Pathophysiology of the Kidney

Regulation of Extracellular Volume and Blood Pressure

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Blood pressure

Water balance

Input/output

Salt balance

Osmolality

BP = heart output \times resistance

Osmolality = \text{total osmoles/volume}
Extracellular fluid volume regulation
OVLTL – organum vasculosum laminae terminalis
SFO – subfornical organ
PVN – periventricular nucleus
SON – supraoptic nucleus

Osmolality regulation
BP regulation

- **Short term**: baroreceptor reflex
- **Intermediate term**: RAS
- **Long term**: water/salt output

Setpoint
AA – afferent arteriole
EGM - extraglomerular mezangial cells
MD - macula densa
β1 – adrenergic receptors

NaCl delivery to macula densa

Renin

Renin

N – nerve
Renin production
1) Decreased
2) Normal
3) Increased
Renin production
1) Decreased
2) Normal
3) Increased
Na⁺

1. Reabsorbed 67%
2. Reabsorbed 25%
3. Reabsorbed 5%
4. Reabsorbed 3%

33% left
8% left
3% left
0.4% left
Osmotic diuretics
acetazolamide

Hydrochlorothiazide

Aldosterone
amiloride

Furosemide
BP = ECV↑ + ECV↓ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺ + Na⁺

Pressure natriuresis
Pressure natriuresis

- Lumen
- Interstitial space
- PROXIMAL TUBULE

- ATP
- \(3 \text{ Na}^+\)
- \(2 \text{ K}^+\)

- BP
- 20-HETE
- Angiotensin II

- 3 \text{ Na}^+
- 2 \text{ K}^+
- \(\text{H}^+\)

- \(\text{ATP}\)
GF = 90 ml/min
Filtered Na⁺ load 12.6 mmol/min

GF = 120 ml/min
Filtered Na⁺ load 16.8 mmol/min

Na⁺ end of proximal tubule

1) 4.2 mmol/min
2) 5.6 mmol/min
3) 8.4 mmol/min
Glomerulotubular balance

GFR

Prox. tubule

35% filtered Na+

Glomerulotubular balance
PROXIMAL TUBULE

from glomerulus

norm. FF

Lumen

Active transport

1

3a

Passive backleak

2

3b

Intersticial space

Blood

Starling forces

\[ P_{PC} = 20 \]

\[ \Pi_{PC} = 33 \]
From glomerulus

↑FF

Lumen

PROXIMAL TUBULE

Active transport

Passive backleak

P_{PC} = 17

\Pi_{PC} = 40
↑ renal arterial pressure

↑ glomerular pressure

↑ renal blood flow

↑ rate of flow through macula densa

↑ GFR

Vasoconstrictive signal

Afferent arteriolar constriction

Tubuloglomerular feedback
PRINCIPAL CELL OF THE CONNECTING TUBULE

- Lumen
- Interstitial space

**Aldosterone effect**

- ENAC
- Na⁺
- K⁺
- ATP
- 3 Na⁺ → 2 K⁺

**Regulatory Factors**

- Renin – ANG II
- ACTH
- ↑ plasma K⁺
Aldosterone effect

- Lumen
- ATP
- 3 Na^+
- 2 K^+
- ENAC
- mRNA
- MR
- Interstitial space
- Nucleus

- Aldosterone effect on the principal cell of the connecting tubule.
Hypertension

↑ BP
↓ renal ang II

↑ afferent arteriolar pressure

↑ glomerular capillary pressure

↑ peritubular capillary pressure

↑ renal interstitial pressure

↓ proximal tubule fluid/salt reabsorption

↑ GFR

↑ diuresis/natriuresis

↓ ECF

↓ BP

↓ renal ang II
Hypertension

Renin

ACE polymorphisms

AT$_1$ receptor

- aldosterone
  - glucocorticoid remediable aldosteronism
  - activated mineralocorticoid receptor
    - Apparent mineralocorticoid excess
    - 11β-hydroxylase deficiency

- $3 \text{Na}^+$ → $2 \text{K}^+$
  - α-adducin polymorphism

- $\text{Na}^+$, $\text{Cl}^-$
  - Gordon’s syndrome

- $\text{Na}^+$
  - Liddle’s syndrome
  - SGK activation

SGK – serum and glucocorticoid-regulated kinase
Congestive heart failure

Hemodynamic changes

Impaired autoregulation

↑ ADH  ↑ SNS  ↑ RAS  ↑ endothelin  ↑ ANF

Salt & water retention

Congestive heart failure
Liver cirrhosis

- Portal hypertension
  - NO
  - Splanchnic + peripheral vasodilation
    - Lymph production
    - Effective circulating volume
      - Cardiac output
        - ADH
        - SNS
        - RAS
          - Sodium & water retention
          - Renal vasoconstriction
            - Renal blood flow
              - Ascites
Nephrotic syndrome

ENaC

* inhibitory peptide
Nephrotic syndrome

Urokinase

Plazminogen

Plazmin

ENaC

Na⁺

* inhibitory peptide
On the basis of preceding two slides, the diuretic regimen of a patient with nephrotic syndrome should include:

1) Furosemide
2) Hydrochlorothiazide
3) Amiloride
- Sodium and water excretion are controlled by multiple overlapping mechanisms. Most of them are related to blood pressure.
- The kidneys have their own mechanisms of regulating sodium excretion. Key among these are pressure natriuresis and RAS.
- The kidneys are the ultimate determinant of blood pressure in the long term via their control of ECF.
- All the physiological controls in the proximal nephron affect the excretion of sodium and water together.
- Aldosterone and AVP in the distal nephron regulate sodium and water independently.
- Long term regulation of sodium excretion (and blood pressure) centres on the actions of aldosterone.
The figures were adapted from:


Servier Medical Art, www.servier.com