Structure and function of the kidney

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Etymology

- *Renal*, is from the Latin word for kidney, rēnēs
- *Nephro-* is from the ancient Greek word for kidney, nephros
- Examples:
  - surgical removal of the kidney is a nephrectomy
  - reduction in kidney function is called *renal dysfunction*.
Suggested readings

• Textbook of Medical Physiology, by Arthur C. Guyton, MD and John E. Hall, PhD
• Primer on Kidney Diseases, edited by Arthur Greenberg
• Brenner and Rector’s The Kidney, 8th edition, edited by Barry M. Brenner
Major functions of the kidney

1) Maintenance of body fluid composition
   a) Electrolyte homeostasis
   b) Water homeostasis
2) Excretion of metabolic end products and drugs
3) Regulation of blood pressure: renin production and sodium balance
4) Production of erythropoietin
5) Production of 1,25 dihydroxy-vitamin D
Major functions of the kidney

1) Maintenance of body fluid composition
   a) Electrolyte homeostasis: Na⁺, K⁺, Cl⁻, H⁺, HCO₃⁻, Ca²⁺, Mg²⁺, PO₄³⁻
   b) Water homeostasis: fluid volume and osmolarity

\[
\text{IN} = \text{OUT} = \text{ingested} + \text{produced} = \text{excreted} + \text{consumed}
\]

urine, feces, sweat
Major functions of the kidney

2) Excretion of metabolic end products and drugs
   a. urea from protein catabolism,
   b. uric acid from nucleic acid metabolism
   c. acid
Anatomy of the kidneys

- Kidney
- Renal artery
- Inferior vena cava
- Abdominal aorta
- Ureters
- Urinary bladder
- Urethra
- Renal vein
- Hilum
Schematic of a bisected kidney

Madsen et al, Brenner and Rector, The Kidney, 8th ed.
The functional unit of the kidney: the nephron

Each nephron filters blood to generate a “filtrate” composed of water and solutes (glomerular filtration), which then passes through a tubule that progressively modifies the filtrate, mainly by reabsorbing desirable solutes and water.
Renal circulation

From Atlas of Human Anatomy, F. Netter
Renal Development - Early Embryonic Structures

Renal Development - Early Embryonic Structures

Embryonic Day 9.5

Kobayashi, *Development*, 2005

Embryonic Day 11

Embryonic Day 18

Schematic of kidney development

- Uncondensed mesenchyme
- Ureteric bud
- Wolffian duct
- Comma-shaped body
- S-shaped body
- Branching ureteric tips
- Condensing mesenchyme
- Renal vesicle
- Collecting ducts
- Nephron

From D. Marciano
Schematic of kidney development

UB = ureteric bud
CM = condensing mesenchyme
UM = uncondensed mesenchyme
RV = renal vesicle

From D. Marciano
Renal Development - Ureteric Bud Branching

Nigam et al.
Renal Development - Ureteric Bud Branching

After 250,000-500,000 branching events a kidney is formed

Hilliard et al 2011
Renal Development Gone Awry - I
Renal Development Gone Awry - I
Renal Development Gone Awry - II
14 yo female is referred to my clinic for high blood pressure, short stature and renal failure

a. Born at 26 weeks (14 weeks early)
b. She has always been small for her age
c. In the last few months she has been increasingly tired
Renal Development Gone Awry - II

Reduced Numbers of Nephrons

Enlarged Nephrons
The functional unit of the kidney: the nephron.

Each nephron filters blood to generate a “filtrate” composed of water and solutes (glomerular filtration), which then passes through a tubule that progressively modifies the filtrate, mainly by reabsorbing desirable solutes and water.
Glomerulus
Glomerular filtration barrier

Glomerular filtration barrier
Scanning EM of podocytes

From Comprehensive Clinical Nephrology, 3rd edition,
Glomerular filtration barrier

- Filtration occurs through 3 layers:
  - fenestrated endothelium
  - glomerular basement membrane
  - slit diaphragm of podocytes

From Comprehensive Clinical Nephrology, 3rd edition, ed. Feehally
Glomerular filtration barrier

- Filtration is selective for size and charge

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<tr>
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<th>MW</th>
<th>filterability</th>
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<td>Urea</td>
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<td>inulin</td>
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<tr>
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<tr>
<td>albumin</td>
<td>69,000</td>
<td>0.005</td>
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</tbody>
</table>

From Comprehensive Clinical Nephrology, 3rd edition, ed. Feehally
Glomerular filtration barrier

- Slit diaphragm proteins: nephrin, podocin, CD2AP, Neph1 and others.
- This complex is crucial for glomerular permselectivity and defects result in nephrotic syndrome.

Disease Example: Congenital Nephrotic syndrome of the Finnish type

• Major clinical characteristic is large amounts of protein in urine.
• First described in 1966 in Finland.
• Approx 1/10,000 live births affected.
• Autosomal recessive pattern of inheritance.
• Starts to manifest in utero (as soon as kidneys begin to function, less than halfway through gestation).
• Usually fatal by age of two.
• Gene was positionally cloned (19q13.1) and named NPHS1 (Kestila et al, Mol Cell 1: 575: 1998).
Congenital Nephrotic syndrome of the Finnish type: Defect in the Nephrin Protein

- NPHS1 has 29 exons and encodes a 1241 aa glycoprotein named nephrin
- Two mutations, Fin-major and Fin-minor, cause >90% of CNS in Finland
- Nephrin is a transmembrane protein of the immunoglobulin superfamily
- Found to localize to the slit diaphragms of glomeruli by immunogold labeling

Congenital Nephrotic syndrome of the Finnish type

Fin major: frame shift-stop → 90 aa
Fin minor: nonsense-stop → 1109 aa

Modern homozygote
65% patients

Fin major/Fin minor
16% patients

Normal human

The functional unit of the kidney: the nephron

Each nephron filters blood to generate a “filtrate” composed of water and solutes (glomerular filtration), which then passes through a tubule that progressively modifies the filtrate, mainly by reabsorbing desirable solutes and water.
Tubular function: basic principles

- The composition of the glomerular filtrate is changed by:
  - **Reabsorption** of filtered substances from the lumen of the nephron to surrounding capillaries
  - **Secretion** of substances from the peritubular capillaries into the lumen of the nephron

Relationship between Cellular Structure and Function
Questions?
Extra Slides not Used
Collecting Duct: Vasopressin

- **Vasopressin** (also known as AVP, argipressin, anti-diuretic hormone, ADH)
  - Made in supraoptic and paraventricular nuclei in the hypothalamus and stored/secreted from the posterior pituitary
  - Released in response to increased plasma osmolality, low BP and Angiotensin II
Collecting Duct: Vasopressin

- **Receptors and effects:**
  - **V1a**
    - On vasculature
    - Coupled to phosphoinositol/Ca pathway → contraction of SM.
  - **V1b**
    - In anterior pituitary
    - Modulates adrenocorticotropic hormone release
  - **V2**
    - Basolateral membrane of principal cells in the distal tubule
    - Increases cAMP → aquaporin channel insertion
    - Pathology: Diabetes Insipidus
Juxtaglomerular apparatus (JGA)

MACULA DENSA + JUXTAGLOMERULAR (JG) CELLS

REGULATE BLOOD FLOW THROUGH GLOMERULUS

MACULA DENSA
- cells located in the DCT in close contact with the glomerulus, sense the composition of tubular fluid

JG CELLS (or granular cells)
- specialized smooth muscle cells in the wall of the afferent arteriole which contain and secrete RENIN

ANGIOTENSINGOGEN (PLASMA PROTEIN) → RENIN → ANGIOTENSIN I → ANGIOTENSIN II → ALDOSTERONE SECRETION → VASOCONSTRICTION
Renin-Angiotensin-Aldosterone System

**Legend**
- Blue: Secretion from an organ
- Red: Stimulatory signal
- Green: Inhibitory signal
- Black: Reaction
- Grey: Active transport
- Black and White: Passive transport

**Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.**

Liver -> Angiotensinogen

Lungs

Kidney

Surface of pulmonary and renal endothelium: ACE

Angiotensinogen -> Angiotensin I

Decrease in renal perfusion (juxtaglomerular apparatus)

Renin -> Angiotensin II

Adrenal gland: cortex

Aldosterone secretion

Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion. H₂O retention

Arteriolar vasoconstriction. Increase in blood pressure

ADH secretion

Pituitary gland: posterior lobe

Collecting duct: H₂O absorption

Sympathetic activity

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Wikipedia.com
Measuring GFR: \( C_x = \frac{U_x \times V}{P_x} \)

- **Markers**
  - Inulin (Mw 5200 d)
    - **Pros:** Fructose polymer, freely filters, physiologically inert,
    - **Cons:** continuous IV infusion, bladder cath with multiple timed urine collections, difficult assay
- **Radionuclide-labeled**
  - I-iothalamate and EDTA or T-mercaptoacetyltriglycin (MAG3)
- **Radiocontrast Markers:**
  - Iothalamate sodium, iohexol, diatrizoate
Regulation of Filtration Pressure

Arterial blood pressure (increases blood flow into the glomerulus)

Glomerulus

↑ Glomerular capillary blood pressure

↓ Net filtration pressure

↑ GFR

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Regulation of Filtration Pressure

- **(a)** Glomerular capillary blood pressure decreases, leading to a decrease in net filtration pressure and a decrease in GFR.
- **(b)** Glomerular capillary blood pressure increases, leading to an increase in net filtration pressure and an increase in GFR.

Vasoconstriction decreases blood flow into the glomerulus, while vasodilation increases blood flow into the glomerulus.
Autoregulation of High Filtration Pressure

- Arterial blood pressure
  - Driving pressure into glomerulus
  - Glomerular capillary pressure
    - $\uparrow$ GFR
      - Rate of fluid flow through tubules
        - Stimulation of macula densa cells to release vasoactive chemicals
          - Chemicals released that induce afferent arteriolar vasoconstriction
            - $\downarrow$ Blood flow into glomerulus
              - Glomerular capillary pressure to normal
                - $\downarrow$ GFR to normal
Saving Sodium
Countercurrent multiplication
Early Embryonic Structures

Mesonephros

Pronephros

Wolffian duct

CLOACA

Metanephros

metanephrogenic blastema

ureteric bud
Proximal Tubule
Proximal Tubule

• Bulk of water and solute reabsorption
  – EXAMPLE: Sodium
    4500 mEq filtered per day - 99.96% reabsorbed with ~ 2 mEq/day excreted
  – Other solutes reabsorbed
    • Potassium
    • Bicarbonate
    • Phosphate
    • Amino Acids
    • Peptides
    • Glucose
Proximal Tubule

- $\text{Na}^+/\text{K}^+$-ATPase is primarily the driving force for solute movement.
- Specialized cellular structure for reabsorption: tall brush border and extensive lateral invaginations.
- Well-developed apical vacuolar endocytotic apparatus.
- Numerous elongated mitochondria provide the energy.
Loop of Henle
Loop of Henle

- Concentrates the filtrate via “countercurrent multiplication”
Countercurrent multiplication

- Loop of Henle generates an osmotic gradient:
  - High water permeability of descending limb
  - Low water permeability of ascending limb prevents dissipation of gradient
  - Active Na transport by Na\(^+\)-K\(^+\)-2Cl cotransporter creates higher osmolarity deeper in the medulla

- Higher extraluminal osmolarity draws out more water from the descending limb to concentrate the filtrate – concentration is maintained by lower water permeability in the ascending limb
Distal Convoluted Tubule
Distal Convoluted Tubule

- Fine tuning of water, sodium and potassium homeostasis via specific transport mechanisms
- Electroneutral NaCl absorption via the thiazide-sensitive NaCl cotransporter
- Regulated by WNK kinases
Collecting Ducts
Collecting Ducts:

- Principal cells
  - Na+ channel (ENaC), regulated by aldosterone
  - Water reabsorption (via aquaporin 2 channels regulated by vasopressin)
  - K+ secretion
- Intercalated cells:
  - Type A: Acid Secretion
    - H+ secretion and HCO3- resorption
  - Type B: HCO3- secretion