RENAL PHYSIOLOGY

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Basic Functions of the Kidneys

- **Eliminate plasma METABOLIC WASTE PRODUCTS and FOREIGN COMPOUNDS**
  The kidney are the primary means for eliminating metabolic waste products (urea, creatinine, uric acid, end products of hemoglobin breakdown, metabolites of hormones), toxins produced by the body or ingested, and other foreign substances (pesticides, drugs, food additives) present in plasma.

- **Regulate WATER AND ELECTROLYTE BALANCE**
  The kidneys adjust their excretion rates to match the intake of water and various ions (sodium, chloride, potassium, calcium, hydrogen, magnesium, and phosphate ions).
• **Help maintain ACID-BASE BALANCE**
  The kidneys contribute to acid-base regulation, along with the lungs and body fluid buffers, by excreting acids and by regulating the body fluid buffer stores.

• **Help regulate ARTERIAL PRESSURE**
  The kidneys play a dominant role in long-term regulation of arterial pressure by excreting variable amounts of sodium and water, and contribute to short-term arterial pressure regulation by secreting vasoactive factors or substances, and renin, that leads to the formation of angiotensin II.
• Synthesize GLUCOSE (gluconeogenesis)
  The kidneys’ capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver

• Have other ENDOCRINE and ENZYMATIC functions:
  – Erythropoietin
  – 1,25-(OH)2vitamin D3 (calcitriol)
  - Prostaglandin, Kinins
Urinary System

Renal Vein

Renal artery

Kidney

Ureter

Urinary Bladder
Functional Anatomy of the Kidney

- **Capsule**: encloses, supports and protects the kidney
- **Cortex**: the outer layer of the kidney; the main site for filtration, reabsorption and secretion processes
- **Medulla**: inner core of the kidney organized in 8 -16 pyramids

**Renal pyramids**: house the loops of Henle and collecting ducts of the nephron

**Renal column**: a passageway located between the renal pyramids and used as a space for blood vessels
- **Renal Papilla:** the tip of the renal pyramid that releases urine into a calyx
- **Calyx:** a collecting sac that transports urine from the papilla to the renal pelvis
- **Renal Pelvis:** collects urine from all of the calyces in the kidney; the urine from the renal pelvis is transported through the ureter to the bladder
The Nephron

- The **functional unit** of the kidney
- **Capable of forming urine** by **filtration** of blood and **reabsorption** and **secretion** of materials

- Consisting of **glomerulus** = cluster of capillaries (filtration) and **epithelial structures**:
  - the **Bowman’s capsule**, surrounds glomerulus, collects the **filtrate**
  - the **tubule**, designed to convert filtrate to **urine** by reabsorption and secretion processes
Tubule Segments of the Nephron

- **Proximal tubule**, with a convoluted and a straight part; located in the cortical region
- **Loop of Henle**, with a **descending limb**, thin, and an **ascending limb** with an initial thin and an ending thick segment
- **Distal convoluted tubule**
- **Connecting tubule**
- **Cortical collecting tubule**
- **Outer medullary collecting duct**
- **Inner medullary collecting duct**
Renal Blood Supply

Renal artery → interlobar arteries → arcuate arteries → interlobular (radial) arteries → afferent arterioles → glomerular capillaries → efferent arterioles → peritubular capillaries → interlobular vein → arcuate vein → interlobar vein → renal vein
Renal Blood Supply

- The vascularisation of the nephron has a unique sequence of vascular elements:
  - High resistance arteriole (afferent arteriole)
  - High-pressure glomerular capillaries (about 60 mm Hg) for FILTRATION
  - A second high resistance arteriole (efferent arteriole)
  - Low-pressure capillary network (peritubular capillaries, about 13 mm Hg) for rapid fluid REABSORPTION from the tubules

- By adjusting afferent and efferent arterioles resistance, the rate of glomerular filtration and tubular reabsorption can be modified according to body homeostatic demands
Cortical and Juxtamedullary Nephrons

- The tubular system of the cortical nephrons (80 - 85 %) is surrounded by an extensive network of peritubular capillaries.
- For the juxtamedullary nephrons (15 – 20 %), long efferent arterioles extend from the glomeruli down into the outer medulla and divide into specialized peritubular capillaries called vasa recta, lying side by side with the loops of Henle deep into the inner medulla.
- Medulla is poorly irrigated, receiving only 1 – 2 % of the total renal blood flow.
Basic Kidney Processes that Determine the Composition of the Urine

Urine formation results from:

1. Glomerular filtration
2. Tubular reabsorption
3. Tubular secretion
Excretion = Filtration – Reabsorption + Secretion

A. Filtration only

- Creatinine, Inulin
- $E = F$

B. Filtration, partial reabsorption

- Ions, Urea
- $E = F - R$

C. Filtration, complete reabsorption

- Glucose, Aminoacids
- $E = 0$

D. Filtration, secretion

- PAH
- $E = F + S$
Glomerular Filtration

- Glomerular filtration
  - Plasma is filtered from the glomerular capillaries into Bowman’s capsule
  - It is the first step in urine formation

- Glomerular filtrate
  - Is the product of glomerular filtration, a protein free plasma
  - It is formed at the site of the renal corpuscle

Renal corpuscle

= Glomerulus + Bowman’s space + Bowman’s capsule
Glomerular Filtration Barrier

- Comprises:
  - Capillary endothelium with fenestrations
  - Basement membrane, has negatively charged proteoglycans; it’s the primary restriction point for plasma proteins
  - Epithelial podocytes (inner membrane of the Bowman’s capsule), with foot processes that interdigitate and are separated by filtration slits connected by a slit diaphragm with pores (4 - 14 nm)
  - The mesangial cells form a contractile network that is continuous with the smooth muscle cells of the afferent and efferent arterioles and supports the glomerular capillary loops
Glomerular Filtration Barrier

Diagram showing the glomerular filtration barrier with labels for Proximal tubule, Podocytes, Capillary loops, Bowman's space, Afferent arteriole, Efferent arteriole, Bowman's capsule, Slit pores, Epithelium, Basement membrane, and Fenestrations.
Inner aspect of glomerular capillaries, showing *fenestrations* of endothelial cells (a view of the glomerular capillary wall from the vantage point of the capillary lumen)
Glomerular capillaries covered by the **foot processes** of **podocytes**
(a view of glomerular capillaries from the vantage point of Bowman's space)
The filtration barrier. From left to right, the capillary lumen (CL); the capillary endothelium with large fenestrations; the lamina rara interna; the lamina densa; the lamina rara externa; multiple foot processes of the podocyte, separated by slit diaphragms (arrow); and a portion of the overarching podocyte cell body (CB).
Composition of the Glomerular Filtrate

Glomerular filtration barrier is a thick, porous structure which determines the filterability of solutes by their size and electrical charge:

- Filterability of solutes is **inversely** related to their size: electrolytes (sodium) and small organic compounds (glucose) are freely filtered; for albumin the filterability is nearly zero (due to both the size and the electrical charge)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Molecular Weight</th>
<th>Filterability</th>
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<tbody>
<tr>
<td>Water</td>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>Sodium</td>
<td>23</td>
<td>1.0</td>
</tr>
<tr>
<td>Glucose</td>
<td>180</td>
<td>1.0</td>
</tr>
<tr>
<td>Inulin</td>
<td>5,500</td>
<td>1.0</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17,000</td>
<td>0.75</td>
</tr>
<tr>
<td>Albumin</td>
<td>69,000</td>
<td>0.005</td>
</tr>
</tbody>
</table>
• Negatively charged large molecules have a reduced filterability compared to positively charged molecules of the same size.

• The filtrate fluid is essentially a protein-free plasma
  → A few low-molecular-weight substances are not freely filtered because they are partially bound to the plasma proteins (almost one half of the plasma calcium and most of the plasma fatty acids).
The glomerular filtration rate (GFR) is about 125 ml/min, or 180 L/day.

The large amount of filtrate allows:

- **rapid elimination** of waste products that depend primarily on glomerular filtration for their excretion.

- **rapid control** of the volume and composition of body fluids by processing the entire plasma about 60 times/day at the renal level (180L/day divided by 3L, the plasma volume).
• Filtration fraction (FF)
  
  • = the fraction of the renal plasma flow that is filtered

  • averages 0.2, meaning that about 20% of the renal plasma flow is filtered by the glomerular capillaries

\[
FF = \frac{\text{GFR}}{\text{Renal Plasma Flow}}
\]
Determinants of the Glomerular Filtration Rate (GFR)

- **Kf** - the capillary filtration coefficient
  - depends on the **hydraulic conductivity** and the **filtering surface area** of glomerular capillaries

- **Net filtration pressure**
  - is the balance between **hydrostatic** (P) and **osmotic** (π) forces in the renal corpuscle

\[
\text{GFR} = \text{Kf} \times \text{Net filtration pressure} = \text{Kf} \times (P_G - P_B - \pi_G + \pi_B)
\]
Forces Favoring Filtration (mm Hg)

- Glomerular hydrostatic pressure: 60
- Bowman’s capsule colloid osmotic pressure: 0

Forces Opposing Filtration (mm Hg)

- Bowman’s capsule hydrostatic pressure: 18
- Glomerular capillary colloid osmotic pressure: 32

Net filtration pressure = 60 − 18 − 32 = +10 mm Hg
• GFR = \( K_f \times (P_G - P_B - \pi_G) \), but major determinants of GFR are \( P_G \) and \( \pi_G \)

• **Glomerular colloid osmotic pressure \((\pi_G)\)**
  - From the *afferent* arteriole to the *efferent* arterioles, the plasma protein concentration *increases* about 20%, due to the loss of fluid, filtered into Bowman’s capsule
    - \( \pi_G \) afferent arteriole < \( \pi_G \) efferent arteriole
  - \( \pi_G \) is influenced by:
    - the *arterial plasma colloid osmotic pressure*: when increases, \( \pi_G \) increases as well and GFR decreases
    - the *filtration fraction*: when increases, protein concentration increases, raising \( \pi_G \) and decreasing GFR
\[ \pi_G \text{ and the filtration fraction (FF):} \]

- A decrease in renal plasma flow with no initial change in GFR tends to increase the FF (\( \text{FF} = \text{GFR}/\text{RPF} \)) \( \rightarrow \) \( \pi_G \) increases \( \rightarrow \) GFR decreases, even though \( P_G \) may remain constant

- An increase in RPF with no initial change in GFR tends to decrease FF \( \rightarrow \) slower rise in \( \pi_G \) \( \rightarrow \) less inhibitory effect of \( \pi_G \) on GFR

Conclusion: even with a constant \( P_G \), a higher RPF increases GFR and a lower RPF decreases GFR due to changes in \( \pi_G \)
Increase in colloid osmotic pressure of plasma flowing through the glomerular capillary
Glomerular hydrostatic pressure ($P_G$) is determined by:

- the arterial pressure
- the afferent arteriolar resistance
- the efferent arteriolar resistance
How?

- Increased **arterial pressure** tends to raise $P_G$ and to increase GFR (this effect is buffered by autoregulatory mechanisms)

- Increased resistance of **afferent arterioles** reduces $P_G$ and GFR

- **Modest efferent constriction** raises $P_G$ and GFR

- **Severe efferent constriction** (more than a threefold increase in resistance) *reduces GFR*:
  
  high $P_G$ $\rightarrow$ high filtration $\rightarrow$ increased protein concentration $\rightarrow$ rapid, *nonlinear* increase in glomerular colloid osmotic pressure due to the osmotic effect exerted by the ions bound to plasma proteins = the **Donnan effect**
Bowman’s capsule hydrostatic pressure ($P_B$)

- changes in Bowman’s capsule pressure do not serve as a primary means for regulating GFR
- an increase in $P_B$ decreases GFR (obstruction of the urinary tract)
## Factors That Can Decrease the Glomerular Filtration Rate (GFR)

<table>
<thead>
<tr>
<th>Physical Determinants</th>
<th>Physiologic/Pathophysiologic Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ $K_f \rightarrow \downarrow GFR$</td>
<td>Renal disease, diabetes mellitus, hypertension</td>
</tr>
<tr>
<td>↑ $P_B \rightarrow \downarrow GFR$</td>
<td>Urinary tract obstruction (e.g., kidney stones)</td>
</tr>
<tr>
<td>↑ $\pi_G \rightarrow \downarrow GFR$</td>
<td>↓ Renal blood flow, increased plasma proteins</td>
</tr>
<tr>
<td>↓ $P_G \rightarrow \downarrow GFR$</td>
<td>↓ Arterial pressure (has only small effect due to autoregulation)</td>
</tr>
<tr>
<td>↓ $A_P \rightarrow \downarrow P_G$</td>
<td>↓ Angiotensin II (drugs that block angiotensin II formation)</td>
</tr>
<tr>
<td>↓ $R_E \rightarrow \downarrow P_G$</td>
<td>↑ Sympathetic activity, vasoconstrictor hormones (e.g., norepinephrine, endothelin)</td>
</tr>
<tr>
<td>↑ $R_A \rightarrow \downarrow P_G$</td>
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**AP**, systemic arterial pressure; **RE**, efferent arteriolar resistance; **RA**, afferent arteriolar resistance
Renal Blood Flow

- The blood flow through both kidneys is about 1100 ml/min, or about 22% of the cardiac output, while the two kidneys constitute only 0.4% of the body weight.

- The high flow to the kidneys exceeds its metabolic needs; the additional flow is necessary to supply enough plasma for maintaining the rates of glomerular filtration.

- The mechanisms that regulate renal blood flow are closely linked to the control of GFR and the renal excretory functions.
Determinants of Renal Blood Flow

RBF = (Renal artery pressure - Renal vein pressure) / Total renal vascular resistance

- close to systemic BP approx. 4 mm Hg
- moderate influence by the systemic BP

Sum of the resistance in:
- interlobular arteries
- afferent and efferent arterioles

Influenced by SNS, hormones, local mechanisms

- **SNS activation** – decreases GFR by vasoconstriction
  - important only in critical conditions
- **Norepinephrine, epinephrine, endothelin** – vasoconstrictors
- **NO** – vasodilator; preserves GFR
- **PG (I2, E2), bradikinin** – vasodilators, act on afferent arterioles
**Angiotensin II**

- **renal vasoconstrictor**, prefferential of the *efferent* arterioles
- produced when *blood pressure is low* or during *hipovolemia*
- rises/maintains GFR
- favors *tubular reabsorption* by decreasing peritubular capillary hydrostatic pressure, secondary to efferent arterioles constriction

Therefore – preserves GFR

- restores blood volume and blood pressure
<table>
<thead>
<tr>
<th>Hormone or Autacoid</th>
<th>Effect on GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>↓</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↓</td>
</tr>
<tr>
<td>Endothelin</td>
<td>↓</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>↔ (prevents ↓)</td>
</tr>
<tr>
<td>Endothelial-derived nitric oxide</td>
<td>↑</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>↑</td>
</tr>
</tbody>
</table>
Autoregulation of GFR and Renal Blood Flow

- It’s a mechanism **intrinsic** to the kidneys

- Keeps the renal blood flow and GFR **relatively constant**, despite **marked changes in arterial blood pressure**
  - prevents large changes in renal excretion of water and solutes with changes in blood pressure:
    - preserves a sufficient GFR when BP lowers
    - prevents excessive loss of water and electrolites when BP rises
An important change in arterial pressure exerts much less of an effect on urine volume due to:

- **Renal autoregulation (tubuloglomerular feedback)** that prevents large changes in GFR
- **Myogenic autoregulation** of renal blood flow and GFR
- **Glomerulotubular balance** = additional adaptive mechanism in the renal tubules that increase the reabsorption rate when GFR rises

Changes in arterial pressure still have significant effects on renal excretion of water and sodium, a phenomenon referred to as **pressure diuresis** or **pressure natriuresis**
With autoregulatory and adaptative mechanisms, variation of arterial pressure between 75 - 160 mm Hg changes GFR only a few percentage points.

Without autoregulatory and adaptative mechanisms:

- A relatively small increase in blood pressure from 100 to 125 mm Hg would cause a similar 25 per cent increase in GFR: from about 180 to 225 L/day.
- Normally, from the 180 L filtered per day, 178.5 L of water are reabsorbed and only 1.5 L of urine are excreted.
- If tubular reabsorption remains constant at 178.5 L/day, this would increase the urine flow to 46.5 L/day.

\[ \text{Excretion} = \text{Filtration} - \text{Reabsorption: } 225 - 178.5 = 46.5 \text{ L/day} \]

\rightarrow \text{a total increase in urine of more than 30-fold.}
Role of Tubuloglomerular Feedback in Autoregulation of GFR

- The juxtaglomerular complex consists of:
  - **macula densa cells** in the initial portion of the distal tubule; come in close contact with the afferent and efferent arterioles
  - **juxtaglomerular cells** in the walls of the afferent and efferent arterioles; they are the major storage sites for renin
Macula densa cells sense variations of fluid volume at **distal tubule** and initiates effects on **afferent** and **efferent** arterioles:

*Low GFR* rises Na+ and Cl- reabsorbtion → low Na+ and Cl- levels in the distal tubule → stimulates *macula densa* which:

- lowers afferent arteriole resistance,
- stimulates renin release from *juxtaglomerular cells*, with **ATII** formation, **efferent arteriole constriction**

→ *increased GFR* = autoregulated
Myogenic Autoregulation of Renal Blood Flow and GFR

= the ability of individual blood vessels to resist stretching during increased arterial pressure

- stretching increases calcium inflow followed by contraction of vascular smooth muscle cells

- helps preventing the increase of GFR with arterial pressure
High Protein Intake and Increased Blood Glucose Rise the Renal Blood Flow and GFR

- Protein ingestion increases with 30% GFR

- Possible mechanism: rise of Na+ absorption together with AA → low Na+ at macula densa → tubulo-glomerular feedback → decreased resistance of the afferent arteriole

- High plasma glucose (diabetes mellitus) increases GFR probably through a similar mechanism