Renal Function

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Kidney Anatomy

- 150-200g each
- lie retroperitoneal just below diaphragm
- divided into:
  - cortex
  - medulla – inner & outer
  - pyramids
  - calyces
  - pelvis
  - ureter

Renal Functions

- water & electrolyte homeostasis:
  - 180L/d of plasma ultrafiltrate in renal corpuscles
  - filtrate passed along nephron
    - tubular reabsorption & excretion
    - 99% water reabsorbed \( \therefore \) ~1.5 L urine/d
  - tubular secretion contributes to excretion of substances from peri-tubular capillaries into nephron
  - final volume & composition = modulated to maintain norm body fluid & electrolyte balance by altering:
    - GFR
    - Tubular reabsorption
    - Tubular secretion
  - Integral in long term regulation of body H2O & electrolytes \( \therefore \) crucial to blood volume & MAP
- Excretion of wastes of metabolism:
  - Urea – protein
  - Creatinine - muscle
  - Urate – nucleic acids
  - Bilirubin – Hb
- Other:
  - Endocrine eg vit D, renin, EPO
  - Gluconeogenesis – in starvation kidneys produced glucose from aa’s
  - Acid-base balance – by varying urinary excretion of HCO3 & H
  - Excretion of chemicals eg drugs/foodstuffs

Concentrations

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<th>Substance</th>
<th>Urine</th>
<th>Plasma</th>
<th>U/P Ratio</th>
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<td>Na</td>
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Nephron

- = renal tubule & glomerulus
- = functional unit of kidney
- human kidney = 1.3 million nephrons
- total length 45-65 mm
- nephron consists of:
  - glomerular tuft & Bowmans Capsule – together = corpuscle
  - filtrate tubule
- different types of nephrons:
  - 85% = cortical or short loop nephrons:
    - short loop of Henle which lacks a thick ascending limb:
      - loop goes from cortex ⇒ outer medulla ⇒ cortex ⇒ distal tubule
  - 15% = juxtamedullary or long loop nephrons
    - their Bowmans Capsule is closer to outer medulla (ie slightly deeper than cortical nephrons)
    - loop of Henle passes deep into inner medullar before returning to distal tubule in cortex
    - ascending limb has thick & thin parts
- collecting ducts penetrate outer & inner medulla
- start to form renal pelvis in deep inner medulla

Bowmans Capsule

- made of:
  - Glomerulus – tuft of capillaries
  - Afferent arteriole – supplies Glomerulus
  - Efferent arteriole – drains Glomerulus
- 2 layers separate blood from glomerular filtrate:
  - Capillary endothelium –
    - Fenestrated 70-90 nm pore
    - Surrounded by
      - Stellate cells (mesangial cells) –
        - in between endothelium & basal lamina
        - function:
          - contractile – involved in regulation of GFR
          - secrete ECM
          - make renin
          - takeup immune complexes
  - glomerular BM =
    - basal lamina AND
By Adam Hollingworth

- **podocytes** – pseudopodia that interdigitate forming filtration slits 25nm wide

- **Specialised epithelium**
  - Function of glomerulus:
    - Permits free passage substance <4nm
    - Totally excludes >8nm
  - Total area of glomerular endothelium in human = 0.8m²

**Prox Convoluted Tubule**
- 15mm long
- 55um diameter
- wall of single cells with tight junctions
- luminal edge of cells have brush border

**Loop of Henle**
- descending & proximal part of ascending limb = thin permeable cells
- distal ascending limb = thick cells with many mitochondria
- cortical (short) nephrons = short loop of Henle
- juxtamedullary nephrons (long) = long loop of Henle extending in medullary pyramids

  - only ~15% all nephrons

**Special Cells**
- juxtaglomerular apparatus =
  - macula densa
  - juxtaglomerular cells

- macula densa:
  - end of ascending thick limb of loop of Henle where it lies adjacent to own glomerulus
  - =modified tubular epithelium at point where DCT touches both afferent & efferent arterioles
  - = chemoreceptors

- juxtaglomerular cells = epitheloid cells in media of afferent arterioles
  - located where afferent arterioles ⇒ enter glomeruli
  - have secretory granules containing renin
  - = intra-renal baroreceptors in afferent arteriole form juxtaglomerula apparatus

- lacis cells
  - = extraglomerular mesangial cells
  - found at junction between afferent & efferent arterioles
  - contain renin
  - contraction ⇒ ↓GFR

- type I medullary interstitial cells:
  - secretory function
  - secrete prostaglandins – PGE₂

**Distal Convoluted Tubule**
- 5mm long starts at macula densa
- no brush border

**Collecting Ducts**
- 20mm long
- pass through cortex, medulla ⇒ pelvis at apex of medullary pyramid
- epithelium made of:
  - principal cells (P)
    - most numerous
    - few organelles
    - Na reabsorption
  - intercalated (I) cells
    - also in distal tubule
    - more organelles
    - acid secretion & HCO₃⁻ transport
Blood Vessels

- afferent arterioles:
  - short straight branches of interlobular arteries
  - divides into multiple capillaries creating tuft in glomerulus
- efferent arterioles:
  - from capillaries in glomerulus
  - little smooth mm
  - each efferent arteriole from 1 glomerulus divides to supply many nephrons
  - cross over of blood – 1 tubule receives blood from many efferents
  - these then break up to form either
    - peritubular capillaries
      - from efferent arterioles in cortex (outer) nephrons
      - surround tubules
    - vasa recta
      - from efferent arterioles in juxtamedullary nephrons
      - loops dip into medullary pyramids with loops of Henle
        - descending –
          - nonfenestrated endothelium
          - facilitated transport for urea
        - ascending –
          - fenestrated
          - function to conserve solutes
  - vasa recta & peritubular capillaries then drain into interlobular veins
- glomerular capillaries only capillary which drains into arteriole
- total surface area of tubules = total surface of renal capillaries
  \[ \sim 12 \text{m}^2 \]
- volume of blood in renal capillary at once = 30-40ml

Lymph

- abundant
- drains via thoracic duct into veins

Capsule

- capsule thin but tough
- capsule limits renal oedema \( \Rightarrow \)↑renal interstitial pressure \( \Rightarrow \)↓GFR \( \Rightarrow \) enhance & prolong anuria in ARF

Innervation of Renal Vessel

- postganglionic symp fibres
  - efferent – many
  - afferent – few
  - distribute to:
    - both arterioles
    - both tubules
    - juxtaglomerular cells
- NA innervation of thick ascending limb of loop of Henle
- cholinergic fibres via vagus ?function
- renorenal reflex:
  - renal afferent effecting contralateral kidney
o ↑ureteral pressure in one kidney ⇒ ↓efferent nerve activity contralateral kidney ⇒ ↑excretion Na & H2O
Renal Circulation

Demand Supply Circulation

• kidney weight = 300g
• @ rest kidneys receive:
  o 400ml blood/100g/min or 1200-1300ml/min
  o 25% CO (1.2-1.3L)
• target of blood flow:
  o 95% cortex (450ml/100g/min):
  o 5% to medulla:
    ▪ outer medulla = 20ml/100g/min
    ▪ inner medulla = ~3ml/100g/min
  o homeostatic & excretory functions require large flow
• basal VO2 =
  o 6mlO2/100g/min or 18mlO2/min (medulla is highest)
  o 7% of total body VO2
  o as metabolically v active
  ⇐ ∴ significant over supply but due to special supply & high metabolic activity

Pressure In Renal Vessels

• when mean arterial bp = 100mmHg,
• glomerular cap pressure ~45mmHg
• pressure drop across glomerulus 1-3mmHg
• pressure drops in efferent arterioles ⇒ pertitubular capillaries = 8mmHg
• renal vein ~4mmHg

Regulation of Renal Flow

\[ \text{RBF} = \frac{\text{MAP} - \text{RVP}}{\text{RVR}} \]

(RVR = constriction of either the afferent or the efferent arteriole (or both) ⇒ ↑RVR)

⇐ as they are in series.

• 3 main systems controlling renal circulation
  1. autoregulation
  2. sympathetic control
  3. hormonal/humeral control

1. Autoregulation
autoregulation of renal blood flow between 70-175mmHg in dog
virtually absent <70mmHg & in diseased kidneys
autoreg of RBF & GFR can be overridden by (even if MAP in autoreg range):
  o SNS – large effect
  o RAA system – esp angiotensin 2 - large effect
  o Prostaglandins
    ⇐ have greater impact on RBF : GFR
autoreg present in denervated, isolated perfused kidney
  can be prevented by drugs which inhibits smooth mm contraction
achieved by:
  o pressure autoregulation –
    ▪ myogenic mechanism in afferent arterioles:
      ⇐ contract in response to stretch & vice versa
    ▪ maintains a constant renal blood flow
  o Tubuloglomerular feedback (TGF):
    ▪ Primarily involved in autoregulating constant GFR
      ⇐ does effect RBF but is a 2nd ary consequence
    ▪ TGF mechanism – macula densa in early distal tubule senses:
      • ↑GFR ⇌ ↑rate of flow of tubular fluid around nephron
      • macula densa sense ↑rate of delivery of Na/Cl (range 20-60mmol)
      • Na & Cl enter sensor cells via Na-K-2Cl contransporter in apical membranes
      • ↑in Na ⇒ ↑NaKATPase activity ⇒ ↑adeonsine formation from basal membrane of cells
      • ⇒ adenosine acts on A1 receptors on mac densa cells ⇒ ↑release of Ca to smooth
        mm of afferent arteriole ⇒ VC ⇒ afferent arteriole vasoC
      • ⇒↓RBF ⇒ ↓GFR of that nephron
    ▪ sensitivity of TGF mechanism is ↑ed with ↓ECF volume & vice versa
    ▪ loop diuretics block reabsorption of Na/Cl by macula densa ⇒ inhibition of TGF mechanism
2. Renal Sympathetic Nerves
  • from T10 – L1
  • some tonic discharge at rest
  • rate of discharge is ↑ed by:
    o hypotension: ↓baroreceptor firing ⇒ ↑SNS output ⇒ ↑VC in systemic vessels and renal vessels
    o exercise ⇒ ↓renal blood flow
    o central SNS stim
  • see mild ↓renal blood flow on rising from supine
graded stimulation of renal nerves:
  1st
  ▪ sensitivity of juxtaglomerular cells – to non neural stimuli. Result is ↑ed renin release
    ⇐ NB no effect on basal renin release (= a B1 effect)
  ▪ ↑renin secretion – direct effect on JG cells of B1 stim
  last
  ▪ ↑Na reabsorb – direct action of NA on renal tubular cells (a1 & b1)
    ⇐ PCT, DCT, ascending limb LOH = richly innervated by SNS
  o renal VC :
    ▪ by mostly a1 receptors, (some a2 effect)
    ▪ initially afferent arteriole
    ▪ greater stim ⇒ efferent constriction as well
    ▪ results in
      • ▪ GFR – see less drop in GFR than RBF due to efferent constriction
By Adam Hollingworth

Renal Function

- ↓ renal blood flow
  [ NA also causes glomerular mesangial cell constriction ⇒ significant ↓ in GFR ]

3. Hormonal/Endocrine Mechanisms

- Angiotensin 2:
  o Low concentrations:
    - Selective vaso afferent arteriole ⇒ ↓GFR ie defend volume
    - ↓ blood flow to medulla
      ← ie opposes PG’s
  o High conc:
    - Mechanism:
      • Also vaso efferent arteriole (in addition to afferent) ⇒ ↓RBF
      • Contraction mesangial cells ⇒ ↓ GFR

- Prostaglandins:
  o PGE2 & PGI2 cause (via GPCRs)
    - Selective afferent dilation
    - Stim of renin secretion – direct effect on JG cells
    - ↑ medullary blood flow
    - Inhibition of mesangial constrictor effects of:
      • AT-2
      • NA
      • ADH
  o Physiological role:
    - dampen renal vaso effects of SNS/ADH/AT2
    - prevent hypoxic renal damage during hypotension - would occur if SNS & AT2 effects unopposed
      ← ⋆: inhibition of PG synthesis combined with hypotension ⇒ profound ↓RBF & renal damage
  o produced in:
    - medullar interstitial cells
    - Collecting Duct cells
    - Arterioles
    - Macula densa cells
  o ↑PG synthesis stim by:
    - SNS
    - AT2
    - ADH
    - TGF

- ADH
  o In high concentrations ⇒
    - renal vaso ⇒ ↓RBF & ↓GFR
    - mesangial cell constriction ⇒ ↓GFR
    - stimulates release of PGs – opposing its actions acting as protection

- ANP – causes ↑↑GFR:
  o Afferent dilator
  o Efferent constrictor
Regional Blood Flow & O2 Consumption

- A/V O2 difference for whole kidney 14ml/L = extraction 8-10% available O2
  - brain 62, heart 114
- Renal VO2 primarily determined by Na reabsorption
- Kidneys very susceptible to ischaemic damage well before ↓ in total DO2:
  - Renal blood flow is autoreg primarily to maintain GFR & Na balance – NOT to meet renal metabolic demand
  - Renal metabolic rate has little autoreg influence over blood flow in peritubular capillaries
  - Countercurrent transfer of O2 in vasa recta causes ↓ in peritubular capillary PO2 as descend into medulla
  - medulla blood flow:
    - low compared to cortex (M= 20ml/100g/min : 450ml/100g/min C)
    - sluggish flow due to architecture of vasa recta
    - BUT is region of kidney with highest metabolic demand (Na reabsorption)
      - is region most susceptible to hypoxia
- Main function of renal cortex is filtration
  - high flow (450ml/g/min), little O2 use
    - (brain 50ml/100g/min)
- function Medulla to maintain osmotic gradient & reabsorb Na
  - low flow (20ml/100g/min), large amount O2 use
    - medulla vulnerable to hypoxia if flow reduced further
- NO, prostaglandins, cardiovascular peptides act in paracrine fashion to autoreg flow & O2 needs

Measurement of Total Renal Plasma Flow & Total Renal Blood Flow

- RPF is different to RBF
- Para- amino- hippurate (PAH) =
  - Organic anion
    - Almost completely cleared from plasma on single pass thru kidneys
    - Freely filtered & actively secreted
    - Extraction ratio ~90% when infused at low rate
      - higher rate ⇒ Tm exceeded & ratio falls
    - Clearance of PAH used to measure effective RPF
      - \[ \text{Cl}_{\text{PAH}} = \frac{\text{U}_{\text{PAH}} \cdot \text{U}_0}{\text{P}_{\text{PAH}}} \]
- This is Fick Principle in disguise….

Fick: \[ Q = \frac{\text{amount consumed (or produced)}/\text{time unit}}{\text{Difference in arterial – venous concentrations}} \]

So….

RPF = \[ \frac{\text{amount of substance excreted}}{\text{time unit}} \]

Renal A – V differences

Assumed renal venous PAH = zero
• Effective RPF underestimates actual RPF by 10% (as only 90% PAH extracted)
  \[ \therefore \text{actual RPF calculated by dividing effective RPF by 0.9} \]
• Normal RPF ~ 700ml/min
• RBF can then be calculated from actual RPF & HCT

\[
RBF = \frac{\text{RPF}}{1 - \text{HCT}}
\]

HCT = haematocrit ie conversion for conc of Hb in plasma
Basic Renal Processes

- Substances presented to the kidneys can undergo the following:
  - Glomerular filtration (GF)
  - Tubular reabsorption
  - Tubular secretion

Urinary excretion = [urine,] \times \text{ urine output} = \text{GF} + \text{tubular secretion} - \text{ tubular reabsorption}

GFR

- GFR healthy person av size = 125ml/min
- Values in women 10% lower after correction for s.a.
- Filtration = 180L/day; urine volume 1L/day
- >99% filtrate is reabsorbed

Glomerular Filtration

- Blood filters from glomerular capillaries \( \rightarrow \) Bowmans Capsule
- Amount filtered dictated by Starlings Forces
- Forces act across thin diffusion barrier consisting of:
  - Capillary endothelium fenestrae
  - Basement membrane
  - Slit diaphragms between podocytes (= capsular epithelial cells)
  - Mesangial cells (stellate cells)

\[
\text{GFR} = K_f \times \text{net filtration pressure}
\]

Where:
\[
K_f = \text{filtration coefficient} \quad \leftarrow \text{affected by contractile state of mesangial cells}
\]
\[
\text{NFP} = \left[ ( \text{GC}\_{\text{HP}} - \text{BC}\_{\text{HP}} ) - \text{GC}\_{\text{OP}} \right]
\]

- Filtration coefficient =
  - surface area \times membrane permeability
  - permeability:
    - of glomerular capillaries to water & solutes = \( v \) high (10-100x non renal values)
  - surface area:
    - can be altered by factors effecting of mesangial cells activity:
      - contraction of cells ie \( \downarrow \text{sa} \):
        - AT2
        - NA
        - ADH
        - TXA2
        - PAF
        - PGF2
        - Leukotrides
        - Histamine
    - Relaxation of cells ie \( \uparrow \text{sa} \):
By Adam Hollingworth

- ANP
- Dopamine
- PGE2
- C-AMP

- NET filtration pressure (NFP)
  - = balance of
    - capillary hydrostatic pressure moving fluid out of capillary
    - hydrostatic pressure in BC opposing movement of fluid out of capillary
    - oncotic pressure in GC
  - (oncotic pressure in BC not included as protein content of filtrate v low under physiological condition)

\[ \text{NFP} = \left[ (\text{GC}_{HP} - \text{BC}_{HP}) - \text{GC}_{OP} \right] \]

- NFP drops along glomerular capillaries because of:
  - no sig change in hydrostatic pressure as is low resistance system
  - ↑ing oncotic pressure – protein free fluid being filtered into BC leaving ↓ly high conc protein behind

- NFP values:
  - @ afferent end GC ~20mmHg
  - @ efferent end GC ~35mmHg
    - sufficient to produce GFR 180L/d (~125ml/min)
    - rise in oncotic pressure imp for water reabsorption later in nephron

- Diagram shows portions of glomerular capillaries don’t normally contribute to filtration
  - filtration exchange is flow limited (not diffusion ltd)

Factors Effecting Starlings Forces

1. Glomerular Capillary Hydrostatic Pressure (GC_{HP})
2. Bowmans capsule hydrostatic pressure (BC_{HP})
3. Glomerular Capillary Oncotic Pressure (GC_{OP})
Renal Function

• **Glomerular Capillary Hydrostatic Pressure** (GC\textsubscript{HP}):
  - Pressure ~60mmHg highr than other capillary beds because:
    - Afferent arterioles = short straight branches of interlobar arteries
    - Efferent arterioles have relatively high resistance
  - GC\textsubscript{HP} falls less along length of vessel (compared with systemic beds) due to high efferent tone
  - Tends to ↑ with ↑MAP – although is minimised by autoreg:
    - Pressure affected by relative resistance of afferent & efferent arterioles – eg:
      - vasoD afferent & vasoC efferent ⇒ ↑GCHP
        - caused by ANP
      - afferent vasoD alone ⇒ ↑GCHP
        - causes:
          - PGE2
          - PGI2
          - ANP
          - NO
      - vasoC afferent & vasoD efferent ⇒ ↓GCHP
      - both vasoC ⇒ maintain GCHP (despite ↓in RBF)
        - causes:
          - NA
          - SNS – NB also causes ↓K\textsubscript{f} (via mesangial constrictor) ⇒ ↓↓ GFR
          - AT2 (need high dose for afferent)
  - **Bowmans capsule hydrostatic pressure** (BC\textsubscript{HP}):
    - Any obstruction to urine flow ⇒ ↑ BC\textsubscript{HP} ⇒ ↓GFR
  - **Glomerular Capillary Oncotic Pressure** (GC\textsubscript{OP}):
    - ↓systemic protein ⇒ ↑GFR and vice versa
    - ↓ed RBF ⇒ filtration of fluid from reduced volume of plasma ⇒ ↑GC\textsubscript{OP} .∴ ⇒ ↓ed NFP
    - NFP & GFR ↓ along length of capillary in proportion to ↑ing GC\textsubscript{OP}

**Summary Control of GFR**

GFR = K\textsubscript{f} x [(GC\textsubscript{HP} – BC\textsubscript{HP}) - GC\textsubscript{OP}]

• **GC\textsubscript{HP}:**
  - Autoreg – pressure & tubuloglomerular feedback
  - SNS stim – 2\textsuperscript{nd} to baroreceptor stim ⇒ afferent (>efferent) vasoC ⇒ ↓GFR & ↓Na filtered excreted
  - RAA system – AT2 – depends on conc of AT2: low ⇒ little change in GFR (vasoC afferent>efferent)
• **GC\textsubscript{OP}**
  - Dehydration ⇒ ↓plasma volume & ↑ conc protein ⇒ ↓GFR
  - ↑plasma volume ⇒ ↓conc protein ⇒ ↑GFR
  - haemorrhage:
    - NET movement protein out of vessels ⇒ ↓serum protein conc ⇒ ↑GFR (innapropriate)
      - overcome by ↑SNS ⇒ ↓NET GFR
• **K\textsubscript{f}**
  - Mesangial constriction (AT2, ADH, NA) ⇒ ↓GFR & ↓Na filtered & excreted
  - Mesangial dilation (dopamine, ANP, PGE2)
**Filtration Fraction**

- RPF ~ 600ml/min or RBF = 1250ml/min
- GFR ~ 125ml/min
- FF = fraction of flow which filtered off into tubule

\[
\text{filtration fraction} = \frac{\text{GFR}}{\text{renal blood flow}}
\]

- norm ~ 20%
- GFR varies less than plasma flow:
  - ↓bp ⇒ less GFR than expect due to efferent arteriole VC ⇒ ↑filtration fraction

**Glomerular Filtrate & Permeability**

- permeability of glomerular cap x50 that of skeletal mm caps
- filtrate contains:
  - water
  - electrolytes
  - glucose
  - amino acids
    - large molecules eg protein, rbcs not filtered
- <4 freely filtered
  - most drugs <1nm
- 4-8 = ↓ing filtration to zero at 8nm
  - between filtration inversionally \(\propto\) to diameter
    - except: -ve charged particles – see half amount filtered compared to neutral substance
    - because proteins in glomerular wall are -ve charge thus repel -ve particles

- Explains ↓ed filtration of albumin as is -ve charge
- Protein in urine norm comes from shedding of tubular cells (<100mg/day)
- Nephritis ⇒ dissipation of -ve charges in glomerular wall ⇒ albuminuria without ↑in size of filtration pores
Measuring GFR

- Requirements for suitable substance to measure GFR:
  - Freely filtered
  - Not reabsorbed or secreted
  - Not synthesized or broken down by tubules
  - Not stored in kidneys
  - Has no effect itself on filtration rate
  - Non-toxic, easy to measure or administer

- Inulin:
  - Polymer of fructose
  - Mw 5200
  - Meets above criteria but inconvenient as must be given by IV infusion until steady state reached
  - Then can take urine & plasma sample

- Creatinine:
  - More convenient, but less accurate
  - Formed from mm creatinine & released into blood stream at ~ constant rate
  - Problems:
    - Secreted into tubules in small amounts & +/- some reabsorption
    - ∴ creatinine clearance gives false high GFR:
      - small at normal GFRs
      - as GFR ↓s ⇒ the proportion secreted : filtered ↑s ⇒ ↑↑ing false high reading
  - Testing requires single blood sample & 24hr urine collection

- Urea clearance:
  - not useful as variable amount reabsorbed (40-60%)
  - called Clearance of X:

  \[
  \text{GFR (ml/min)} = \frac{U_x \cdot V}{P_x}
  \]

  \( U_x \) = concentration of X in urine
  \( V \) = urine flow / unit of time
  \( P_x \) = arterial plasma level of X

Serum Creatinine & Urea Concentrations as indicators change in GFR

- Plasma creatinine should be stable value: amount produced = amount excreted
- if ↓GFR:
  - initial ↓ creatinine filtering ⇒ +ve balance ⇒ ↑ serum creatinine
  - movement of equilibrium with higher serum creatinine
- Relationship of creatinine & GFR not linear:
  - inverse log relationship ie GFR needs to be half normal before ⇒ abnormal serum creatinine
- Serum urea = even less accurate than creatinine as GFR indicator cos:
  - normal range = wide
  - varies with protein intake
  - varies with changes tissue catabolism
  - urea absorbed to variable degree (ADH dependant)
Functional Changes in GFR

- Factors effecting GFR:
  - renal blood flow
  - changes in hydrostatic pressure – glom cap or Bowmans capsule
  - systemic bp
  - afferent or efferent constriction
  - ureteral obstruction
  - oedema of kidney in tight renal capsule
  - glom cap permeability
  - glom ultrafiltration coefficient
  - conc of plasma proteins ie oncotic pressures
  - effective filtration surface area

Tubular Function

General Intro

- tubules may:
  - tubular secretion – add to filtrate
  - tubular reabsorption
  - do both concurrently

- anatomy:
  - nephron = one cell thick
  - basement membrane separates cells from peritubular capillaries
  - tight junctions at luminal membrane between nephron cells

- hydrostatic pressure in peritubular capillaries < oncotic pressure ∴ NET reabsorption of fluid

- amount substance excreted/time = amount filtered + net amount transferred

- clearance of substance
  - = GFR if no Tx
  - >GFR if NET secretion
  - < GFR if NET reabsorption

Mechanisms of Tx

- 2 routes for reabsorption of fluid & solutes:
  - transcellular - across luminal & basolateral membranes of luminal cells
  - paracellular – between cells, across tight junctions

1. Transcellular methods

- primary active transport:
  - Na moved out of tubular cell across basolateral membrane ⇒ peritubular capillaries
  - Against electrochem gradient
  - Uses Na/K/ATPase
  - ∴ now low Na [intracellular] which creates gradient for Na to move into cell from the tubular lumen
  - the low Na [inside] created by Na/K/ATPase also used for reabsorption of glucose, aa, Cl, K, H2O via 2nd active transport. (see below)

- Simple diffusion:
  - Transcellular – obeying Ficks Law
  - (also see paracellular via tight junctions)

- Facilitated diffusion:
o = a substance crosses a membrane down its electrochemical gradient by binding with a carrier protein
o substance will display (as opposed to simple diffusion):
  ▪ specificity
  ▪ competition
  ▪ saturation
• secondary active transport:
o 2 substances move across membrane at same time using same protein carrier:
  ▪ 1 moves down its electrochem gradient ⇒ releasing energy
  ▪ energy used to move other substance against its gradient
e.g Na reabsorbed into cell from lumen down gradient creates energy to move e.g gluc, aa’s
o = cotransporter if 2 substances moving same direction
o = counter-transport if move in different directions
• endocytosis –
o mostly prox tubule
o reabsorbs small proteins & peptides via active process
o protein bind receptor ⇒ ATP ⇒ ADP

2. Paracellular Methods
• solvent drag:
o not controlled
o secondary to Na & water
o water by osmotic movement drags small solutes with it
• simple diffusion:
o through tight junctions
  (also transcellular)

Paracellular Leak
• tubular reabsorption & secretion (active processes) are both opposed by diffusion (passive) of substance being transported down its gradient via diffusion
  ↦ mostly at tight junctions (also transcellular small))
• ∴ magnitude of paracellular leak = one of determinents of max transport or gradient which can be established across tubules
• degree of leakiness depends on location & permeability of tight junctions:
o leaky =
  ▪ PCT
  ▪ Small intestine
  ▪ Gall bladder
o Tight =
  ▪ DCT
  ▪ CD
o allows passage of some water & electrolytes
• active transport systems have a max rate = transport max (Tm)
  ↦ rate ∝ to amount of substance up to Tm when saturation reached
  rate also
Cellular Transport by Location

Figure 57.3 Cellular transport model for the proximal tubule. The Na+/K+ ATPase transports Na⁺ from the interior of the cell across the basolateral membrane, creating a low intracellular Na⁺ concentration and a negative intracellular electrical potential, which causes Na⁺ to diffuse from the tubular lumen into the cell through the brush border. Glucose and amino acids are cotransported with Na⁺ through the brush border of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membrane. Hydrogen ions are cotransported with Na⁺ from the interior of the cell across the brush border membrane and into the tubular lumen. Movement of Na⁺ into the cell down an electrochemical gradient established by the Na+/K⁺-ATPase on the basolateral membrane, provides the energy for transport.

Figure 57.4 Cellular transport model for the thick ascending limb of the loop of Henle. The Na⁺/K⁺/2Cl⁻ cotransporter in the luminal membrane transports these ions into the tubular cell using the potential energy provided by the Na⁺/K⁺-ATPase. Ca²⁺ is reabsorbed by all nephron segments through transepithelial and paracellular routes.

Figure 57.5 Cellular transport model for the distal convoluted tubule (DCT). The basolateral membrane Na⁺/K⁺-ATPase maintains a low intracellular Na⁺ concentration. Na⁺ is absorbed from the lumen through a luminal membrane Na⁺/Cl⁻ cotransporter. Active Ca²⁺ reabsorption occurs in this segment.

Figure 57.6 Cellular transport model for the cortical collecting tubule. The Na⁺/K⁺-ATPase maintains a high intracellular K⁺ and low intracellular Na⁺, favoring their passive diffusion across the luminal membrane through specific channels.
By Adam Hollingworth

Reabsorption By Substance

Reabsorption by Location

<table>
<thead>
<tr>
<th>Location</th>
<th>Na</th>
<th>H2O</th>
<th>Cl</th>
<th>Urea</th>
<th>Gluc</th>
<th>K</th>
<th>HCO3</th>
</tr>
</thead>
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<tr>
<td>PCT</td>
<td>65</td>
<td>65</td>
<td>As Na</td>
<td>50</td>
<td>100</td>
<td>50</td>
<td>85</td>
</tr>
<tr>
<td>LH</td>
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<td>15-25</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>5</td>
<td>↑↓15</td>
<td>10</td>
<td>0-15</td>
<td>0-15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Na Reabsorption

- Na transport coupled to H+, gluc, amino acids, organic acids, phosphate across tubule walls
- Na reabsorbed by cotransport in:
  o Prox tubule
  o Thick ascending loop Henle
  o Distal tubules
  o Collecting ducts

\[\text{Na actively reabsorbed from all parts of renal tubule except thin portion of Loop of Henle}\]

- Na moves by cotransport or exchange in tubular lumen ⇒ tubular epithelial cells
- Then actively pumped into interstitial space by Na,K,ATPase in basolateral membrane

\[\text{3Na out, 2K in}\]

- Most of Na actively transported into lateral intercellular spaces
  \[\text{space between tubular cells tight junctions}\]
- Amount of Na reabsorption by location (& diuretic targets):
  o 65% prox tubule (Na-H exchange) (carbonic anhydrase inhibitors)
  \[\text{also Na-glucose & Na-amino acid co-transporters}\]
  o 25% thick ascending loop (Na-2Cl-K cotransporter) (loops)
  o 5% distal convoluted tubute (Na-Cl cotransporter) (thiazides)
  o 4-5% collecting ducts (ENaC channel) (spironlactone)

\[\text{this portion regulated by aldosterone}\]
Glomerulotubular balance: (Nb diff to Tubulo-glomerular feedback)

- intrarenal mechanism
- an ↑GFR ⇒ ↑reabsorption of solutes & also water in mostly prox tubule
  \[\leftarrow: \text{PCT reabsorbs a constant } \% \text{ Na filtered (but amount changes)}\]
- imp for Na as fine tuning in NET movement of Na happens in seconds after change in GFR
- sensor mechanism thought:
  - oncotic pressure in peritubular capillaries:
    - high GFR ⇒ high oncotic pressure of blood leaving in efferent arterioles ⇒ ↑reabsorption of Na in tubules
  - can be overridden by extra renal influences eg haemorrhage & saline infusions

Water Reabsorption

- 180L fluid filtered through glom/day
- urine volume 1L/day
- water reabsorb =
  - PT 65%
  - Descending limb LH 15-25%
  - DT 0%
  - CD 15% (depends on ADh levels)
- Reabsorption occurs by
  - diffusion through cell membranes & tight junctions
  - osmosis predominant method – reabsorption of Na (& other solutes) ⇒ ↓osmotic P of luminal fluid
- ascending loop of Henle = impermeable to water ⇒ delivers dilutes tubular fluid to DCT/CD
- facts:
  - at least 87% of filtered water reabsorbed
  - reabsorption of rest of filtered water can be varied without affecting total solute excretion
  \[\leftarrow: \text{urine concentrated: water retained in excess of solute}\]
  \[\text{urine dilute: water lost in excess of solute}\]

Aquaporins

- =water channels ⇒ rapid diffusion of water across cell membrane
- 13 aquaporins found (1,2,3,4 impnt in kidney)

Water in Proximal Tubule

- aquaporin 1 found on basolateral & apical membrane of prox tubules
- allows water movement out of tubule along osmotic gradients ⇒ maintenance of isotonicity
- 60-70% of filtered solute & water removed by end of prox tubule
- without aquaporin 1 response to dehydration would be ineffective

Water in Collecting Duct

- aquaporin 2 found in collecting ducts
- ADH/vasopressin causes insertion aquaporin channels into membranes ⇒ water reasorption

Chloride Reabsorption

- Occurs transcellular & paracellular
- Movement
  - mostly coupled to Na reabsorption
  - exception is in CD type B intercalated cells:
    - Cl reabsorption indep of Na/K/ATPase
    - Cl counter-transport with HCO3 ions produced from intracellular carbonic acid
      \[\leftarrow: \text{dependant on basolateral membrane H-ATPase pump}\]
Glucose Reabsorption

- All glucose reabsorbed in PCT by cotransport with Na
- Early portion of prox tubule reabsorbs:
  - Glucose
  - Amino acids
  - HCO3
- Later prox tubule – Na reabsorbed with Cl
- Glucose is removed from filtrate (urine) by 2nd active transport with Na
- Gluc filtered at 100mg/min and virtually all should be reabsorbed
- Amount reabsorbed ∝ to amount filtered (ie plasma gluc level P_G) upto TmG (Tm glucose)
  \[ \Leftarrow \text{: once } > \text{TmG } \Rightarrow \uparrow \text{ing glucose in urine} \]

- Humans with norm GFR ie 125ml/min
- TmG
  - in women = 300mg/min
  - in men = 375mg/min
  - average >15mmol/L = complete saturation @125ml/min
  - \[ \text{15mmol/L x 125ml/min } = 1.88\text{mmol/min} \]

- Glucose actually start appearing in urine (ie before transport saturation):
  - 200mg/dL (10-12mmol/L) = s-glucose
  - cos not all tubules identical working optimally to TmG
  - deviation from ideal = splay
  - splay is inversely ∝ avidity of transport mechanism to bind glucose

Glucose Transporter Mechanism

- Gluc reabsorption same as mechanism in intestines
- Gluc & Na bind to Na dependant gluc transporter (SGLT) 2
  - present in apical membrane
- Na moves down elec/chem. Gradient & gluc follows into cell
- Na then pumped out of cell into interstitium
- Gluc via GLUT 2 transports it into interstitium
- Rate of transport of gluc d isomer much higher than l isomer
  - as SGLT 2 binds d isomer specifically

Urea Reabsorption

- Areas of reabsorption:
  - PCT ~50% of filtered urea by passive diffusion
    - linked to water reabsorption
  - Inner medullary CDs: 10% urea reabsorbed
    - ADH ↑s permeability of urea
  - LOH, DCT, cortical CDs are impermeable to urea
Protein Reabsorption
- Only small amount of protein filtered through glomerular
- Albumin in filtrate 10mg/L
- Most albumin reabsorbed by tubules & norm urinary protein ~100mg/day
- Method of reabsorption = endocytosis at tubular luminal membrane
  - Large protein molecules ⇒ lysosomes ⇒ broken down to aa’s ⇒ diffuse into peritubular capillaries
- TM also exists for protein ⇒ exceeded ⇒ large proteinuria

Tubular Secretion of Anions & Cations

PCT Secretion of Organic Anions
- Secretes organic anions into lumen by an active carrier
- Substances secreted this way:
  - Organic anions:
    - Uric acid –
      - also filtered at glomerulus & reabsorbed by tubule BUT secretory mechanisms is impt in regulation of plasma concentration
    - Bile salts
    - FA’s
    - Prostaglandins
  - Drugs & exogenous chemicals:
    - Para-aminohippuric acid (PAH)
    - Penicillin
    - Probenecid
    - Aspirin – highly plasma protein bound. Secretion vital for clearance from plasma

PCT Secretion of Organic Cations
- Also actively secretes organic cations eg:
  - Creatinine
  - Ach
  - Catecholamines
  - Histamine
- Eg drugs secreted this way:
  - Pethidine
  - Morphine
  - atropine
Control of Fluid & Electrolyte Balance

- control of Na & water excretion
- Na is main determinant ⇒ ECF volume ⇒ plasma volume

Regulation of Na Excretion

- Na filtered in large amounts
- Actively reabsorbed out of all portions of tubule except descending loop of H
- 96-99% filtered Na norm reabsorb
- amount of Na in body is prime determinant of ECF volume
- regulatory mechanisms exist to adjust Na excretion to amount ingested:
  - 1mEq/d low salt diet
  - 400mEq/d high salt diet

Mechanisms

Na excretion = Na filtered - Na reabsorbed
= (GFR x s-[Na]) - Na reabsorbed

- Na excretion depends on control both:
  - GFR
  - Na reabsorption
- In terms of long term Na excretion; Na reabsorbed is more imp than GFR because:
  - GFR autoregulated
  - Glomerulotubular balance:
    - Changes Na reabsorption in response to primary change GFR
    - ie ~ 65% constant
    - intrarenal process
    - blunts changes in Na excretion caused by minor GFR changes
      - don’t confuse with TGF

Control of Na reabsorption (∴ hence Excretion)

1. GTB
2. Aldosterone
3. SNS – direct
4. AT2
5. ANP
6. ADH
7. Intrarenal physical factors
8. Pressure naturessis & diuretics
9. Misc

1. Glomerulotubular Balance (GTB)
   - see prev section on GTB
2. Aldosterone
   - from adrenal cortex zona glomerulosa
   - = most imp controller of Na reasoroption
   - acts on
     - principal cells in cortical CDs (most imp)
     - late DCT
• causes:
  o ↑activity of basolateral NaKATPase ⇒
    ▪ ↑K in cell ⇒ ↑driving gradient for K out of cell into renal tubule
      ← NB K excretion is a function of renal tubular flow (↑flow maintains gradient for
      excretion of K into tubular fluid
    ▪ ↓Na in cell ⇒ ↑driving gradient for Na reabsorption from tubular fluid through ENaC on
      apical membrane
  • works to fine tune remaining 2% of Na which hasn’t already been reabsorbed
    ← last 500mmol if ~26000mmol filtered
  • aldosterone ⇒
    o renal effects:
      ▪ ↑Na reabsorption with ↑K & ↑H secretion
      ▪ ↑Na reabsorp with Cl
    o extra renal:
      ▪ ↑reabsorption from sweat glands, salivary ducts, intestinal mucosa
      ▪ K movement into cells (with adren & insulin) - ↑s activity f 3Na/2K/ATPase
• Control of aldosterone secretion:
  o ↑ed secretion:
    ▪ AT2 – via RAA (most impt)
    ▪ ACTH – high conc = direct effect; low conc = permissive effect
    ▪ ↑Serum K = direct stim effect on Z glomerulosa
    ▪ (↓serum Na – reverse of below)
  o ↓ed secretion:
    ▪ ↑Serum Na = direct inhibition of Z glomerulasa
      ← = minor role; more impt is plasma volume via RAA system
    ▪ dopamine
    ▪ ANP
• hormones take 10-30 mins to act
  ← time for steroids to alter protein synthesis via action on DNA
3. SNS activity
• direct effect via α-1 ⇒
  o ↑reabsorption
  o effect predominant in PCT but also ascending LOH & DCT
4. AT2
• direct effect mainly on PCT
• indirect via:
  o aldosterone ⇒ ↑peritubular cap oncotic pressure
  o efferent art vaso C (high conc) ⇒ ↑FF
     ← indirect methods work via RIHP (see next)
5. ANP
• 28 aa peptide hormone
• from atrial mm in response to stretch
• effects of ANP:
  o intra-renal:
    ▪ mesangial relaxation ⇒ ↑GFR
    ▪ afferent a vasoD & efferent vasoC ↓: ↑FF ie defend GFR
    ▪ direct effect on medullary CD ⇒ ↑excretion
  o extra renal:
    ▪ vasoD or resistance & capacitance vessels
    ▪ ↓response of vaso smooth mm to vasoConstrictors
    ▪ ↓response of Z Glomerulosa to stim for aldosterone release
    ▪ ↓ADH secretion
6. ADH
   • effects:
     o ↑ H2O permeability in CDs
     o direct effect on principal cells to ↑Na reabsorb
     ← synergistic effect enhanced in presence of aldosterone

7. Intrarenal Physical Factors
   • ↑Renal interstitial hydrostatic pressure (RIHP) ⇒ ↓Na reabsorp & vice versa
   • RIHP =
     o Directly proportional to hydrostatic pressure
     o Inv prop to oncotic pressure peritubular capillaries
     o Eg:
       ▪ Volume depletion ⇒ ↓peritubular cap hydro static pressure (↓MAP & reflex ↑SNS renal vasoC) ⇒ ↑Na reabsorb (by ↓ing RIHP)
       ▪ Dehydration without loss protein ⇒ ↑plasma oncotic pressure ⇒ ↓RIHP ⇒ ↑Na reabsop (& ↓GFR)
       ▪ Efferent a vasoC ⇒ ↑GFR & ↑FF. An ↑FF ⇒ ↑oncotic P in peritubular capillaries due to ↑ed proportion of protein free portion plasma filtered ⇒ ↓RIHP
       ← ie ↑peritubular oncotic P can occur even if systemic oncotic pressure normal

8. Pressure Natriuresis & Diuresis
   • = most impt controller of blood volume
   • has infinite gain
   • can control MAP & blood volume precisely back to norm
   • ↑MAP ⇒ ↑Na excretion (ie ↓ed reabsorption) due to:
     o intra-renal:
       ▪ ↑GFR due to ↑GC_Hp (minor effect)
       ▪ ↑renal art pressure ⇒ ↑peritub cap hydrostatic P . . . . ↑RIHP ⇒ ↓Na reabsorb
     o extrarenal ie inhibition of SNS outflow to kidney (baroreflex)
       ▪ ↓RAA
       ▪ ↑ANP secretion in atrium (Bainbridge reflex)
       ▪ ↓ADH secretion (baroreflex & ↓AT2)

Misc
   • Other causes ↑Na reabsorb:
     o Cortisol
     o Oestrogen
     o GH
     o Thyroid hormone
     o Insulin
   • Other cause ↓Na reabsorb:
     o Glucagon
     o Progesterone
     o PTH
     o Renal vasoldilators:
       ▪ PGs
       ▪ kinins

Regulation of K Excretion
   • total body K ~60mmol/L /kg
   • location:
     o 90% ICF
     o 8% bone
     o 2% CF
• 100mmol ingested/day in diet
• excretion:
  o 10mmol out in faeces
  o 90mmol in renal
• K freely filtered & 85-90% reabsorbed under normal circumstances
  \(\Rightarrow\) remainder = excreted
• certain conditions can cause reabsorption or NET secretion
• K handling /location:
  o PCT: (~50% reabsorbed)
    ▪ reabsorbed by **paracellular diffusion**
    ▪ movement driven by:
      • concentration gradient created by water reabsorption
      • lumen +ve potential across late PCT
      • solvent drag (small amount)
    ▪ also secretes K (with descending limb LOH):
      • straight portion of PCT
      • interstitial K comes from passive reabsorption from medullary CDs
        \(\leftarrow\) : K recycled – similar to urea
  o LOH (40% reabsorb):
    ▪ (some secretion in descending as mentioned above)
    ▪ thick ascending limb:
      • passive reabsorb – paracellular 2\(^{nd}\) to lumen +ve potential
      • active reabsorb va Na/K/2Cl co transporter
    ▪ : thick ascending LOH reabsorb 40% filtered (+ whatever secreted into PCT & descending limb)
      \(\leftarrow\) : 10% of filtered left to \(\Rightarrow\) DCT
  o DCT – very little action on K
  o Cortical CDs (CCD)
    ▪ = site of control of overall K excretion
    ▪ differences of NET K movement over physiological range due to movement of K in CCDs
    ▪ cells involved:
      • principal cells actively secrete K into tubule – under aldosterone control
      • intercalated cells type A (less numerous) – actively reabsorb
        \(\leftarrow\) : norm K level = NET secretion. If ↓s-K = NET reabsorb with cessation of secretion
    ▪ movement of K in CCD can be altered by K movement in more prox nephron with use of diuretics

**Control of K secretion by CCDs**
1. serum K conc
2. aldosterone
3. Tubular fluid flow rate & diuretics
4. Acid base changes
• serum K conc:
  o ↑s-K \(\Rightarrow\) ↑ed uptake by basolat Na/K/ATPase (from interstitium) \(\Rightarrow\) ↑intracellular K \(\Rightarrow\) ↑ed gradient for K secretion into tubule
• aldosterone:
  o effects of aldosterone:
    ▪ ↑ K secretion by Principle cells
    ▪ ↑number of basolat Na/K/ATPase pumps & ↑no open K (and Na) channels in lum
    ▪ removed by active reabsorption in prox tubules
    ▪ secreted into fluid by distal tubules
  o aldosterone influenced by RAA system & direct serum k conc
    \(\leftarrow\) RAA exhibits greater control of aldosterone system than s-K
Renal Function

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.serum Na more impt than serum K

- changes in aldosterone secretion due to Na changes can regulate Na with no effect on K cos:
  - amount of K secretion in CCD influenced by rate fluid delivery to these ducts
  - K secretion occurs by passive movement out along gradient into lumen
  - ↓ secretion enhanced by large volume as maintain low lumen conc

- ↓ secretion when flow through CCD low
eg hypovolaemia = high aldosterone but NET K secretion = normal

- tubular fluid flow rate
  - described above with aldosterone
  - diuretics acting on PCT, LOH, DCT ⇒
    - ↑ K secretion
    - 2 mechanisms:
      - inhibition of K reabsorb
      - ↑ flow through CCD by inhibiting reabsorption Na in more prox nephron
    - explains why diuretics in pt with 2nd hyperaldosteronism (congestive heart failure)
      ⇒ ↓↓↓ serum K
      ⇒ aldosterone & ↑ ed fluid through CCDs

- (NB water diuresis with ↓ ADH is not accompanied by ↑ K excretion:
  - ADH direct stim K secretion (luminal channels in P cells)
    ⇒ ↓↑↓ K out via ↑ secretion and ↑ flow thr CCD = norm K excretion)

- Acid base changes
  - Resp & met alkalosis = ↑ secretion K:
    - K movement into cell during alkalosis in exchange for H ⇒ ↑ intracellular K in P cells of CCD ⇒ ↑ ed gradient for excretion
  - Acute resp acidosis (& some met acidosis) = intial ↓ K excretion per same mechanism for alkalosis
    - BUT chronic acidosis ⇒ ↑ ed K secretion by unknown mechanism

Regulation of Water Excretion

- Av adult ingests ~ 2.5L water/day
  - 1.2 litre fluid
  - 1litre food
  - ~350ml metabolic water

- loses:
  - ~900ml insensible – skin & lung
  - ~100ml faeces
  - ~50ml sweat

- kidney need to excrete 1.5litres

- every day body needs to get rid ~700msom wastes (electrolytes, urea, waste):
  - min daily obligatory UO = ~500ml/day @ max conc of 1400mmol/L

- ~180L water filtered/day
- norm 99.4% reabsorb ⇒ ~litre to be excreted
- effect of ADH (on solute load of ~700mosm/day):
  - max = ↑99.7% reabsorb ⇒ 500ml excrete (urine osmolality ~1400mosm/L)
  - no ADH = ~87% reabsorb ⇒ 24L excretion (urine osmolality ~30mosm/L)

- water diuresis after large intake water starts @ 15min, peak at 40min
- water reabsorb mechanism:
By Adam Hollingworth

Renal Function

- Diff in osmolality lumen : interstitial fluid. This created by reabsorption solutes (Na, Cl, glucose, aa)
- Solute reabsorb actively ⇒ ↓luminal osmolality & ↑interstitial osmolality ⇒ gradient to drive water reabsorb across cells +/- tight junctions
- Permeability of cells & tight junctions vary along nephron 2nd to physiological control

Locations of Water Reabsorption

- PCT = 65%
- LOH = 10-15%
- DCT = none
- CD = highly variable

PCT
- 65% filtered Na & water here
- Water permeability large
- Passive water movement following Na
- Osmolality (& Na conc) of PCT fluid remain ~ same plasma
- Osmotic diuresis ⇒
  - Norm process = active reabsorb Na ⇒ ↓osmolality of tubule fluid ⇒ ↑water reabsorb
  - But osmotic diuretic not able to be reabsorbed . ⇒ see ↑in its conc in tubule
  - ∴ Oncotic load in tubule ⇒ ↓water reabsorb ⇒ ↓ing Na conc in tubule fluid below that of plasma
  - ↓ing Na conc in tubule fluid ⇒ gradient favouring flow of Na back into tubule fluid (passive paracellular diffusion)
  - In contrast to active transcellular Na reabsorb
  - ∴ NET movement of Na out of tubule fluid is ↓ed
- Total effect is excretion large quantity of NaCl & even more quantity of water

LOH
- 25% filtered Nacl reabsorb
- 10-15% water reabsorb
- Descending = reabsorb water NOT NaCl
- Ascending = reabsorb NaCl NOT water
- Delivers hypotonic fluid to DCT
- Tubular fluid osmolality and conc of Na & Cl = < plasma
- But difference is less for osmolality due to addition of urea to tubule fluid

DCT
- Hypotonic fluid enters containing % filtered:
  - 10% NaCl
  - 20% filtered water
- Impermeable to water
- Further reabsorp of Na occurs ⇒ ↑ing hypotonicity of fluid

Collecting Ducts
- Permeability subjected to physiological control ie low to very high depending on ADH
- If permeability is high ie high ADH:
  - CDs reabsorb so much water that luminal fluid equilibrates with plasma capillaries (~300mosm/L)
  - Post equilibration CDs behave similar to PCT ie reabsorb equal solute & water
  - Cortical CDs reabsorb > water than medullary CDs
- Helps to preserve high medullary interstitial fluid osmolality
- Vasa recta carry water away
- If permeability is low:
Water Intoxication

- 16ml/min max urine flow in water diuresis
- intake of water > this for prolonged time ⇒ swelling of cells by uptake of water from hypotonic ECF severe
- in extreme swelling of brain ⇒ convulsions ⇒ coma
- also see water intoxication:
  - no ↓ water intake after exogenous vasopressin
  - endogenous vasopressin secretion to non osmotic stim eg surgery (SIADH)

Loop Of Henle

Main Role LOH

- creating high interstitial osmolality in medulla
  (also inner medullary CD – urea diffusing out)
- high interstitial osmolality essential for concentrated urine if needed:
  - initial filtrate = same osmolality as plasma = 300mosmol/kg
  - max urine osmolality = 1400mosmol/kg
- in presence of ADH ⇒ ↑ water reabsorption via CDs due to high medullary interstitial osmolality

Thin Descending Limb

- 15% filtered water removed in descending limb
 ↩️ 20% filtered water remains and is presented to distal tubule
- descending limb of loop is permeable to water (aquaporin 1)

Ascending Limb LOH

- whole ascending limb impermeable to water
- thin ascending:
  - Na & Cl move out by passive diffusion – equilibrate with interstitium
- Thick ascending:
  - Na, Cl, K actively reabsorbed from tubular fluid by Na-K-2Cl cotransporter
    - called diluting segment – ↑ed conc of water : to solute in tubular fluid
    - Removal of Na, Cl, K from tubular fluid and redistribution into interstitium ⇒ ↑gradient for movement of water out of permeable descending limb into hypertonic interstitium
    - ⇒ hypertonic descending limb
    - Na-K-2Cl contransporter = prime cause for high interstitial osmolality
      (aided by diffusion of urea from inner medullary CDs)
  - Na also move by paracellular diffusion
    - Down electrochem gradient
    - sig reabsorption seen due to:
      - +ve elc potential in lumen
      - high Na paracellular permeability
- ️ @top of ascending limb tubular fluid now hypotonic to plasma
Distal Tubule
- relatively impermeable to water
- continued removal of solute > water ⇒ further dilution and hypotonicity

Collecting Ducts
- ducts have 2 portions:
  - cortical portion
  - medullary portion
- change in volume & osmolality in ducts depends on vasopressin ⇒ ↑permeability
- aquaporin 2 – stored in vesicles in cytoplasm of principal cells
- vasopressin acts on Vasopressin V2 receptor (cAMP, protein kinase A) ⇒ rapid insertion of vesicles into apical membranes of cells:
  - water move out of hypotonic tubular fluid into
    - cortical collecting ducts (10% filtered water) ⇒
    - medullary collecting ducts (5% filtered water)
- without vasopressin:
  - collecting duct mostly impermeable to water
    - about 2% filtered water can be reabsorbed without
  - tubular fluid remains hypotonic ⇒ large amount fluid into renal pevis
- with vasopressin max urine osmolality = 1400 ie x 5 that of plasma (99.7% of water reabsorb)
- without vasopressin max 13% filtered water excreted with UO 15ml/min

Channels:
- Na-K-2Cl into cell via 2nd active transport
- NaK ATPase into interstitium
- Cl into interstitium – needs Barttin protein in cell membrane
- K in and out via ROMK and other K channels
Medullary Interstitial Fluid Osmolality

Step 1 (B):
- Active transport of NaCl from thick ascending ⇒ interstitium ⇒
  - ↑osmolality interstitium
  - Diluting fluid in tubular lumen
- ↑ed interstitial osmolality cause:
  - Water move out of descending limb ⇒ osmotic equilibrium between interstitium & lumen
  - Descending limb = eg 400
- NB Water reabsorption in descending limb is linked to NaCl reabsorption in ascending limb but they are separate processes ie if no flow or snapshot then I & DL = 400, AL = 200

Step 2 (C) = flow start
- Isoosmotic filtrate delivered to start of descending limb
- Tubular fluid becomes concentrated along descending limb and moves around hairpin into ascending limb

Step (D) = stop flow
- NaCl pumped out of ascending limb
  - More NaCl pumped out at bottom due to higher conc than at top of limb

Step E⇒H = repetition
- See ↑ing concentrations of interstitium & tubular fluid @inner medulla (bottom of LOH) due to:
  - ↑ing gradient of conc from cortex ⇒ inner medulla
  - Process of B ⇒ D repeated
  - Water leaves upper descending limb to dilute interstitium but as fluid gets more conc descending down, less water water leaves tubular fluid
- At some point interstitium reach its max osmolality:
  - This defined by level at which NaCl with diffuse back (paracellular) into ascending limb
CounterCurrent Multiplier Mechanism Summary

• = mechanism where concentration effect in the medullary interstitium is multiplied by counter-current flow of tubular fluid within 2 limbs of the LOH
  ⟷ only occurs in juxtamedullary nephrons

• gradient:
  o produced by loops of Henle as countercurrent multipliers
  o maintained by vasa recta – countercurrent exchangers

• loop of H multiplier depends on:
  o Thick ALH:
    ▪ impermeable to water BUT relative permeable to NaCl
    ▪ active transport of Na & Cl out of lumen into cell
    ▪ limiting factor for osmolality across epithelium (~200mosm/kg) = passive paracellular back flux into lumen of Na
  o thin ALH:
    ▪ also reabsorbs Na & Cl
    ▪ done by ion movement (not active transport) – may involve urea
  o DLH:
    ▪ Driving force for movement of water out of DLH is NaCl reabsorption in ALH
    ▪ Interstitium & DLH equilibrate osmolality due to high permeability of water
    ⟷ ALH continues to reabsorb NaCl ↓. ⇒ ~200 lower osmolality than corresponding DLH/Interstitium
    ▪ Tubular fluid is concentrated as moves down DLH due to water diffusion out tubule
    ▪ Interstitium relatively becomes ↑conc as move down as less water to move out of tubule
  o Thin ALH:
    ▪ NaCl start to passes out of tube along conc gradient
    ▪ NET movement of NaCl decreases as rise up ALH ie as conc gradient decreases along diluting segment
  o Osmolality:
    ▪ Max interstitial osmolality @hairpin (inner medulla) = 1400mosm/kg
    ▪ Min @start of DCT - ~100mosm/kg = hypo-osmotic
  o Gradient:
    ▪ 200 mosm/kg gradient is maintained across ascending limb at any horizontal level by active transport
    ▪ this gradient multiplied by counter-current flow in loop
  o steady state situation:
    ▪ NaCl entering medullary interstitium from ALH AND
    ▪ Water entering medullary interstitium from DLH
    ⟷ both taken away by peritubular capillaries as result of Starlings forces

  • juxtamedullary nephrons have gradient spread over longer distance:
    o longer loops
    o thin ascending limbs
    o osmolality at apex greater
Counter-Current Exchange of Vasa Recta

- counter-current exchange of ons & water in hairpin loops of vasa rectae
- does not include bulk flow of medullary interstitial fluid into capillaries due to norm Starling Forces
- vessels closely assoc with LOH:
  - descending vessels into medulla:
    - water – lost from vessels (diffuse out)
    - NaCl – absorbed into vessels (diffuse in)
    - @ tip of LOH osmolality ~1200mosm/kg
  - ascending vessels out of medulla (process reversed):
    - water – absorbed
    - NaCl – lost
    - @ end of vasa recta fluid leaving ~320mosm/kg
- process of movement of water & NaCl is passive diffusion
- vasa rectae have slow/sluggish blood flow
- recirculation of water & solutes prevents osmotic gradient in medullar from being washed out
  - allow Na & urea to remain in interstitial spaces
  - maintenance of hypertonicity at base/apex LOH

Role of Urea

- reabsorbed loop of Henle
- urea contributes to
  - ~50% of medullary osmolality due to urea
    - ↓: impt in determining max osmolality of urine
    - ↑: concentrating ability of urine
- cortical & outer medullary sections of CDs
  - impermeable to urea
  - water is reabsorbed from these segments ⇒ ↑luminal urea conc
- high conc of urea in prox CD ⇒ ↑ed diffusion out of CD lumen in inner medullary CD
  - diffusion out further ↑ed by ADH
- in urea diffusion area: ↑ed diffusion out of urea ⇒ ↑ed movement out of lumen. ↓: interstitial urea conc remains high
  - Nb urea & water movement indep of each other but balance each other

- urea conc of inner medullary interstitial fluid equilibrates with urea conc in CD
  - ↓: the NaCl in the interstitium need only balance the tubular solutes other than urea
- urea transporters move urea by facilitated diffusion
- amount of urea in interstitium varies with urine filtered which depends on diet input
• while making conc urine:

<table>
<thead>
<tr>
<th>Interstitial fluid @ tip of inner medulla</th>
<th>urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea 650</td>
<td>urea 700</td>
</tr>
<tr>
<td>Na+Cl 750</td>
<td>non-urea solutes 700</td>
</tr>
<tr>
<td>(Na,Cl,K,urate, creatinine etc)</td>
<td></td>
</tr>
</tbody>
</table>

• amount of urea in medullary interstitium & urine varies with amount filtered into lumen

\[ \downarrow \text{depends on dietary protein intake} \]

\[ \downarrow \text{ie high protein diet } \uparrow \text{ ability of kidneys to conc urine} \]

### Osmotic Diuresis

• osmotic diuresis = large amount of unreabsorbed solute in renal tubules \[ \Rightarrow \uparrow \text{urine volume} \]

• solute not reabsorbed in prox tubule \[ : \Rightarrow : \]
  - hold water in tubule
  - \[ \downarrow \text{conc gradient to facilitate Na pumped out of prox tubule} \text{(NHE)}: \]
    - Na conc falls when water reabsorption \[ \downarrow \text{ed} \] as more dilute fluid in tubule
    - Limiting conc gradient is reached & further prox Na reabsorption is prevented \[ \Rightarrow \text{more Na in tubule fluid} \Rightarrow \text{more water stays with it} \]
    - \[ \downarrow \text{loop of Henle presented with } \uparrow \text{volume of isotonic fluid:} \]
      - \[ \downarrow \text{ed Na conc, } \uparrow \text{ed amount of Na/time} \]
    - \[ \downarrow \text{medullary hypertonicity} \Rightarrow \downarrow \text{reabsorption of Na & water} \]
      - \[ \downarrow \text{because limiting conc gradient for Na reabsorption is reached} \Rightarrow \downarrow \text{Na, K, Cl reabsorption from ascending LH} \]
    - \[ \uparrow \text{fluid through distal tubule but } \downarrow \text{osmotic gradient through medullary pyramids} \Rightarrow \downarrow \text{less water reabsorbed in collecting ducts} \]
    - \[ \downarrow \Rightarrow \text{overall } \uparrow \text{urine volume & } \uparrow \text{excretion of Na} \]

• process can be initiated by substance that
  - are filtered but not reabsorbed eg mannitol
  - substance which exceeds reabsorption capacity of tubules eg glucose

• DM:
  - High BSL \[ \Rightarrow \text{glucose in filtrate high } \Rightarrow \text{exceed TmG} \Rightarrow \text{glucose remain in tubules} \]

• Difference between osmotic diuresis & water diuresis:
  - Water:
    - Amount water reabsorbed in prox nephron = normal
    - Max urine flow 16ml/min
  - Osmotic:
    - \[ \uparrow \text{ed urine flow from } \downarrow \text{ed water reabsorb in prox nephron} \Rightarrow \uparrow \uparrow \uparrow \text{urine volume} \]
    - as load of excreted solute \[ \uparrow \text{s conc of urine closes in on that of plasma} \]
      - \[ \downarrow \text{despite max vasopressin secretion} \]
Relation of Urine Conc to GFR

- size of osmotic gradient along medullary pyramids ↑ed when rate of flow through loop of Henle ↓ed
- dehydration ⇒ ↓GFR ⇒ ↓volume fluid into countercurrent system ⇒ ↓flow rate in loop ⇒ ↑urine conc
- when GFR is low urine can become concentrated even without vasopressin
- if no vasopressin & 1 constricted renal art:
  - constricted side ⇒ ↓GFR ⇒ hypertonic urine
  - non constricted ⇒ norm GFR ⇒ hypotonic urine

Free Water Clearance

- gain or loss of water by excretion of a concentrated or dilute urine
- free water clearance

\[ \text{CH}_{20} = \frac{V - \text{Uosm}}{\text{Posm}} \]

- CH20 = -ve when urine is hypertonic; +ve when hypotonic
- Max ADH CH20 = -1.3ml/min
- No ADH 14.5ml/min

Important Facts About Urine Concentration

- max conc urine
  - = 1400mosm/kg
  - may contain no Na ie solute may be urea, creatinine, urate, K etc
  - may be no NaCl in urine but NaCl remains the most imp solute in medullary interstitium in creating conc urine (draws water out of CDs)
- excretion of large amounts of Na always ⇒ excretion large amount of water
- excretion of large amounts of water can occur with no excretion of Na:
  - ↓ due to ↓ADH ⇒ ↑water excretion with no change in Na transport

Diuretics

- water ⇒ ↓vasopressin
- alcohol ⇒ ↓vasopressin
- large amount of osmotically active substance ⇒ osmotic diuresis
- xanthines eg caffeine ⇒
  - ↓reabsorption of Na
  - ↑GFR
- carbonic anyhydrase inhibitors (diamox) ⇒ ↓H secretion ⇒ ↑Na & K excretion
- thiazides ⇒ inhibit Na-Cl cotransported in early portion of distal tubule ⇒ ↑Na & Cl loss
- loops ⇒ inhibit Na-K-2Cl cotransporter in thick ascending loop of H
- K sparing diuretics (spiro) ⇒ inhibit Na-K exchange in collecting ducts by:
  - Inhibiting action of aldosterone
Effects of Disordered Renal Function

- Frequent findings in renal disease:
  - Protein, leucos, red cells & casts in urine
  - Loss of conc ability of urine
  - Uraemia
  - Acidosis
  - Abnormal retention of Na

Loss of Concentrating & Diluting Ability

- In renal disease often ↓conc ↑volume ⇒ polyuria
- Early disease – lose concentrating ability
- Advanced disease – lose conc & dilute ability ⇒ osmolality of urine fixed at plasma level
  - caused by
    - disruption of countercurrent mechanism
    - loss of functioning nephrons ∴ remaining ones must:
      - excrete more osmotically active substances ⇒ osmotic diuresis effect
        - normal for osmolality of plasma & urine equal
      - ↑filtration ⇒ progressive damage in prox tubule cells ⇒ +ve feedback cycle
- eventually oliguria or even anuria

Uraemia

- = breakdown products of protein metab accumulate in plasma
- symptoms lethargy, anorexia, N&V, confusion, muscle twitch, seizure, coma
- signs:
  - anaemia 2nd to ↓EPO
  - 2nd hyperparathyroidism 2nd to ↓active Vit D
- plasma urea & creat high
  - although symptoms from ↑ing organic acids & phenols

Acidosis

- common in chronic renal failure – unable to excrete acid products of metabolism
  - urine max acidified; acidosis because ↓ed renal tubular production NH4 ⇒ ↓secretion H
- renal tubular acidosis = specific unable to acidfy urine

Abnormal Na Handling

- CRF: retain Na ⇒ oedema
- 3 causes of Na retention in renal failure:
  - acute GN: ↓amount of Na filtered
  - nephrotic syndrome: low plasma protein ⇒ ↑ECF ⇒ ↑aldosterone secretion ⇒ ↑Na retention
  - heart failure
Renal Clearance

- renal clearance = clearance of a substance is volume of plasma cleared from it by the kidneys/unit time

\[
Cl_k = \frac{\text{rate of elimination}}{\text{Plasma [ ]},} = \frac{[ ]_{k} \cdot UO}{\text{plasma [ ]},}
\]

The Bladder

Filling

- ureter walls have smooth mm – spiral, longitudinal, circular bundle
  - no distinct mm layers
- peristaltic contractions 1-5x/min
- ureters pass obliquely through bladder wall which keeps ureters closed inbetween peristalsis

Emptying

- smooth mm arranged
  - spiral,
  - long
  - circular = detrusor mm
    - contraction of this mm \(\Rightarrow\) bladder emptying
- internal urethral sphincter:
  - mm fibres pass either side of urethra
  - not a formal sphincter
- external urethral sphincter:
  - true sphincter of skeletal mm
- bladder epithelium made of superficial flat cells, & deep cuboidal cells
- micturation =
  - spinal reflex facilitated & inhibited by higher brain centres
    - gives voluntary control
  - perineal & external mm relax
  - detrusor contracts
  - int urethral sphincter serves to prevent retrograde ejaculation only
  - how voluntary urination initiated
- post micturation:
  - female urethra empties by gravity
  - male expelled by contractions of bulbocavernosus mm
- delay of micturation = learned ability to maintain ext urethral sphincter tone
- bladder filling \(\Rightarrow\) no initial rise in pressure
- degree of plasticity to bladder lining ie tension not maintained on prolonged stretch
- cystometrogram = pressure vs volume in bladder :
  - initial \(\uparrow\)pressure (Ia)
    - long flat segment (Ib) \(–\) law of lapace ie pressure in sphere = 2x wall tension/radius
    - \(\uparrow\)as \(\uparrow\)tension, radius also \(\uparrow\)s :: minimising \(\uparrow\)in pressure
  - sudden \(\uparrow\)pressure when micturation begins (II)
- urge to void 1st felt \(\sim\)150ml; fullness \(\sim\)400ml
**Reflex Control**

- bladder smooth mm has inherent contractile activity
  - threshold for this activity is higher than stretch receptor reflex from bladder wall
  - needs intact nerve supply
- nerves:
  - afferent = pelvic nerves
  - efferent = parasympathetic
- reflex in sacral portion of spinal cord
- 300-400ml ⇒ reflex contraction
- sympathetic nerves no function in peeing
  - in males prevent retrograde ejac
- higher centre mediation of reflex:
  - facilitatory - pontine region & post hypothalamus
  - midbrain – inhibitory
- able to voluntary initiate spinal reflex to start pee even if bladder empty

**Micturition**

- inhibit:
  - anticholinergics
  - sympathomimetics (flow)
- enhance:
  - cholinergics
  - alpha blockers (flow)

**Effects of Deafferentation**

- abolish dorsal sacral roots (no afferent nerves) ⇒
  - no reflex contraction of bladder
  - becomes:
    - thin walled
    - hypotonic
  - some contractions remains – intrinsic response to smooth mm stretch

**Effects of Denervation**

- both afferent & efferent nerve destroyed
- bladder flaccid & distended initially
- then mm of decentralised bladder becomes active ⇒ many contraction waves ⇒ frequent dribbling
- bladder shrinks & hypertrophied
  - hypertrophic vs hypotonic cause not known

**Effects Spinal Cord Transection**

- during spinal shock:
  - bladder flaccid & unresponsive
  - will overfill ⇒ urine dribbling through sphincter
- post spinal shock:
  - voiding reflex returns but no voluntary control or higher centre mediation
- some paraplegics train self to initiate voiding by stroking thighs ie mild mass reflex
- spastic neurogenic bladder:
  - some instances
  - voiding reflex hyperactive
  - ↓volume
  - hypertrophied