Objectives

1. Define osmolality and osmotic pressure
2. Review the central and kidney mechanisms involved in the regulation of osmolality
3. Review the response to a water load and water deprivation in normal physiology
4. Understand disorders of hypo-osmolality: "appropriate" vs. "inappropriate" ADH
5. Understand disorders of hyper-osmolality

Readings

Rose and Rennke, pages 67-93.
Rennke and Denker, pages 69-98.

I. Osmolality: definitions and important concepts

A. Osmole - mole of solute times the number of ions or particles formed upon its dissociation in solution, e.g. 1 millimole of NaCl in 1 liter of water has an osmolality of approximately 2 milliosms/kg when dissolved. This assumes 100% dissociation into Na^+ and Cl^-, when in fact dissociation is approximately 85%.

   1. Osmolality reflects total number of particles in solution
   2. Osmotic pressure is based in the number of osmotically active particles in solution

B. Osmotic equilibrium / osmotic pressure: Free movement of water across cell membranes to maintain equal intracellular and extracellular osmolality. This maintains cell volume.

   1. Osmotic gradients develop when semi-permeable membranes separate two compartments with different osmolalities. Water movement will equalize osmolalities. A substance that freely diffuses across the membrane will equalize its concentration and ***will not*** generate an osmotic gradient (e.g. urea).

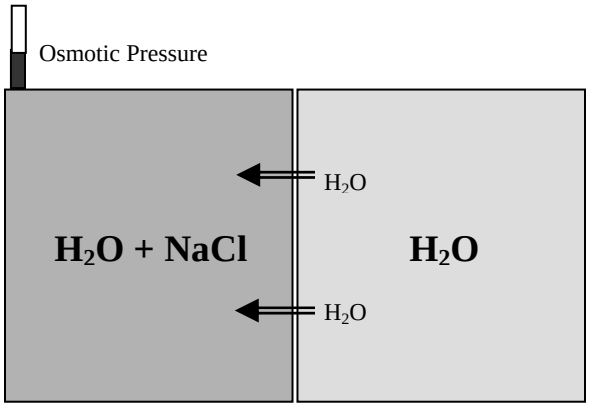

Figure 1

   2. Osmotic factors: potassium (intracellular), sodium (extracellular), and proteins (plasma) maintain distribution of water in the three compartments
   3. Water comprises 55-60% of lean body mass in men, 45-50% in women

C. Plasma osmolality - sum of the osmolalities of the individual solutes in the plasma

1. Primary solutes - Na^+, Cl^-, urea, glucose, other anions/cations, plasma proteins

   a. Sodium - primary extracellular solute due to Na^+/K^+-ATPase. Na^+ freely diffuses across capillary membranes, and thus is an ineffective osmole at intravascular/interstitial barrier. The ***concentration*** of sodium in the plasma reflects ***water*** *(not sodium)* content.

   b. Plasma proteins - primary osmole in the vascular space to maintain plasma volume

2. Assessment (normal range: 280-290 mosmol/kg)

   a. direct measurement

   b. estimate

      $$\mathbf{P_{osm} = 2 \times plasma\ [Na^+] + [glucose]/18 + [BUN]/2.8}$$ *(convert from mg/dL to mmol/L)*

      Since BUN and glucose add very little under normal circumstances:

      $$\mathbf{P_{osm} \approx 2 \times P_{Na}}$$

D. Water balance – normal homeostatic mechanisms aim to maintain serum osmolality within a narrow range (280-285 mOsm/kg)

1. Hyperosmolality/hypernatremia occurs if water loss is greater than water intake

   a. Leads to net water loss in excess of solute

   b. Hypernatremia does not occur if thirst is intact and there is access to water

2. Hypoosmolality/hyponatremia occurs if water intake is greater than water loss

   a. Leads to net water retention in excess of solute

II. Regulation of Plasma Osmolality

A. Sensors - osmoreceptors in anterior hypothalamus

B. Mediators

1. Antidiuretic hormone (ADH), a.k.a. arginine vasopressin (AVP), is released from the supra-optic and para-ventricular nuclei of the hypothalamus

   a. Primarily triggered by increased P_{osm} above approximately 280 mOsm/kg

      i. Below 280 mOsm/kg, ADH should be completely suppressed

      ii. Increases sharply as osmolality rises through the normal range (to 5-10 pg/ml)

   b. Also released in response to decreased effective circulating volume, such as profound (>10%) volume depletion, HF, cirrhosis, and nephrotic syndrome

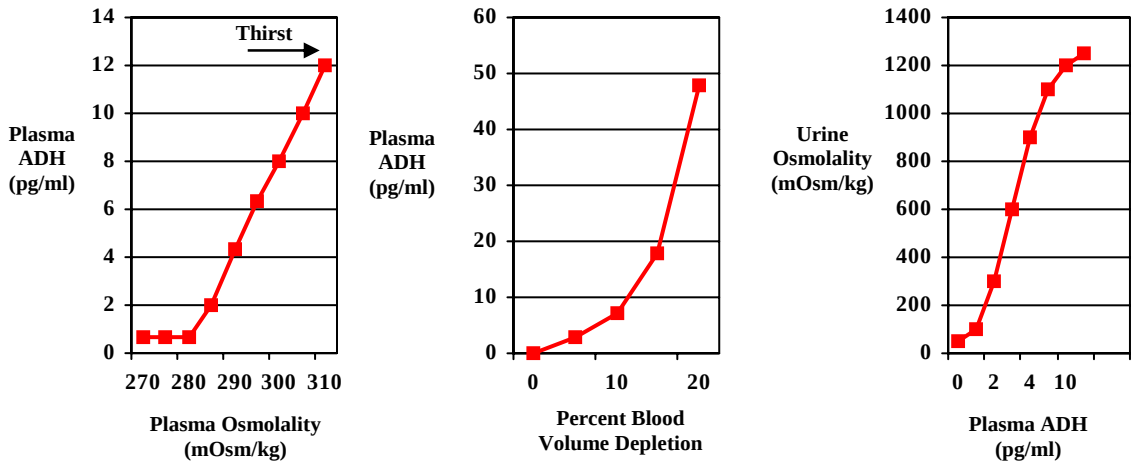

Figure 2

2. Thirst –most important defense against hyperosmolality

   a. Triggered at P_{osm} ≈290 mOsm/kg

   b. Other stimuli - eating, AII, social

C. Effectors – The kidney is able to excrete or retain water by concentrating or diluting the urine. This ability requires adequate GFR, functional tubules, a hypertonic medulla, and the presence or absence of ADH

1. Factors involved in generating hypertonic medullary interstitium

a. Countercurrent multiplier: the LOH is designed as a parallel arrangement of ascending and descending limbs with variable water permeability

i. descending limb water *permeable* - water exits tubule into interstitium, resulting in a "concentrated" solution being delivered to ascending limb

ii. ascending limb water *impermeable* - solute is extracted from the thick ascending limb via the $Na^+/K^+/2Cl^-$ co-transporter and extruded into interstitium

iii. maximal concentration of 1200-1400 mOsm/kg (urea is the major component) is achieved in the deep renal medulla

iv. urine exiting loop is dilute at 100 mOsm/kg

2. Dilute filtrate – As the DCT remains impermeable to water, Na^+ and Cl^- continue to be reabsorbed by the Na^+/Cl^- co-transporter resulting in a maximally dilute filtrate of 50 mOsm/kg as it enters the collecting tubule

3. Collecting duct: limited permeability to water in absence of ADH

a. Without ADH, urine "passes through" and U_{osm} remains 50-60 mOsm/kg (maximally dilute).

b. With ADH, pre-formed water channels from cytoplasmic vesicles are inserted in the luminal membrane, which allow osmotic equilibration with the interstitium. A maximally concentrated urine with a U_{osm} of 1200-1400 mOsm/kg is produced.

III. Normal Physiologic Response to Dietary Variability

A. Water load

As water enters the ECF, a decrease in P_{osm} is sensed by the hypothalamus. The drop in P_{osm} leads to a reduction in ADH release, a fall in the number of water channels in the collecting duct, less H_2O reabsorption in the collecting duct, and water excretion with maximally dilute urine (~ 50 mOsm/kg).

B. Water deprivation

1. An increase in P_{osm} > 280 mOsm/kg is sensed by the hypothalamus and leads to the release of ADH. ADH mediates the insertion of water channels (called aquaporins) into the collecting duct. Water is reabsorbed through these channels down its osmotic gradient into the hypertonic medulla. The result is that water is retained and concentrated urine is produced (> 600 mOsm/kg).

2. Increase in P_{osm} > 290 mOsm/kg stimulates thirst and H_2O intake.

C. Role of daily osmole load in determining urine output

	INTAKE		OUTPUT			NET
	Osmoles (mOsm)	H_20 (L)	Osms or $U_{osm}V$ (mOsm)	V (L)	U_{osm} (mOsm/L)	ΔP_{osm}
1. "Typical"	600	1.5	600	1.5	400	↔
2. Celebration Day	600	3.0	600	3.0	200	↔
3. Tea & Toast	300	1.5	300	1.5	200	↔
4. High Salt Diet	900	1.5	900	1.5	600	↔
5. Extreme min	600	0.5	600	0.50	1200	↔
6. Extreme max	600	12	600	12	50	↔

Table 1

1. Urine osmolality is determined by ADH, which is modulated both by water and osmole intake.

2. Goal is to excrete the daily ingested osmoles and water, and maintain plasma osmolality (*homeostasis*).

3. The diluting and concentrating ability of the kidney allows for wide variation in water (and osmole) intake.

4. Disorders that "fix" the U_{osm} (i.e. paralyze the ability to modulate urine concentration) impair the kidney's ability to respond to changes in dietary intake. Under those circumstances, the proportion of water and osmoles ingested determines plasma osmolality.

IV. Disorders of Hypo-Osmolality

A. Definition – Hypo-osmolality is a condition that occurs when P_{osm} fall below 280 mOsm/kg. Water balance is disrupted from either excessive water intake or inadequate water excretion.

1. Excessive water intake – psychogenic polydipsia

a. Clinical characteristics

i. euvolemic (sub-clinical volume expansion)

ii. U_{osm} < 100 mOsm/kg – a normal hypothalamus and renal response

2. Decreased water excretion (i.e. inappropriately concentrated urine)

a. When P_{osm} < 275 mOsm/kg, ADH should be unmeasurable and U_{osm} should be less than 100 mOsm/kg (usually less than 50)

b. If U_{osm} > 100 mOsm/kg in this situation and kidney function is normal, then ADH and water channels must be present (because U_{osm} is now inappropriately high)

c. Next step is to evaluate if the presence of ADH is *appropriate* or *inappropriate*

3. Multi-factorial – water intake that exceeds a mildly impaired diluting ability

B. Causes of Hypo-osmolality

1. "*Appropriate* ADH" – ADH release is triggered by the carotid baroreceptors

a. Causes: ineffective circulating volume, heart failure, cirrhosis

b. Evaluation: history and physical examination to determine volume status, and the presence of heart failure or cirrhosis

c. Treatment lies with the underlying condition

i. volume depletion – ECF volume expansion

ii. heart failure – improve cardiac function and water restriction

iii. cirrhosis – liver transplantation, water restriction

2. "*Inappropriate* ADH" (i.e. no discernible trigger for ADH release)

a. Hypothyroidism, cortisol deficiency, syndrome of inappropriate ADH (SIADH)

b. SIADH is a diagnosis of exclusion. It is often seen in pulmonary disorders (pneumonia, TB, asthma, pneumothorax), CNS disorders (infection, tumor, vascular event), tumors (small cell lung cancer), drugs (cyclophosphamide, chemotherapy, carbamezapam, anti-psychotics), nausea, and severe pain.

c. Diagnosis can be made from history and testing for above conditions

d. Treatments include addressing the underlying condition and water restriction

3. Reset Osmostat – altered threshold for ADH release

    a. Plasma sodium stable

    b. Urine dilutes and concentrates to maintain an osmolality below 280 mOsm/kg

    c. Important to distinguish because this condition does not require treatment

4. Impaired kidney function: U_{osm} > 100 mOsm/kg.

    a. ADH is suppressed, indicating normal hypothalamic response

    b. Kidney progressively loses the ability to reach the extremes of concentration and dilution. Eventually, U_{osm} approaches P_{osm} (a.k.a. *isosthenuria*)

    c. Treat with fluid (and solute) restriction

C. Clinical Manifestations

1. Symptoms – symptoms are most severe with a rapid decrease in osmolality, thought to be due to swelling of brain cells leading to increased intracranial pressure

    a. nausea, vomiting, mental confusion, seizures

    b. usually occur when P_{osm} < 250 mOsm/L (P_{Na} 120 mEq/L) or with rapid development

2. Findings

    a. Volume status is **VARIABLE (KEY POINT!!)**

	Clinical Assessment of the Volume of Extracellular Fluid		
	Contracted	**"Euvolemic"**	**Expanded**
Causes	Diarrhea, vomiting, excessive sweating, poor water intake, diuretic use	SIADH, hypothyroidism, adrenal insufficiency	Heart failure, cirrhotic liver disease, nephrotic syndrome
Plasma Osmolality	Low	Low	Low
Urine Osmolality	> 500 (mOsm/L)	> 100 (mOsm/L)	> 100 (mOsm/L)
Urine Volume	Usually decreased	Varies with intake	Usually decreased
Urine [Na]	< 20	> 40	< 20
Response to 0.9% saline infusion	Clinical and biochemical improvement	No change or worsening of hyponatremia	Little change in hyponatremia, worsening of edema

Table 2

3. Laboratory Results

   a. P_{osm} – basis of diagnosis (usually P_{Na} reflects P_{osm} – remember $P_{osm} \approx 2 \times P_{Na}$). Note: water shifts out of cells from hyperglycemia may cause a low P_{Na} but normal P_{osm}. This is called pseudohyponatremia.

   b. U_{osm} - essential for indicating the kidney's response mediated by ADH

   c. U_{Na} and FE_{Na} - tests of sodium avidity may give clues regarding volume status

D. Treatment - Treat the Underlying Disorder

1. Hypo-osmolality due to water overload – restrict water intake and allow appropriate excretion of water by kidneys

2. Hypo-osmolality due to decreased water excretion

   a. H_2O restriction

   b. Increased solute intake

      Sodium deficit = body weight in kg x 0.5-0.6 x (Na^+ desired – Na^+ actual)

   c. Decrease "fixed" osmolality (furosemide, demeclocycline, lithium) – agents to decrease U_{osm}

   d. The table illustrates the rationale for the above treatments

	INTAKE		**OUTPUT**			**NET**
	Osmols (mosm)	H_20 (L)	Osms or $U_{osm}V$ (mosm)	V (L)	U_{osm} (mosm/L)	ΔP_{osm}
"Typical"	600	1.5	600	1.5	400	↔
Fixed U_{osm}	600	1.0	600	1.0	600	↔
Fixed U_{osm}	600	**2.0**	600	1.0	600	↓
COMMENT: WATER INTAKE OF > 1 LITER LEADS TO WATER RETENTION						
Fixed U_{osm}	600	**0.5**	600	1.0	600	↑
COMMENT: RESTRICTION TO LESS THAN 1 LITER LEADS TO NET LOSS OF 0.5 L OF H_2O TREATMENT: FLUID RESTRICTION						
Fixed U_{osm}	**900**	1.5	900	1.5	900	↔
COMMENT: INCREASING OSMOL INTAKE INCREASED WATER TOLERANCE TREATMENT: INCREASE OSMOL INTAKE – Na^+, PROTEIN (UREA), K^+						
Fixed U_{osm}	600	2.0	600	2.0	**300**	↔
COMMENT: DECREASING THE "FIXED" OSMOLALITY INCREASED WATER TOLERANCE TREATMENT: REDUCE CONCENTRATING ABILITY OF THE KIDNEY						

Table 3

3. Special points related to defects in water excretion in patients with volume disturbances – i.e. "appropriate" ADH

    a. Increased osmole intake will correct P_{osm} in CHF and cirrhosis. However, since total body Na^+ is high in these states, you want to limit excess Na^+. Increased protein will work for CHF, but may cause encephalopathy in cirrhosis.

    b. Demeclocycline is hepatotoxic and nephrotoxic.

4. Rate of Correction

    a. Usually, correction of P_{Na} should be limited to 0.5 mEq/L/hr, with maximum of 12 mEq/L/24 hours

    b. Symptoms - If patient is symptomatic (i.e. seizures), correction can occur as fast as 1.5-2 mEq/hr **until** symptoms improve (generally at 120 mEq/L)

    c. Rate of development - Chronic hypo-osmolality, especially if asymptomatic, should be corrected slowly. Acute hypo-osmolality can be corrected more rapidly.

    d. Gender (young women) and comorbid conditions (alcoholism) require careful monitoring and more gradual correction.

    e. Risks of overly rapid correction include seizures, mental status changes, and central pontine myelinolysis. Central Pontine Myelinolysis is a result of brain cell shrinkage related to rapid osmotically-driven water exit from brain cells. It can present with symptoms of paresis, dysarthria, and dysphagia, and effects may be permanent. **Bad!!!**

V. Disorders of Hyper-Osmolality

A. Definition – Hyper-osmolality is a condition that occurs when P_{osm} rises above 300 mOsm/kg. Water balance is disrupted by inadequate water intake or excessive water excretion.

1. Inadequate water intake can lead to hyper-osmolality in the setting of a normal ADH response and normal kidneys

    a. U_{osm} > 600-800 mOsm/kg

    b. Requires either:

        i. Impaired access to water (infants, nursing home patients), or

        ii. Hypodipsia –impaired thirst sensation can be a result of a CNS lesion

2. Excessive water excretion – inappropriately dilute urine

B. Causes of excessive water excretion

1. Neurogenic (central) diabetes insipidus – reduced ADH synthesis

a. U_{osm} < 400 mOsm/kg (can be as low as 50 mOsm/kg if there is zero ADH)

b. P_{Na} often normal because of intact thirst sensation – patients drink large volumes of water

c. Becomes clinically evident only when access to water is impaired – fasting before surgery, anesthesia

d. Caused by CNS injury (stroke, trauma, surgery) or idiopathic (most common)

e. Diagnosed by observing U_{osm} rise in response to ADH administration

2. Nephrogenic diabetes insipidus – reduced ADH effect on collecting duct

a. U_{osm} < 400 mOsm/kg

b. Caused by drugs (lithium), tubulointerstitial disease, and congenital abnormality

c. Can respond to ADH-effect enhancers – NSAIDs (prostaglandins have an inhibitory effect on ADH), chlorpropamide, high dose ADH (if partial defect)

3. Osmotic Diuresis

a. $U_{osm} \approx$ 300 mOsm/kg (isosthenuria) - water losses exceed solute losses

b. Caused by hyperglycemia, mannitol, glycerol, and high protein feedings that drag water out

4. Hypertonic solute administration with kidney failure (very rare)

C. Clinical Manifestations

1. Symptoms: THIRST, depression of consciousness, focal neurologic findings (rare)

a. usually occurs once P_{osm} > 330 mOsm/kg (P_{Na} of 160 mEq/L)

b. related to shrinkage of CNS cells

2. Findings

a. Euvolemic – ECF volume depletion usually not present as only 1/12 of water loss comes from plasma volume (2/3 from ICF, 1/4 from interstitium).

3. Laboratory

a. P_{osm} – the basis of diagnosis

b. U_{osm} – an essential diagnostic tool to assess the appropriateness of the kidney response

D. Treatment

1. Water Resuscitation

$$\text{Water deficit} = \text{Body weight in kg} \times 0.5\text{-}0.6 \times [(P_{Na} - 140) / 140]$$

The same principles regarding the rate of correction are applicable to hypernatremia. Correction of P_{Na} should be limited to 0.5 mEq/L/hr, with maximum of 12 mEq/L/24 hours. Overly rapid correction can cause cerebral edema and brain herniation

2. Saline administration may actually be harmful and will worsen hypernatremia hyperosmolality in diabetes insipidus

3. Impairing kidney diluting ability may assist in therapy – thiazide diuretics will prevent maximal urinary dilution and NSAIDs may antagonize ADH

4. Exogenous ADH administration in central DI

VI. Summary

Disorders of water balance manifest themselves as hypoosmolality and hyperosmolality. Hypoosmolality (often recognized by hyponatremia) reflects a water-overload state from water intake in excess of water excretion. Psychogenic polydipsia is an example of water intake exceeding the excretory capacity of the kidney. Water excreting defects are evident by a urine osmolality above 100 mOsm/L, and can reflect either dysfunction of the distal convoluted tubule or the presence of ADH. The DCT is the tubular segment responsible for maximally diluting the filtrate. ADH presence can be appropriate (from decreased baroreceptor stimulation in heart failure, cirrhosis, or nephrotic syndrome) or inappropriate (in hypothyroidism, adrenal insufficiency, drug, etc.). Treatment requires restoring water balance by reducing water intake and augmenting water excretion.

Hyperosmolality (often recognized by hypernatremia) reflects a water-depleted state from inadequate water intake or excessive water excretion. A concentrated urine reflects inadequate water intake, where a sub-maximally concentrated urine reflects a concentrating defect. Concentrating defects result from a loss of medullary hypertonicity from dysfunction of the loop of Henle, or absence of ADH effect. Central diabetes insipidus is a condition of underproduction

of ADH from the brain. Nephrogenic diabetes insipidus is a condition of unresponsiveness of the collecting tubule to ADH. Treatment requires repleting water, and limiting water loss.

VII. Self-Assessment Problems

Problem 1.

A 50-year-old man is seen in the emergency room complaining of 8 days of severe nausea, vomiting, and diarrhea. During this time, he has lost 9 pounds. He is unable to eat food, but continues to drink water. In the emergency room, the following vital signs and lab tests were obtained:

	Blood Pressure	Heart Rate
Supine	120/75	90
Upright	100/60	120

Blood		
Sodium	125	mEq/L
Potassium	3.3	mEq/L
Chloride	92	mEq/L
Bicarbonate	23	mEq/L
BUN	62	mg/dL
Creatinine	2.3	mg/dL
GFRe	36	ml/min/1.73m^2
Osmolality	270	mOsm/kg

Urine		
Sodium	???	mEq/L
Osmolality	950	mOsms/kg

1. Is this patient's total body sodium content increased, normal, or decreased?
2. What would you predict the urine sodium concentration to be?
3. Why is this serum sodium concentration low?
4. What therapy would you suggest?

Problem 2.

A 65-year-old woman with a long smoking history is admitted to the hospital for evaluation of hemoptysis of two weeks duration. Her blood pressure is 120/80, with no orthostatic changes. The admission chest x ray demonstrates a right lower lobe mass consistent with a malignant tumor. Initial laboratory results show:

Blood		
Sodium	100	mEq/L
Potassium	3.5	mEq/L
Chloride	72	mEq/L
Bicarbonate	25	mEq/L
Osmolality	220	mOsm/kg

Urine		
Sodium	30	mEq/L
Osmolality	230	mOsms/kg

5. Is this patient's total body sodium increased, normal or decreased?

6. Why is the serum sodium concentration low?

7. What is the pathophysiology of this patient's fluid and electrolyte disorder?

8. What therapy would you suggest?

Problem 3

This 24-year-old patient (pre-op weight 90 kg) is seen two days after surgery for removal of a craniopharyngioma. Serum electrolytes, BUN, and creatinine concentrations were normal pre-operatively. On the day of consultation, repeat labs tests show:

Blood		
Sodium	160	mEq/L
Potassium	4.3	mEq/L
Chloride	121	mEq/L
Bicarbonate	26	mEq/L
Osmolality	335	mOsm/kg

Urine		
Osmolality	100	mOsms/kg

9. What is the most likely cause for this fluid and electrolyte abnormality, and what is the pathophysiology?

10. How would your interpretation be altered if the urine osmolality was 400 mOsm/kg H_2O?

11. What treatment would you suggest for this patient?