osmolality → osmotic movement of water out of cells
- Hyperkalaemia: due to ↑intracellular [K+] due to osmosis with ↑concentration gradient from ICF to ECF → arrhythmias
- Metabolic acidosis: ↓[Na+] > ↓[Cl] → ↓SID
- Anaphylaxis
- Vein irritation
- Tissue necrosis with extravasation
- Swelling of brain if BBB disrupted

Explain how a metabolic alkalosis develops in an adult patient with a small bowel obstruction and nasogastric losses >1000ml per day for 5 days. Give a brief account of the physiological principles determining fluid replacement: PAST QUESTION

Define:
- metabolic alkalosis = primary acid-base disorder which causes the plasma HCO3 to ↑ to a level higher than expected
- in an adult with SBO, the stimulus for alkaline intestinal, pancreatic, and bile secretions will be minimal as tube drainiage prevents acid from reaching the duodenum

Nasogastric loss comprises H2O +
- Na: 50mmol/L
- K 10mmol/L
- H 100mmol/L
- Mg 2mmol/L
- Cl 150mmol/L
- HCO3 0mmol/L
- ~1.5L gstric guice produced / day
- therefore ongoing NG loss → hypovolaemia, metabolic alkalosis (loss of H), hypokalaemia

Development + maintenance of metabolic alkalosis
- development of metabolic alkalosis: net loss of H from ECF
- maintenance of alkalosis: hypovolaemia: triggers compensatory mechanisms which prevent correction of metabolic alkalosis
  - PT: maximal Na reabsorption due to hypovolaemia → Cl reabsorption → HCO3 reabsorption to maintain electroneutrality associated with Na reabsorption → worsens metabolic alkalosis
  - DT: ↑RAAS → ↑aldosterone → ENac channel insertion into apical membrane → ↑Na reabsorption at cost of ↓K and ↓H reabsorption → worsens alkalosis + hypoalaemia
- compensatory reaction = hypoventilation: ↑PaCO2: expected PaCO2 = 0.7[HCO3] + 20mmHg (range +/- 5)

principles determining fluid replacement are: correction of Cl / K / ECF depletion
- appropriate therapy = NS + KCl
- other therapies when ECF vol normal or high: acetazolamine (inhibits proximal HCO3 reabsorption)
- if require rapid correction of metabolic alkalosis: supplemental infusion of ammonium chloride (NH4Cl)

Outline the effects of rapid injection of 100ml of hypertonic iodine containing angiography contrast medium in an otherwise healthy adult: PAST QUESTION

Iodine containing contrast agents used to ↑visibility of internal structures on imaging modalities using x-ray
- usually derivatives of 2,4,6-triiodobenzoic acid
- 2 common types:
  - Ionic e.g. iotroxate
    - Older; high osmolality (1000-2000mOmol/L) → ↑adverse effects
  - Non-ionic e.g. iopromide, iopamidol, iodixanol
    - Newer; more expensive
    - Non-ionic iodine containing monomers or dimers with lower osmolality → ↓adverse effects
- Properties
  - CCS; high viscosity
  - Mainly renal clearance with some biliary elimination
  - t½ = 1-2 hrs (normal renal function)

Physiological effects

- CNS: metallic taste; feeling of urination
- CVS: sig fluid load; may precipitate cardiac failure
- Renal: nephrotoxicity – may precipitate tubular necrosis; prehydration + NAC may be renoprotective
- Immune: anaphylactoid reactions
- Thyroid: may suppress thyroid hormone production (Wolff-Chaikoff effect); paradoxically stimulate thyroid hormone overproduction (Jod-Basedow effect)
- Vascular: extravasation → irritation