Disorders of Sodium and Water

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**COMPOSITION OF BODY FLUIDS**

Total Body Water (TBW)
- Comprises ~60% of body weight
- Two thirds of TBW is inside cells (intracellular fluid [ICF] ~ 40% of body weight)
- One third of TBW is outside cells (extracellular fluid [ECF] ~ 20% of body weight)

Solute Composition of Body Water (H2O)
- Predominant solutes in ECF:
  - Sodium (Na+)
  - Chloride (Cl–)
  - Bicarbonate (HCO3–)
- Predominant solutes in ICF:
  - Potassium (K+)
  - Protein
  - Phosphate–
- Normal ECF osmolality, 275 to 290 mOsm/kg H2O
- ECF and ICF are in osmotic equilibrium, at steady state

**PHYSIOLOGY OF Na BALANCE**

Background
- Definition: Na balance is difference between intake (usually oral or intravenous) and excretion (usually renal, gastrointestinal, and perspiratory)

Mechanisms of Renal Na Excretion
- Na freely filtered (~25 mol/d in healthy humans)
- >99% reabsorbed; normal fractional Na excretion is <1%
- About 65% reabsorbed along proximal tubule (PT), 25% along loop of Henle, 6% along distal convoluted tubule (DCT), and 3% along collecting duct (CD)
- Primary energetic driving force for Na (and other solute) reabsorption is Na/K adenosine triphosphatase in basolateral membrane of renal tubules
- Na reabsorption along PT is mediated partly by apical Na/H exchange (NHE3)
- H2O, but not solute, removed from thin descending limb of Henle loop, increasing luminal Na concentration as fluid approaches tip
- Na, but not H2O, reabsorbed along thin and thick ascending limbs of Henle loop, thereby diluting tubule fluid; along thick ascending limb, Na traverses an apical Na-K-2Cl cotransport pathway (NKCC2)
- Na, but not H2O, reabsorbed along DCT, predominantly via an apical Na-Cl cotransporter (NCC or NCCT)
- Na reabsorbed along connecting tubule and CD, largely via an apical Na channel (ENaC)

Regulation of Renal Na Homeostasis
- Renal Na homeostasis responds to “effective arterial blood volume” (EABV), a virtual volume that reflects “fullness” of arterial tree
- Na reabsorption varies inversely with arterial pressure, a phenomenon called “pressure natriuresis”
Na reabsorption along PT regulated by peritubular protein concentration and other "physical factors"; increase in filtration fraction (glomerular filtration rate/renal plasma flow) causes peritubular oncotic pressure to increase, stimulating reabsorption

This link between filtration and reabsorption called glomerulotubular balance

Proximal Na reabsorption (largely NHE3) also stimulated by hormones, including angiotensin II; circulating angiotensin II levels are regulated by renin, secreted by juxtaglomerular apparatus in response to EABV contraction or low luminal thick ascending limbs of Henle loop NaCl concentration

Na reabsorption along second half of DCT, the connecting tubule and CD (collectively termed the "aldosterone-sensitive distal nephron"), regulated by aldosterone, which stimulates ENaC (abundance and/or activity) and NCC; aldosterone secretion regulated directly by angiotensin II, and by serum K concentration

Natriuretic peptides stimulate guanylyl cyclase along CD, generating cyclic guanosine monophosphate and inhibiting apical cation channels; natriuretic peptides also increase glomerular filtration rate; atrial natriuretic peptide secretion stimulated by atrial stretch

Regulation of Renal H₂O Excretion

Urinary osmolality typically ranges between 50 and 1,200 mOsm (mmol)/kg H₂O

Countercurrent multiplication generates medullary hypertonicity in part via Na-K-2Cl cotransporter (NKCC2) at apical membrane of thick ascending limb cells

Countercurrent multiplication along thin limbs requires active transport by other segments and differential solute and H₂O permeability

Tubule fluid leaving loop of Henle is always dilute compared with plasma

Arginine vasopressin (AVP), the antidiuretic hormone (ADH = AVP), regulates H₂O excretion:

When AVP absent, H₂O channels (aquaporin 2) are absent from apical membrane of CD cells; dilute tubule fluid leaves kidney

AVP activates V2 receptors on basolateral membrane of CD cells

AVP stimulates adenylyl cyclase in CD cells; when AVP present, H₂O channels (aquaporin 2) move into apical membrane, permitting H₂O to be reabsorbed,

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PHYSIOLOGY OF H₂O BALANCE

Background

H₂O balance is difference between intake (usually oral or intravenous) and excretion (usually renal, gastrointestinal, perspiratory, and insensible)

H₂O intake controlled by thirst, taste, habit, and physicians; thirst regulated partly by serum osmolality and by angiotensin II

Typical H₂O intake ranges from 1 to 5 L/d

H₂O excretion regulated by factors that adjust renal excretion and by nonrenal losses (insensible, perspiratory, and gastro-intestinal losses)

Mechanisms of Renal H₂O Excretion

H₂O freely filtered at glomerulus (~150 L/d)

About 67% reabsorbed along PT, about 10% along loops of Henle, and about 22% along collecting duct, under typical conditions

Proximal reabsorption is isosmotic, so rates determined by solute reabsorption

H₂O reabsorbed along descending limb of loop of Henle, driven by medullary hypertonicity

Solute, not H₂O, reabsorbed along ascending limbs; ascending limb thus dilutes urine

Solute, not H₂O, reabsorbed along DCT; the DCT dilutes urine

H₂O variably reabsorbed along cortical and medullary collecting ducts, via a regulated apical H₂O channel (aquaporin 2)
driven by medullary hypertonicity, concentrating urine

ADDITIONAL READING

DISORDERS OF Na BALANCE

Background
- Na balance disorders are disorders of ECF volume
- Serum Na concentration may be high, low, or normal

Hypovolemia

Causes
- Extrarenal losses:
  ▪ Blood
  ▪ Gastrointestinal
  ▪ Perspiratory
  ▪ “Third space”
- Renal losses (salt wasting):
  ▪ Adrenal steroid deficiency:
    ○ Inherited:
      □ Hypoaldosteronism (eg, aldosterone synthase defect)
      □ Addison disease
    ○ Acquired:
      □ Addison disease
  ▪ Kidney tubule diseases:
    ○ Inherited, with hyperkalemia:
      □ Bartter syndromes: types I (bumetanide-sensitive Na-Cl cotransporter dysfunction), II (K channel dysfunction), and III (basolateral Cl channel dysfunction), V (activating mutations of calcium sensing receptor)

- Bartter syndrome with sensorineural deafness (resulting from deficiency in Cl channel β subunit, Barttin) (Bartter syndrome type IV)
- Gitelman syndrome: NCC dysfunction
- Inherited, with hyperkalemia:
  □ Pseudohypoaldosteronism type I (ENaC dysfunction): autosomal dominant (mineralocorticoid receptor defect) or autosomal recessive (ENaC defect)
- Acquired:
  □ Renal disease, especially interstitial
  ▪ Drugs, especially diuretics

Treatment
- Identify and treat underlying disease
- Volume repletion with normal saline
- High-salt diet
- Fludrocortisone (synthetic mineralocorticoid)

Hypervolemia

- Occurs when Na retention is “inappropriate”

Primary Na retention

- Causes hypertension, not edema
- Example: hyperaldosteronism
- Reviewed in Core Curriculum in Nephrology on Hypertension (August 2004 issue)

Secondary Na retention

Causes.
- Congestive heart failure; secondary to inadequate cardiac output or diastolic dysfunction
- Cirrhosis of liver; secondary to systemic vasodilation
- Nephrotic syndrome; mixed, resulting from intrinsic stimulation of renal NaCl reabsorption and hypoproteinemia

Diagnosis.
- History
- Physical examination (edema, ascites, jugular pressure, pulmonary crackles, S3, others)
- Laboratory (brain natriuretic peptide concentration, urine Na, urine protein-
creatinine ratio, serum albumin and creatinine)

**Treatment**

- Treat underlying disease process
- Restrict Na intake (keep intake <100 mEq/d, restrict H₂O only if hyponatremia develops)
- Diuretics:
  - Loop diuretics usually first line for edema:
    - Start with low dose and double until diuretic threshold reached (noticeable increase in urine output)
    - Usually administer twice daily
    - Common side effects are hypokalemia, prerenal azotemia, and metabolic alkalosis
  - DCT diuretics (thiazides):
    - Sometimes useful alone
    - Commonly combined with loop diuretics to treat resistance
    - Common side effects are hypokalemia, prerenal azotemia, and metabolic alkalosis
  - CD diuretics (spironolactone, eplerenone, triamterene, amiloride):
    - First-line treatment for cirrhotic ascites
    - Commonly combined with loop or DCT diuretics to prevent hypokalemia
    - Common side effects include hyperkalemia and metabolic acidosis
  - Proximal tubule diuretics (carbonic anhydrase inhibitors):
    - Rarely used except combined with loop and DCT diuretics, to treat resistance or metabolic alkalosis
    - Common side effects include hyperkalemia and metabolic acidosis
  - Natriuretic peptides:
    - Nesiritide (brain natriuretic peptide) infusion
  - Combine diuretic classes if resistance develops; usually combine a loop and a DCT diuretic
- Ultrafiltration or hemodialysis

**ADDITIONAL READING**


**DISORDERS OF H₂O BALANCE**

**Background**

- Are manifested by changes in serum osmolality and/or Na concentration
- Are classified on the basis of ECF volume

**Hyponatremia**

**Factitious (normotonic) hyponatremia**

- Results from laboratory artifact (high concentrations of proteins or lipids)

**Hypertonic hyponatremia**

- Results from non-Na osmoles in serum (often glucose or mannitol) drawing Na-free H₂O from cells ([Na] declines by ~1.6 mEq/L for each 100-mg/dL [5.6-mmol/L] increase in glucose)

**Hypotonic hyponatremia**

**Dilutional.** Urine is dilute (<100 mOsm/kg H₂O):

- H₂O intake exceeds dilutional capacity ("psychogenic polydipsia," requires as much as 12 L/d in normals); treatment is to reduce H₂O intake
• Dilutional capacity limited by low solute intake (“beer drinkers potomania”); treatment is to reduce intake and increase solute intake

**Hypovolemic.** Urine is concentrated:
- Urine [Na] is usually <20 mEq/L, except with diuretic drugs and salt wasting, where it is inappropriately elevated; urine [Cl] concentration is low, even if urine [Na] concentration is not, when volume depletion results from vomiting
- Losses of Na and H₂O stimulate ADH appropriately (eg, sweat or gastrointestinal); losses replaced with hypotonic fluids, owing to thirst
- Diagnosis: by history, physical examination (orthostatic hypotension, low jugular venous pressure, tachycardia, low arterial pressure, dry mucous membranes), and laboratory (high hematocrit and serum protein)
- Treatment is normal saline

**Euvolemic.** Urine is concentrated; urine [Na] usually >20 mEq/L:
- Syndrome of inappropriate ADH secretion (SIADH):
  - Tumors
  - Central nervous disorder
  - Drugs (eg, antidepressants)
  - Others
  - Idiopathic
  - Hypothyroidism or glucocorticoid insufficiency
- Diagnosis: by history, absence of signs of volume depletion or overload, and laboratory (low plasma uric acid)
- Treatment:
  - Some causes reversible (eg, nausea, drugs, glucocorticoid insufficiency)
  - Aggressiveness of treatment depends on severity, chronicity, and symptoms
  - “Rapid” treatment for symptomatic and acute:
    - Raise serum Na by 1 to 2 mEq/L/h until symptoms resolve; generally aim to increase no more than 12 mEq/L in first 24 h
    - Hypertonic saline (3%) at 1 to 2 mL/h/kg body weight
    - Furosemide can be used simultaneously to block concentrating capacity and increase Na excretion to match input
  - Reduce correction rate once symptoms resolve or [Na] >125 mEq/L
  - Urine may become dilute during therapy; careful monitoring needed to avoid excess correction
- “Chronic” treatment:
  - H₂O restriction always appropriate
  - Aquaretics, when necessary:
    - Demeclocycline
    - AVP V2 receptor antagonists (investigational)
    - Oral urea
    - Loop diuretics plus NaCl

**Hypervolemic.** Urine concentrated, Na often <20 mEq/L, except in renal failure:
- AVP secreted because “effective arterial blood volume” reduced (ECF volume deficits, when severe, overcome AVP inhibition by hypotonicity)
- Causes include congestive heart failure, cirrhosis, nephrotic syndrome, kidney failure
- Treatment includes oral H₂O restriction (and continued Na restriction)
- Angiotensin-converting enzyme inhibitors and loop diuretics can help increase Na, when cause is congestive heart failure
- Aquaretics (V2 receptor antagonists, currently investigational drugs) may be useful
- Dialysis

**Hypernatremia**

**Hypervolemic**
- Hypertonic infusion (eg, NaHCO₃)
- Tube feeding

**Hypodipsic**
- Usually only when it occurs with other factors:
  - Elderly or very young
  - Altered mental status
  - Prolonged exertion

**H₂O loss**
- Extrarenal (urine Na <20 mEq/L):
  - Insensible and perspiratory
  - Gastrointestinal
- Renal:
Osmotic diuresis (osmotic diuresis, post-obstruction; urine Na >20 mEq/L)

- Diabetes insipidus (dilute urine, urine Na variable):
  - Nephrogenic (ADH resistance):
    - Hereditary: X-linked (V2 receptor), autosomal recessive (aquaporin-2)
    - Acquired: hypercalcemia, hypokalemia, chronic kidney disease, drugs (lithium most common), many others
  - Central (ADH insufficiency):
    - Idiopathic (50%)
    - Autoimmune
    - Tumors
    - Trauma
    - Autosomal dominant
    - Others

**Diagnosis**

- History: history of exertion, fever, thirst, diarrhea, polyuria, access to H₂O, drugs
- Physical examination: signs of EABV depletion, neurological deficits
- Laboratory tests:
  - Measure urinary osmolality, Na and K
  - Calculate electrolyte-free H₂O reabsorption:

\[
TeC_{H₂O} = V \cdot \left( \frac{U_{Na} + U_K}{P_{Na}} - 1 \right)
\]

where \( TeC_{H₂O} \) is the electrolyte-free water reabsorption, \( V \) is urine volume, \( U_{Na} \) is urine Na concentration, \( U_K \) is urine K concentration, and \( P_{Na} \) is plasma Na concentration

If this value has negative sign, it represents ongoing H₂O losses that must be replaced

- H₂O deprivation test for hypernatremia associated with dilute urine (restrict H₂O until 3% to 5% body weight loss or 3 consecutive urine osmolalities within 10%; serum Na must exceed 144 mEq/L); follow patient for signs of excess volume depletion; interpretation:
  - Urine osmolality >800 mOsm/kg H₂O = normal
  - Urine osmolality <300 mOsm/kg H₂O = complete diabetes insipidus
  - Urine osmolality 300 to 800 mOsm/kg H₂O = partial diabetes insipidus
  - Response to exogenous vasopressin defines central versus nephrogenic
  - Plasma vasopressin levels correlated with plasma and urinary osmolality often needed in equivocal cases

**Treatment**

- Hypovolemic hypernatremia, with saline
- Euvolemic hypernatremia, with D5W
- Deficit = current body H₂O × (actual plasma Na concentration/desired plasma Na concentration)
- Aim to correct at <0.5 mEq/L/h and usually ≤10 mEq/d
- Note that ongoing free H₂O excretion both insensible and renal must be replaced

**ADDITIONAL READING**