Objectives

Describe how human kidneys regulate salt and water balance

Outline the actions of antidiuretic hormone (ADH) and aldosterone

Consider genetic disorders influencing ADH and aldosterone activity

Appreciate how understanding the basis of rare disorders furthers our understanding of normal function
1. Hypothalamus detects too little water in blood.

5. Blood water level returns to normal.
Filter 1600L of blood/day
180L of ultrafiltrate
1.5 L of urine
1. Hypothalamus detects too little water in blood
2. Pituitary gland releases ADH
3. Kidneys maintain blood water level
4. So less water is lost in urine (urine more concentrated)
5. Blood water level returns to normal
ADH (Vasopressin, AVP) stimulates synthesis of aquaporin-2 (AQP) water channel proteins and their transport to the apical surface of collecting duct principal cells.
Antidiuretic Hormone

Synthesised in hypothalamus, stored in posterior pituitary
Stimulated by
  \( \uparrow \) plasma osmolality (threshold 275 - 290 mosm/L)
  \( \downarrow \) blood volume, \( \downarrow \) blood pressure

Leads to water reabsorption in kidneys
  Primary site of action is collecting tubule
  Binds to basal V2 receptor
  \( \rightarrow \) aquaporin 2 (AQP2) inserted into apical membrane
  Withdrawal of AVP
  \( \rightarrow \) endocytosis of AQP2
"Darn it! Mitosis! And just before a big date!"
Sodium Reabsorption

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Renin Release

1. Decrease in blood pressure detected by baroreceptors (pressure-sensitive cells).
2. Decrease in sodium chloride levels in the ultrafiltrate of the nephron.
3. Sympathetic nervous system activity
Distal convoluted tubule

Collecting Duct
Na

3Na

2K

Nucleus

MR

Aldosterone

Na-K-ATPase

K

(ROMK)

(ENaC)

Lumen

Interstitium

+
Aldosterone

Released from adrenal medulla in response to

- Angiotensin II
- Hyperkalaemia

Actions

Na retention

- Immediate effect to increase apical membrane permeability to sodium
- Also enhanced gene transcription & de novo synthesis of Na-K-ATPase

K excretion
"Oh, come on, Alan - think. Use your nucleus!"
Nephrogenic Diabetes Insipidus

Prevalence 1-2/1 000 000.
Failure of ADH response
Polyuria can be 10 L per day
X-linked recessive caused by mutations in the gene coding for the V2 receptor
Liddle’s syndrome

High blood pressure and low potassium
Autosomal dominant, rare
Caused by mutations in genes that control degradation of sodium channel (ENaC)
ENaC remain ‘open’ at the cell surface leads to reabsorption of sodium followed by water which leads to hypertension.
ADRENAL CORTICAL HORMONE SYNTHESIS

Cholesterol
- 20,22-desmolase (CYP11A1)
- 17α-hydroxylase (CYP17)

Pregnenolone
- 17α-hydroxyprogrenolone
- 17,20-desmolase (CYP17)

17-hydroxypregnenolone
- 3β-hydroxysteroid dehydrogenase (3β-HSDII)

Progesterone
- 21-hydroxylase (CYP21A2)

11-deoxycorticosterone
- 11β-hydroxylase (CYP11B1)
- 18-hydroxylase (CYP11B2)

Corticosterone
- 18-oxidase (CYP11B2)

11-deoxycortisol
- 11β-hydroxylase (CYP11B1)

Cortisol
- 11β-hydroxysteroid dehydrogenase

Aldosterone

Glucocorticoids

Dehydroepiandrosterone
- 16α-hydroxylase

16α-hydroxydehydroepiandrosterone

Androstenedione
- 3β-hydroxysteroid dehydrogenase (3β-HSDII)
- aromatase

Androgens

Testosterone
- 5α-reductase

Dihydrotestosterone
- 17β-hydroxysteroid dehydrogenase

Estradiol
- aromatase

Estrone
- aromatase

Estriol
ADRENAL CORTEX HORMONE SYNTHESIS

Cholesterol
  20,22-desmolase (CYP11A1)
  17α-hydroxylase (CYP17)

Pregnenolone
  17,20-desmolase (CYP17)

17-hydroxyprogrenolone
  3β-hydroxysteroid dehydrogenase (3β-HSDII)

Progestrone
  21-hydroxylase (CYP21A2)

11-deoxycorticosterone
  11β-hydroxylase (CYP11B1)

11-deoxycortisol
  18-hydroxylase (CYP11B2)

Cortisol
  11β-hydroxylase (CYP11B1)

Corticosterone
  18-oxidase (CYP11B2)

18-hydroxycorticosterone

Aldosterone

17α-hydroxyprogesterone
  21-hydroxylase (CYP21A2)

Dehydroepiandrosterone
  16α-hydroxylase

16-OH-dehydroepiandrosterone

Androstenedione
  3β-hydroxysteroid dehydrogenase (3β-HSDII)

Testosterone
  17β-hydroxysteroid dehydrogenase

5α-reductase

Dihydrotestosterone

Estrone
  aromatase

Estradiol
  aromatase

Estriol

Estrogen

Androgens

5α-reductase
21 Hydroxylase deficiency

Salt-losing congenital adrenal hyperplasia (CAH)
Autosomal recessive 1 in 16,000
Low levels of cortisol and aldosterone but high levels of androgen.
Poor feeding, weight-loss and vomiting
Low blood pressure, low blood sugar, low sodium, high potassium
Virilisation in females
Summary

99% of filtered water is reabsorbed in kidneys
most by passive diffusion along with sodium
collecting ducts are impermeable to water except when ADH present
ADH secreted by pituitary in response to increased plasma osmolality

90+% of sodium is reabsorbed
different mechanisms in different parts of the tubules
aldosterone acts at distal nephron to reabsorb sodium
aldosterone secreted by adrenal glands when blood pressure falls
Cheap cilia toupees