D. Renal physiology

a. Describe the functional anatomy of the kidneys and explain the physiology of renal blood flow.

The kidneys are paired organs located in the retroperitoneum. Each consists of a cortex, medulla and pelvis which is connected to the ureter which carries urine from the kidney to the bladder. Each kidneys is supplied by a renal artery from the aorta and drained by one or more renal veins to the IVC. The medulla consists of papillae which correspond with the calyces of the collecting system. The medulla and cortex above each papilla composes a lobe.

Innervation of the kidney is by sympathetic noradrenergic nerves.

The renal artery divides into interlobar and then arcuate arteries. These divide into cortical radial arteries which run radially towards the cortical surface. Perpendicular to the cortical radial arteries arise the afferent arterioles, each of which supplies a glomerulus. The afferent arteriole is muscular and regulates flow into the glomerulus.

The glomerulus consists of a group of specialized capillaries, having fenestrated endothelium, a narrow basement membrane and a surrounding of podocytes, all of which allow filtration of fluid into the space surrounding the capillary tuft: Bowman’s space.

The glomerulus is drained by the efferent arteriole which plays a regulatory role like the afferent arteriole. It supplies the peritubular capillaries which surround the cortical tubules and also vascular bundles which extend into the medulla and surround the loops of Henle (the descending and ascending vasa recta).

Total renal blood flow (RBF) is 1.1 l/min (20% of CO)

RBF
determined by MAP and renal vascular resistance
autoregulating over a wide MAP (90 to 200 mmHg)
myogenic mechanism
tubuloglomerular feedback
high Na⁺ and Cl⁻ at macula densa stimulates adenosine production
↓ by constriction of either afferent or efferent arteriole
sympathetic tone (noradrenaline)
angiotensin II
response to macula densa or direct effect of flow on granular cells or sympathetic stimulation of granular cells to increase renin secretion from granular cells
adenosine
local mediator from JGA
afferent constrictor, efferent dilator
ADH in high concentrations
possibly thromboxanes, leukotrienes, endothelin
opposed by
renal PGE₂ and PGI₂ release
ANF from heart (afferent dilator, efferent constrictor)
possibly dopamine, bradykinin
90% to cortex, 10% to medulla

b. Describe glomerular filtration and tubular function.

Glomerular filtration
bulk flow of fluid from glomerular capillary to Bowman’s space
volume = 20% of RPF (filtration fraction), ≈ 125 ml/min
barriers to filtration
endothelial fenestrae
basement membrane
podocytes
all negatively charged
composition
water
freely filtered solutes
small, unbound ions and molecules
partly filtered solutes
macromolecules MW 7000 to 70000
less filtration if negatively charged
dextran 70 5-10%, albumin 0.02%
GFR = \( K_f \cdot NFP \) (filtration coefficient x net filtration pressure)
\[ NFP = (P_{GC} + \Pi_{BC}) - (P_{BC} + \Pi_{GC}) \]
in capillary transit
\( \Pi_{BC} = 0 \), \( P_{GC} \) and \( P_{BC} \) change little, \( \Pi_{GC} \) rises from 21 to 33 mmHg
NFP falls from 24 to 10 mmHg
determinants
\( K_f \)
decreased in disease (↓ glomerular surface area)
\( P_{GC} \)
↑ MAP, efferent constriction
↓ afferent constriction
\( P_{BC} \)
↑ obstruction
\( \Pi_{GC} \)
↑ plasma oncotic pressure, low RBF
Tubular functions
mechanisms
diffusion
simple transfer of a substance across the tubular epithelium down its electrochemical gradient
small lipid-soluble molecules diffuse through membranes
ions diffuse through channels
facilitated diffusion
transfer of molecules across the tubular epithelium down a electrochemical gradient via specific transmembrane proteins which bind and release the substrate
displays saturability, specificity and competition
primary active transport
transfer of ions or molecules against their electrochemical gradient via a specific transmembrane protein which consumes ATP
four identified transporters: \( \text{Na}^+ - \text{K}^+ \), \( \text{H}^+ \), \( \text{H}^- - \text{K}^+ \) and \( \text{Ca}^{2+} \)-ATPase
secondary active transport
transfer of multiple ions or molecules across a membrane by a specific transmembrane protein in which one substrate is transported down its electrochemical gradient, providing energy for the transport of the other substrates against their electrochemical gradients
classified as cotransport or countertransport according to whether substrates travel in the same or opposite directions
endocytosis
uptake of large molecules by invagination of the cell membrane, forming vesicles
solvent drag
transfer of small ions or molecules by mass movement of water (solvent) through pores
sites of transport
basolateral membrane
the only site of primary active transport
luminal membrane
site of diffusion, facilitated diffusion and secondary active transport
paracellular
diffusion across tight junctions between cells
site of Na⁺ and Cl⁻ diffusion in parts of the tubule

c. Explain the countercurrent mechanisms in the kidney.

The loop of Henle maintains a high tissue osmolarity in the renal medulla, allowing for reabsorption of water and the production of a concentrated urine. It uses a countercurrent multiplier.

loop of Henle
descending limb
high permeability to water
low permeability to Na⁺ and Cl⁻
water reabsorption due to high tissue osmolarity secondary to NaCl reabsorption in ascending limb

ascending limb
low permeability to water
high permeability to Na⁺ and Cl⁻
active reabsorption of NaCl in thick limb and passive in thin limb
a small gradient across the tubule is multiplied by the flow through the loop to produce a high tissue osmolarity in the medulla and a hypoosmotic tubular fluid at the distal end of the loop

vasa recta
medullary blood vessels travel parallel to the loop of Henle
start in cortex, run straight to medulla and return to cortex
this allows for countercurrent exchange to produce a high plasma osmolarity in the medullary part of the vasa recta and a return close to normal on returning to the cortex
there is an overall increase in osmolarity of plasma in the vasa recta due to reabsorption of NaCl (and urea)

collecting ducts
run from cortex to medulla
variable permeability to water
increased by ADH
receive hypotonic or isotonic fluid
actively reabsorb NaCl in the cortex according to ADH and aldosterone levels
passively reabsorb water (and urea) from the medullary collecting duct due to the high tissue osmolarity (maintained by the ascending loop)

d. Explain the mechanisms involved in the regulation of renal function.
local autoregulation
constriction of afferent arterioles maintains constant RBF for MAP 80-200 mmHg
  myogenic mechanism
tubuloglomerular feedback
  ↑ GFR
  ↑ NaCl concentration at end of loop
  ↑ NaCl uptake by macula densa
  release of adenosine
  afferent constriction, efferent dilation
  ↓ GFR and RBF
glomerulotubular balance
  reabsorption of Na⁺ is a roughly constant proportion of GFR
  ↑ GFR → ↑ reabsorption of Na⁺ and water in PCT
  tends to stabilize tubular flow over changes in GFR
neurological sympathetic
  response to hypotension (baroreceptor), hypoxia, acidosis or stress
  noradrenergic sympathetic innervation (and circulating adrenaline)
  β₁ adrenergic response of granular cells
  ↑ renin release
  α₁ adrenergic response in PCT
  ↑ Na⁺ reabsorption
  α adrenergic vasoconstrictor response in afferent and efferent arterioles
  ↓ RBF, GFR
endocrine renin
  enzyme cleaved from prorenin in granular cells
  released controlled by
  afferent arteriolar baroreceptors (hypotension)
  macula densa (↓ NaCl uptake)
  sympathetic response
  angiotensin II, ANF (inhibition)
cleaves circulating angiotensinogen to angiotensin I
angiotensin II
  octapeptide cleaved by ACE from angiotensin I
  acts at AT₁ and AT₂ receptors
  vasoconstrictor of renal and other arterioles
  efferent > afferent constriction (↑ Kᵢ)
  increases release of aldosterone and ADH
  directly increases Na⁺ reabsorption
  increases sympathetic activity
  increases thirst
prostaglandins PGE₂ and PGI₂
  synthesized and released in response to
  sympathetic activity
  angiotensin II
  vasodilators limiting the local action of vasoconstrictors
ANF
  peptide hormone
  released from atrial cardiac muscle in response to dilation
  actions (via cGMP)
  ↓ Na⁺ reabsorption in collecting ducts
  afferent vasodilator, efferent vasoconstrictor in kidney (↑ GFR)
  increases plasma filtration as lymph in spleen
aldosterone, renin, ADH release

aldosterone
steroid hormone produced by zona glomerulosa of the adrenal cortex
released in response to
ACTH
↑ plasma K+
angiotensin II
inhibited by ANF
acts on collecting ducts
↑ Na+ reabsorption
↓ K+ reabsorption
↑ H+ secretion
also acts on all other sites of Na+ transport (sweat, gut etc.)

ADH
peptide hormone synthesized in supraoptic and paraventricular nuclei
released from posterior pituitary neurones in response to
hypotension (7-10% volume change → low pressure baroreceptors)
↑ osmolarity (change of 1-2%)
overcome by volume effect
angiotensin II
sympathetic activity, stress
drugs (chlorpropamide, barbiturates)
actions
V1
vasoconstrictor acting on smooth muscle
V2
↓ collecting duct permeability to water (via ↑ cAMP)
results in insertion of aquaporin 2 in membrane
↑ release of VIIIc and vWF
other vasoactive agents at the kidney (role uncertain)
TXA2, leukotrienes, endothelin, dopamine, bradykinin, many others

e. Outline the endocrine functions of the kidney.

Functions of the kidney
regulation of water and ion balance
removal and excretion of metabolic waste products from the blood
removal and excretion of foreign chemicals from the blood
gluconeogenesis
endocrine functions
renin secretion
from granular cells of the JGA
converts circulating angiotensinogen to angiotensin I
rate limiting step in production of angiotensin II
erythropoietin secretion
glycoprotein hormone (168 amino-acids, 4 sugar residues)
produced in interstitial renal cells
t1/2 5 h
release stimulated by renal hypoxaemia or hypoperfusion
stimulates maturation of erythroid precursors in bone marrow
1,25-dihydroxyvitamin D production
produced by 1-hydroxylation of 25-hydroxyvitamin D
produced in proximal tubule cells
synthesis stimulated by PTH
rate-limiting step in production of active 1,25-(OH)2D3
acts to increase plasma Ca2+
f. Describe the role of the kidneys in the maintenance of acid-base balance.

H⁺ ion regulation

increased by
- gain in CO₂ from metabolism
- non-volatile acids from metabolism of protein and other molecules
- loss of HCO₃⁻ in GIT fluid or urine

decreased by
- loss of CO₂ in lungs
- metabolism of organic anions (e.g. lactate)
- loss of H⁺ in GIT fluid or urine

normal concentration of H⁺ flux is diet: high protein → acid load

H⁺ concentration (pH) is controlled by buffering
- intracellular phosphate and proteins (greatest capacity)
- extracellular HCO₃⁻/CO₂ (precise control)
  - PCO₂ controlled by respiratory system
  - HCO₃⁻ regulated by kidneys

\[ \text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2} \]

mechanism

HCO₃⁻ filtered at glomerulus
- actively reabsorbed in PCT (80%), ascending loop (15%) and collecting ducts
- type A intercalated cells secrete H⁺ into lumen
  - active H⁺ ATPase pump in luminal membrane
  - Na⁺/H⁺ countertransport in PCT and loop
  - H⁺,K⁺ ATPase in collecting ducts
- produce HCO₃⁻ from CO₂ and OH⁻ via carbonic anhydrase
- HCO₃⁻ moves into blood via Na⁺ cotransport or Cl⁻ countertransport
- luminal H⁺ combines with HCO₃⁻ to form CO₂ which diffuses into cells
- H⁺ secretion is increased by high PCO₂ and low pH independently

minimal active HCO₃⁻ secretion by type B intercalated cells in collecting ducts
- increased in alkalosis (?mechanism ?importance)

some secreted H⁺ in collecting ducts is lost in urine, causing net addition of HCO₃⁻ to blood
- H⁺ combines with HPO₄²⁻ and may be excreted in urine
- 75% of HPO₄²⁻ is reabsorbed
- other anions and buffers also contribute to H⁺ loss
  - e.g. ß-hydroxybutyrate or acetoacetate in DKA
- bound H⁺ excreted in this way is “titratable acid”

glutamine is catabolized in PCT
- glutamine → 2 NH₄⁺ + 2 HCO₃⁻
- with secretion of NH₄⁺ into lumen and HCO₃⁻ into blood
- NH₄⁺ mostly ends up being excreted in urine
- catabolism increased in acidosis
- reabsorption reduced in acidosis
compensation for acid-base disorders

respiratory

acidosis

- high CO₂ and low pH
- ↑ NH₄⁺ secretion
- full HCO₃⁻ reabsorption (increased H⁺ secretion)
- ↑ titratable acid

alkalosis

- low CO₂ and high pH
- ↓ NH₄⁺ secretion
- ↓ H⁺ secretion causes HCO₃⁻ loss
- no titratable acid
- (↑ HCO₃⁻ secretion)

metabolic

acidosis

- low pH and low CO₂ (low HCO₃⁻)
- ↓ filtered load of HCO₃⁻
- full HCO₃⁻ reabsorption despite ↓ H⁺ secretion
- ↑ NH₄⁺ secretion
- ↑ titratable acid

alkalosis

- high pH and high CO₂ (high HCO₃⁻)
- ↑ filtered load of HCO₃⁻
- HCO₃⁻ loss despite ↑ H⁺ secretion
- ↓ NH₄⁺ secretion
- (↑ HCO₃⁻ secretion)

generation of acid-base disorders

hypovolaemia

- ↑ aldosterone
  - Na⁺ retention, K⁺ and H⁺ loss

metabolic alkalosis

Cl⁻ depletion

- ↓ HCO₃⁻ secretion, ↑ H⁺ secretion

metabolic alkalosis

K⁺ depletion

- ↑ NH₄⁺ secretion, H⁺ secretion

metabolic alkalosis

these factors combine in

diuretic use: volume depletion and K⁺ depletion
prolonged vomiting: alkalosis, volume depletion, Cl⁻ and K⁺ depletion

g. Describe the role of the kidneys in the maintenance of fluid and electrolyte balance.

normal flux

water

- intake
  - drink 1.2 l, food 1.0 l, metabolism 350 ml
- output
  - insensible 0.9 l, sweat ≥50 ml, faeces 100 ml, urine 1.5 l

NaCl

- small obligatory loss in sweat and faeces

urine balances the remainder of dietary intake

both freely filtered, reabsorbed

- water by osmotic pressure from solute reabsorption
- Na⁺ by active transport
Cl mainly passive

PCT
reabsorbs 65% of NaCl and water independent of GFR (isoosmotic)
Na⁺ reabsorbed in cotransport with glucose etc., countertransport with H⁺
NaCl reabsorbed in coupled organic base transporter
isotonic filtrate

loop
passive water reabsorption
active NaCl reabsorption (Na⁺, K⁺, 2Cl⁻ cotransport, Na⁺/H⁺ countertransport)
produces hypotonic filtrate (80-100 mOsm/l)
25% of Na⁺ reabsorbed

DCT
impermeable to water
active NaCl reabsorption (cotransporter) 5% reabsorbed
reduces osmolarity

collecting ducts
variable water permeability (according to ADH)
controls free water loss
active Na⁺ reabsorption by principal cells (according to aldosterone)
active Cl⁻ reabsorption by B intercalated cells (with HCO₃⁻ secretion)

control
Na⁺ content determines ECF volume and systemic filling pressure
ANF release
blood pressure
baroreceptor response
sympathetic tone, renin, AT II, aldosterone, ADH
pressure natriuresis

pathology
cardiac failure
low BP, GFR
↑ renin, AT II, aldosterone, ADH
inappropriate Na⁺, water retention
opposed by ANF

nephrotic syndrome
↑ protein filtration, loss in urine
↓ oncotic pressure, loss of plasma volume to interstitium
intravascular depletion
Na⁺, water retention despite expanded ECF volume

primary hyperaldosteronism
initial Na⁺ retention
↑ BP, GFR, ANF
return to Na⁺ balance at higher ECF volume

potassium balance
98% intracellular, buffers changes in ECF concentration
movement into ICF
↑ by insulin, adrenaline, alkalosis

PCT
freely filtered, 55% reabsorbed in PCT (diffusion)

loop
active reabsorption in Na⁺, K⁺, 2Cl⁻ cotransporter
diffusion due to transtubular potential
30% reabsorbed

DCT, cortical collecting duct
reabsorption by H⁺/K⁺ countertransport in type A intercalated cells
secretion by principal cells with Na⁺ reabsorption
↑ by aldosterone, plasma [K⁺], fluid delivery to duct
some ↑ with ADH (opposed by ↓ flow)

pathology
alkalosis
↑ intracellular K⁺
↑ K⁺ loss from collecting ducts
K⁺ depletion

calcium balance
turnover 0.1-0.2 mmol/kg/day
free fraction filtered (45%)
  40% protein bound
  15% complexed with organic anions
PCT and loop
passive reabsorption >60% of filtered load
dependent on Na⁺ reabsorption
↑ Na⁺ loss causes ↑ Ca²⁺ loss
DCT
active reabsorption
basal Ca²⁺ ATPase and Na⁺/Ca²⁺ countertransporter
secondary luminal reabsorption
inhibited in acidosis
control
PTH
peptide hormone secreted by parathyroids
↑ by low [Ca²⁺]
actions
↑ Ca²⁺ mobilization from bone
↑ DCT Ca²⁺ reabsorption
↓ phosphate reabsorption
↑ vitamin D hydroxylation
1,25-(OH)₂D₃
above
calcitonin
peptide hormone secreted by parafollicular thyroid cells
↑ by high [Ca²⁺]
actions
minor role
↓ bone resorption
GH
↑ Ca²⁺ excretion and intestinal absorption
cortisol
↑ Ca²⁺ excretion and ↓ intestinal absorption

phosphate balance
5-10% protein bound
rest freely filtered
75% of load reabsorbed in PCT (Na⁺ cotransport)
↑ reabsorption due to
1,25-(OH)₂D₃, insulin
↓ reabsorption due to
PTH, glucagon

h. Describe the role of the kidneys in the maintenance of osmolarity.
receptors
  osmoreceptors in hypothalamus (paraventricular)
  control ADH secretion from posterior pituitary
  controls free water loss and thirst

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

proteins and peptides
  little protein is present in filtrate (10 mg/l)
  endocytosis of large proteins
    e.g. albumin, GH
    merge with lysosomes → amino acids
    low T_n so easily saturates if filtration of proteins increases
  small polypeptides
    catabolized in lumen by peptidases
    active uptake of amino acids, di- and tri-peptides
    site of metabolism of small peptide hormones (e.g. AT II)
  damaged tubular cells release some proteins into urine
urea
  freely filtered
  50% reabsorbed in PCT (with water)
  concentrated in filtrate in loop and DCT (impermeable)
  facilitated diffusion absorption in collecting tubule (under ADH control)
organic anions and cations (including many drugs)
  non-specific active secretion in PCT
  several carrier proteins
  displays competition and T_n
organic acids and bases
  secretion or reabsorption depends on concentration gradient of diffusible species
  acids AH ↔ A^- + H^+
    acid species is diffusible
    reabsorbed at low urine pH
    secreted at high urine pH
    e.g. bile salts, fatty acids, uric acid
    acetazolamide, furosemide, penicillin, probenecid, salicylates, sulfas
  bases B^- + H^+ ↔ BH^+
    basic species is diffusible
    secreted at low urine pH
    reabsorbed at high urine pH
    e.g. ACh, choline, catecholamines, 5HT, histamine
    atropine, cimetidine, pethidine, morphine, local anaesthetics

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

Clearance
  the volume of plasma which is completely cleared of a substance per unit time
  \( C_r = \frac{\text{rate of excretion}}{\text{plasma concentration}} \)
  so if a urine specimen of volume V is taken over time t and the concentration of X is
measured in plasma ($P_x$) and urine ($U_x$):

$$C_x = U_x V ÷ P_x t$$

**GFR**

- if a substance is
  - freely filtered
  - not actively secreted or reabsorbed by tubules
  - not synthesized or metabolized in tubules
- its clearance must equal GFR
- e.g. inulin (an exogenous polysaccharide)
  - in practice inulin is inconvenient as it equilibrates throughout ECF so a long
    infusion time is required to yield stable plasma levels
- in practice creatinine is used
  - continuous production from muscle (altered by exercise)
  - freely filtered
  - secreted by tubules (about 10% of excreted quantity)
  - slight overestimate of GFR, but plasma creatinine is also an overestimate
  - a halving of GFR should result in a doubling of plasma creatinine, so a single
    measurement of plasma creatinine can be used to estimate GFR based on age,
    weight and sex using the Cockcroft-Gault equation (males):

  $$\text{creatinine clearance (ml/min)} = \frac{(140-\text{age}) \times \text{weight (kg)}}{72 \times \text{creatinine (in mg/dl)}}$$

  (creatinine in mg/dl is 11 times the level in mmol/l)

- urea can also be used
  - 40-60% is reabsorbed
  - $2 \times C_{\text{urea}} \approx \text{GFR}$

**RPF**

- if a substance is
  - filtered and actively secreted so that its concentration in venous blood from the
    kidney is zero
- its clearance must equal RPF
- as 10-15% of RBF is supplied to non-secreting tissue, no substance can meet these
  criteria
- a substance which is completely cleared from blood supplied to secretory tissue of the
  kidney is used to measure effective RPF (ERPF)
- e.g. para-aminohippurate
  - freely filtered and actively secreted
  - not reabsorbed
  - completely cleared at low plasma concentrations

$$\text{ERBF} = \frac{\text{ERPF}}{(1 - \text{Hct})}$$

**k. Describe the physiological effects and clinical assessment of renal dysfunction.**

**l. Explain the effects of hypovolaemia on renal function.**

**m. Explain the effect of general anaesthesia on renal function.**