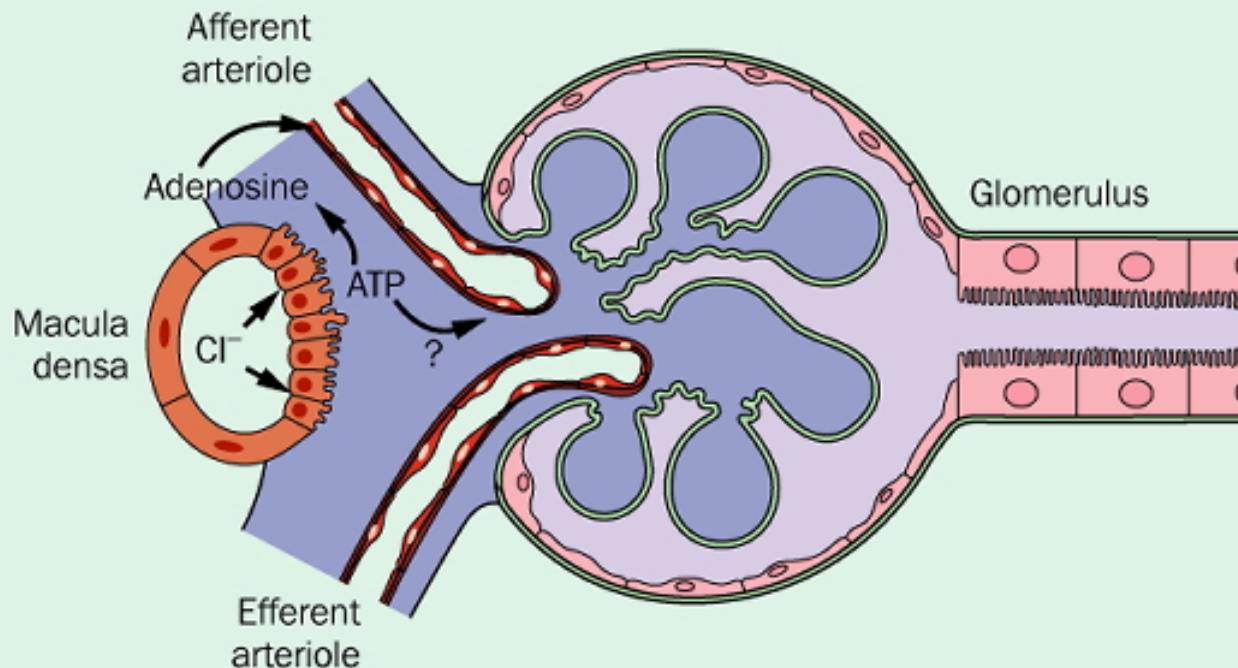


Tubuloglomerular feedback



VASOPRESSIN SECRETION

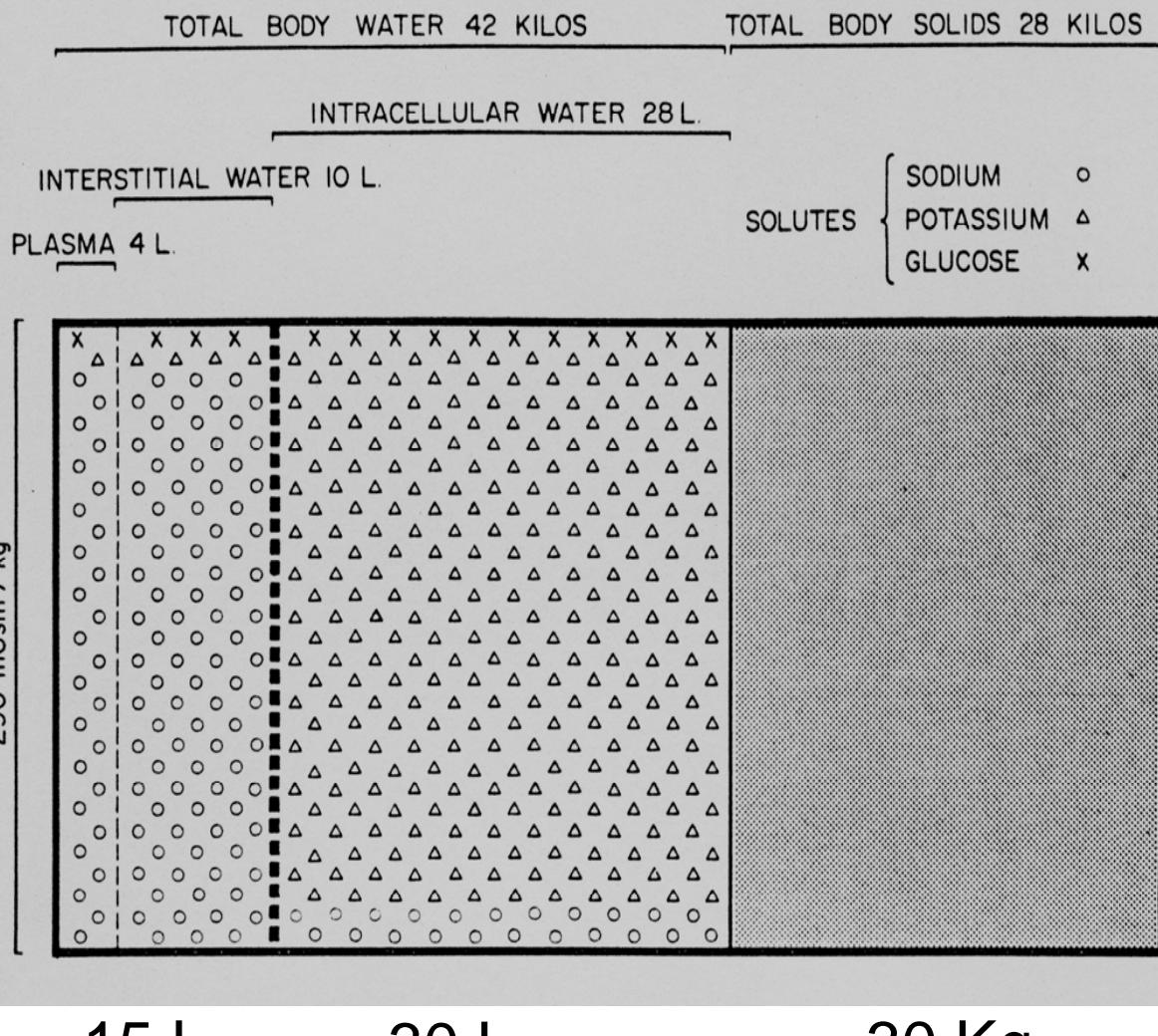
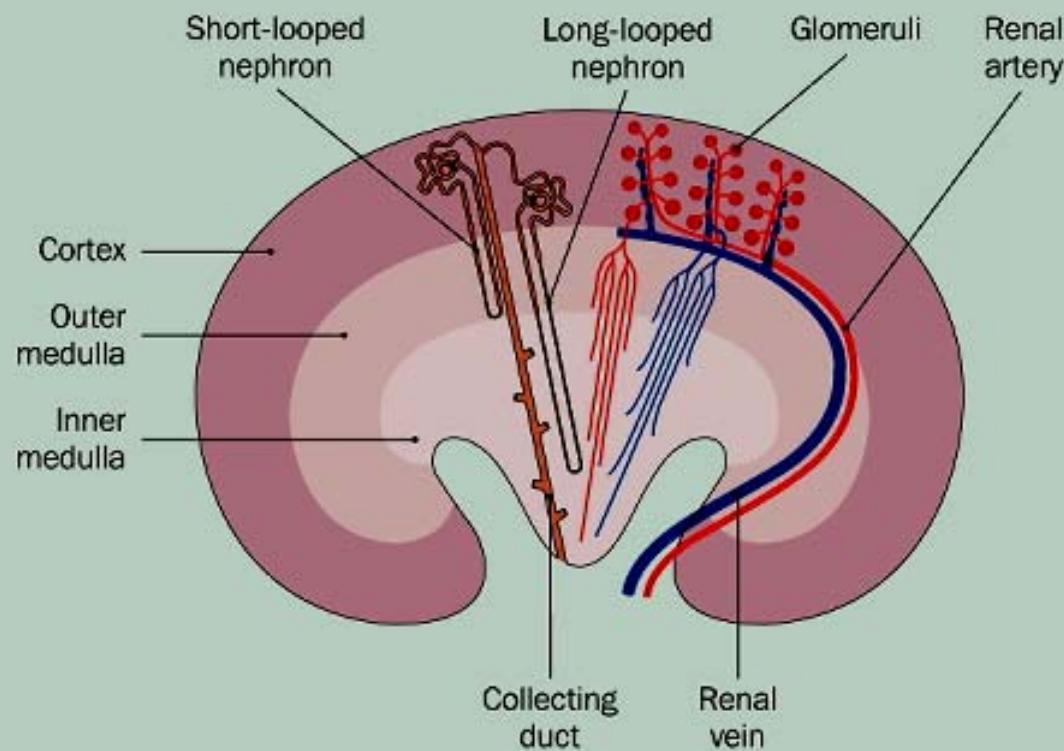


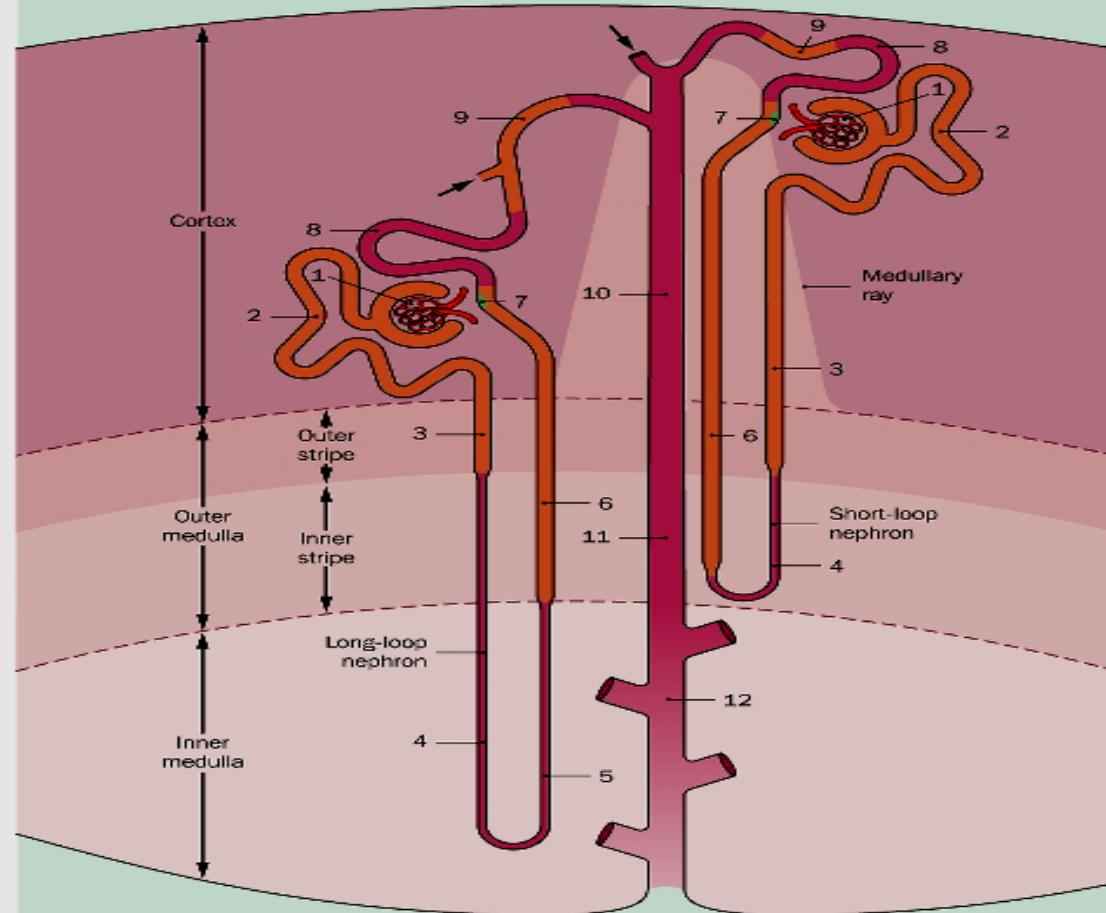
FIG. 1. Volume and solute compositions of body water in healthy adults. The values shown are for a typical 70-kg man.

Robertson GL, Ch 36 in
Seldin & Giebisch: The Kidn

Coronal section through a unipapillary kidney

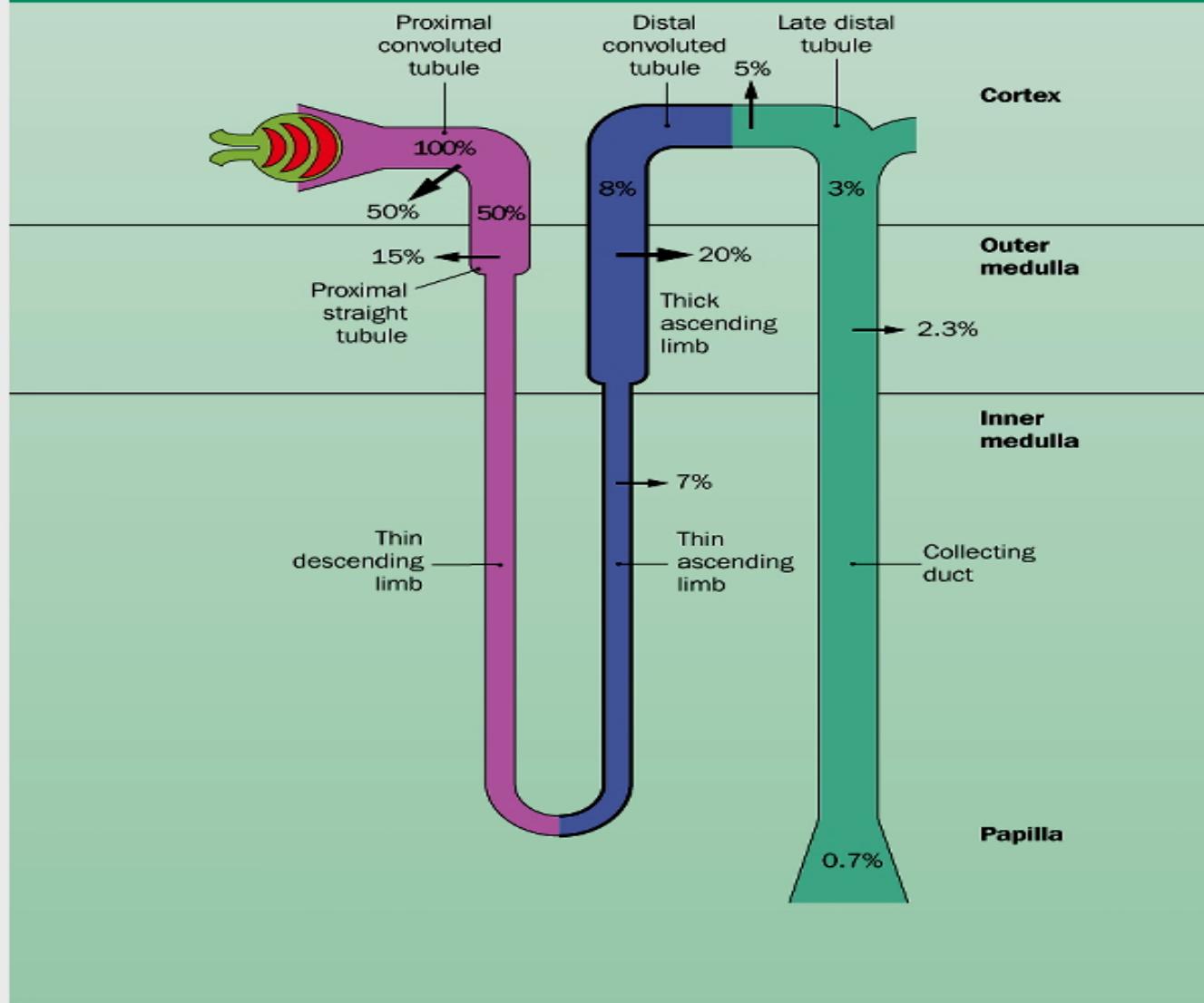


The nephron and collecting duct system

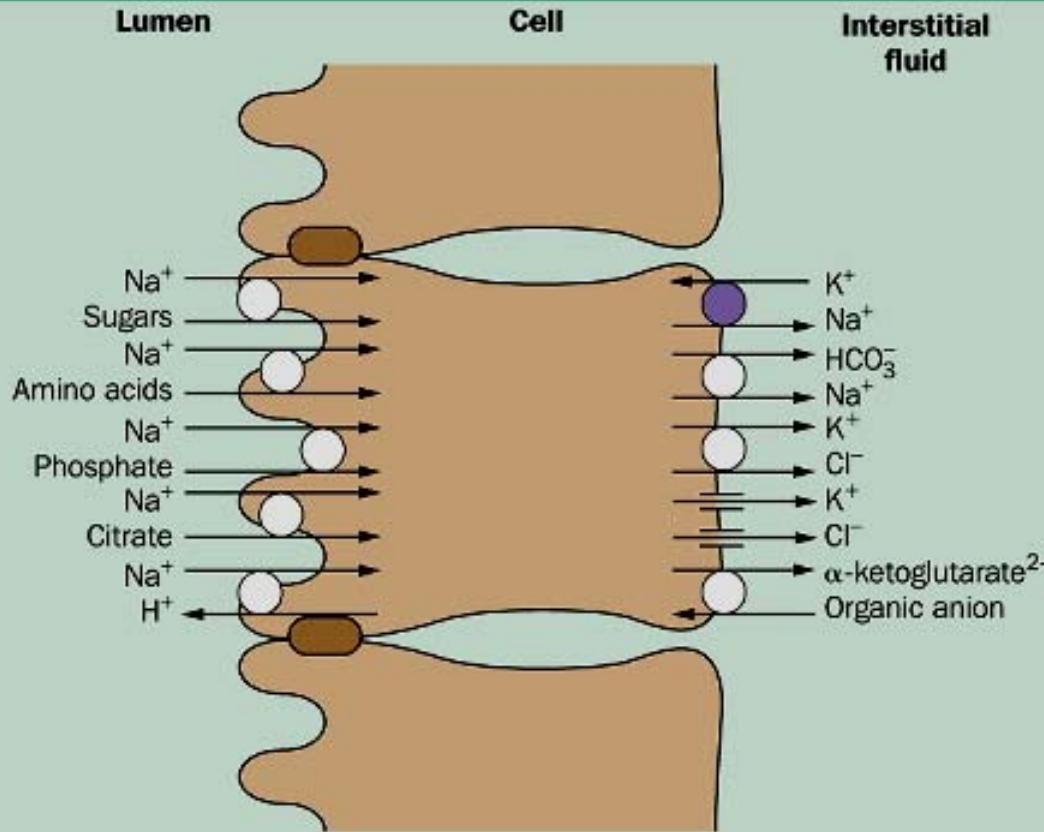


- | | |
|---|-------------------------------------|
| 1. Renal corpuscle | 7. Macula densa |
| 2. Proximal convoluted tubule | 8. Distal convoluted tubule |
| 3. Proximal straight tubule | 9. Connecting tubule |
| 4. Descending thin limb | 10. Cortical collecting duct |
| 5. Ascending thin limb | 11. Outer medullary collecting duct |
| 6. Distal straight tubule
(thick ascending limb) | 12. Inner medullary collecting duct |

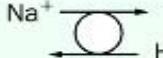
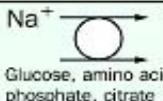
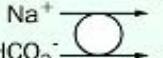
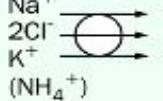
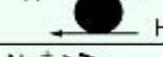
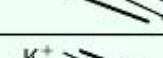
Renal sodium handling



Proximal tubular transporters

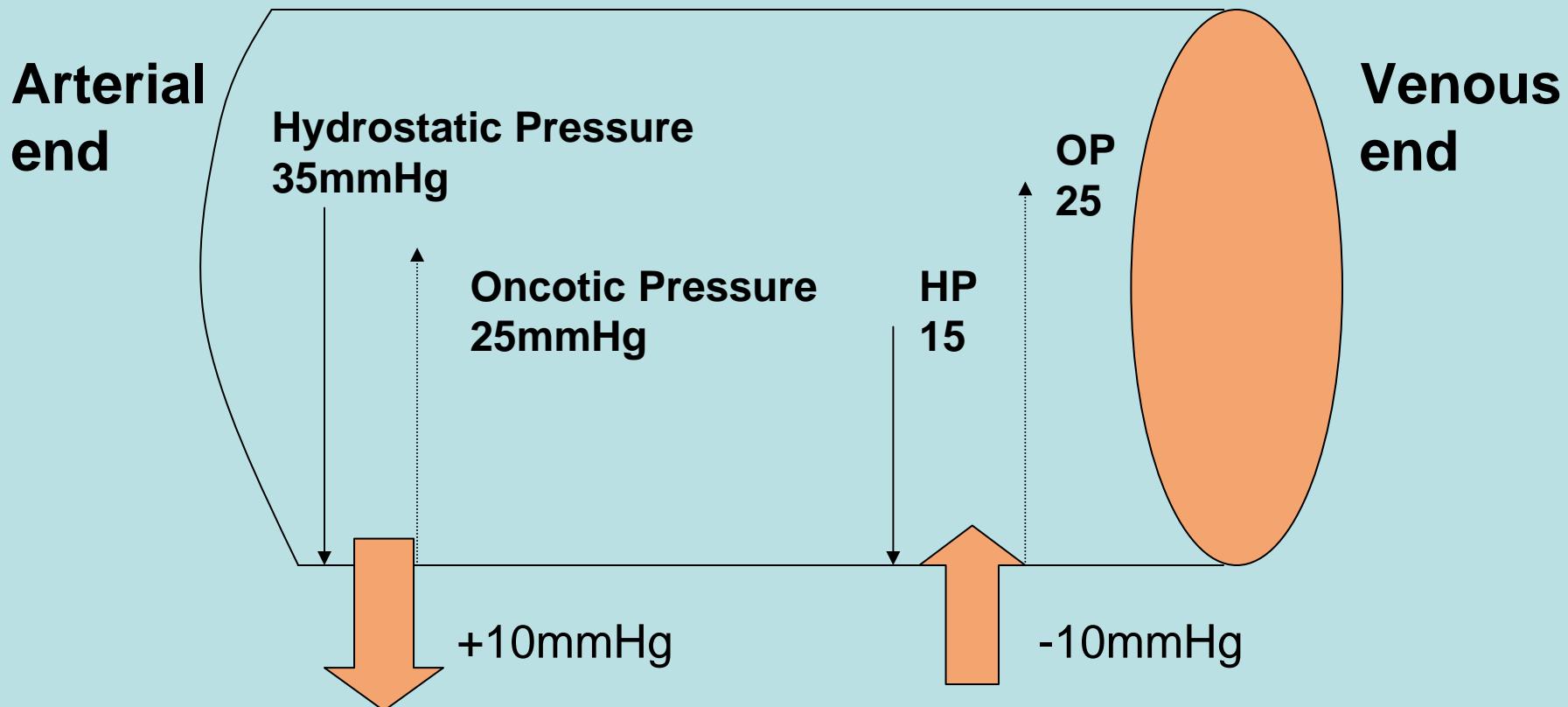


Major membrane transporters in the nephron

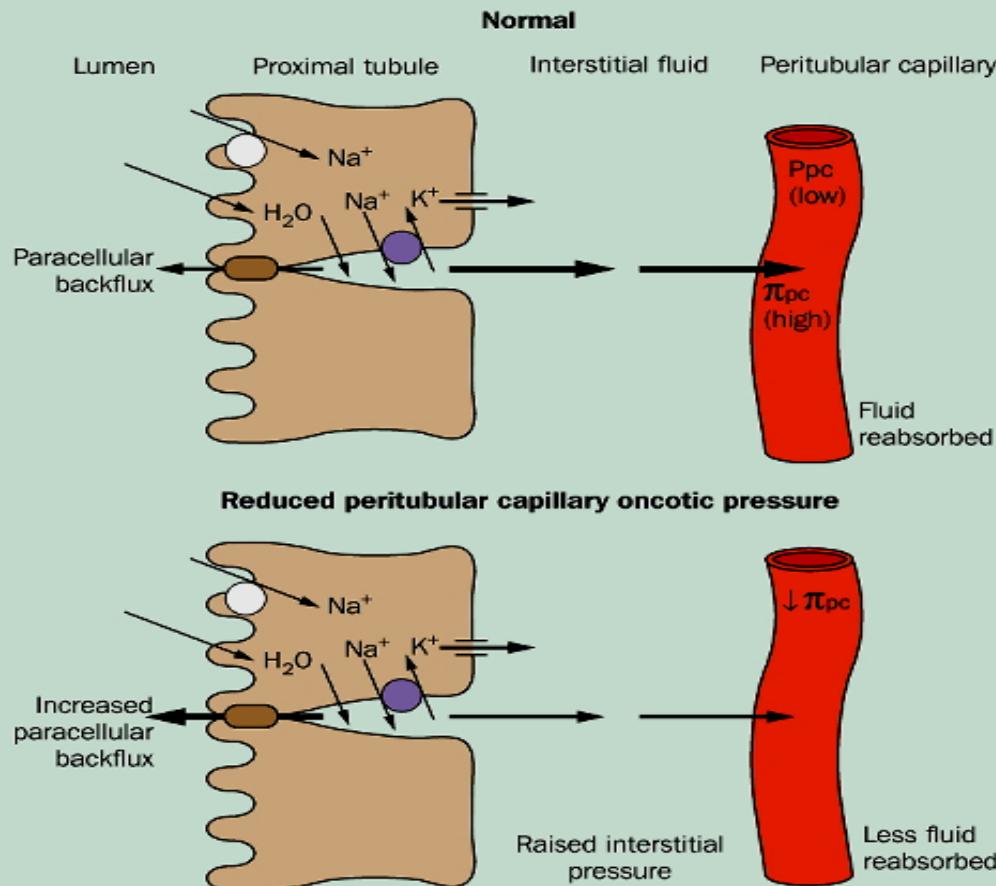
Transporter	Type	Segmental (nephron) location	Membrane location (apical/basolateral)
	Sodium pump	Ubiquitous	Basolateral
	Sodium/hydrogen antiporter	Ubiquitous	Apical (NHE2 and 4) Basolateral (NHE1; 'housekeeping')
	Sodium-dependent cotransporter	Proximal tubule	Apical
	Sodium/bicarbonate cotransporter	Proximal tubule and thick ascending limb	Basolateral
	Sodium/chloride/potassium cotransporter	Thick ascending limb (NKCC2)	Apical (NKCC2)
	Sodium/chloride cotransporter	Early distal tubule	Apical
	Potassium/hydrogen exchange pump	Distal nephron (α intercalated cells)	Apical
	Sodium channels	Distal nephron (principal cells)	Apical
	Potassium channels	Thick ascending limb Distal nephron Ubiquitous	Apical Apical Basolateral

Capillary Circulation

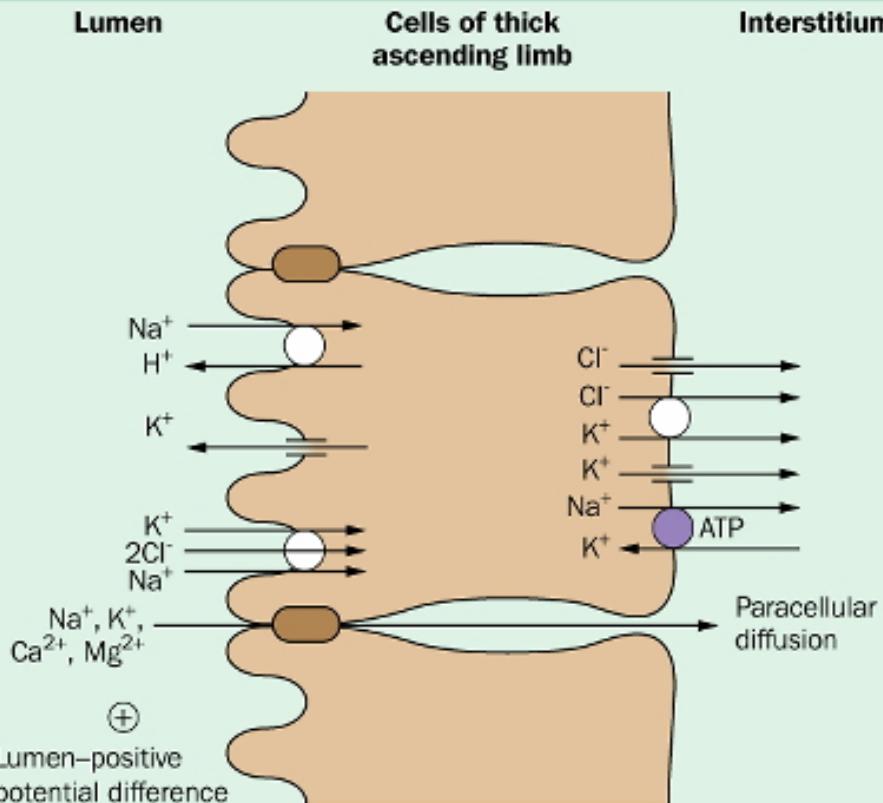
Starling Forces



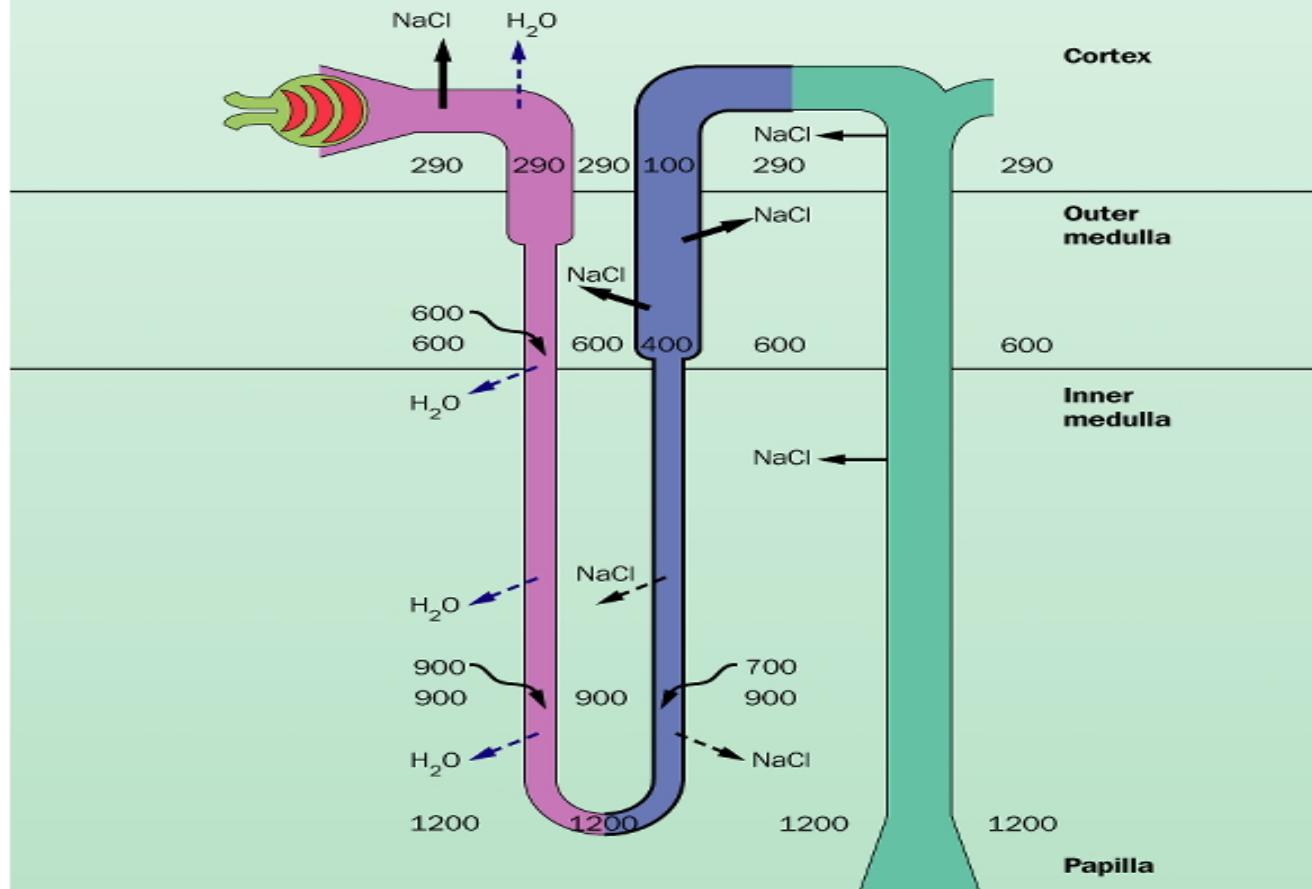
Peritubular capillaries modulate fluid reabsorption



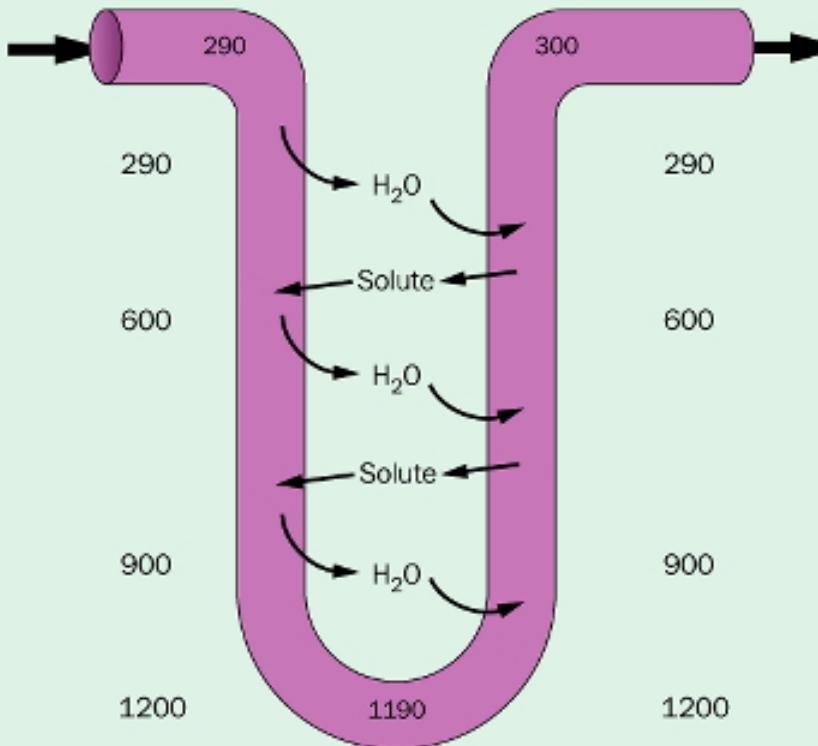
Transport mechanisms in the thick ascending limb



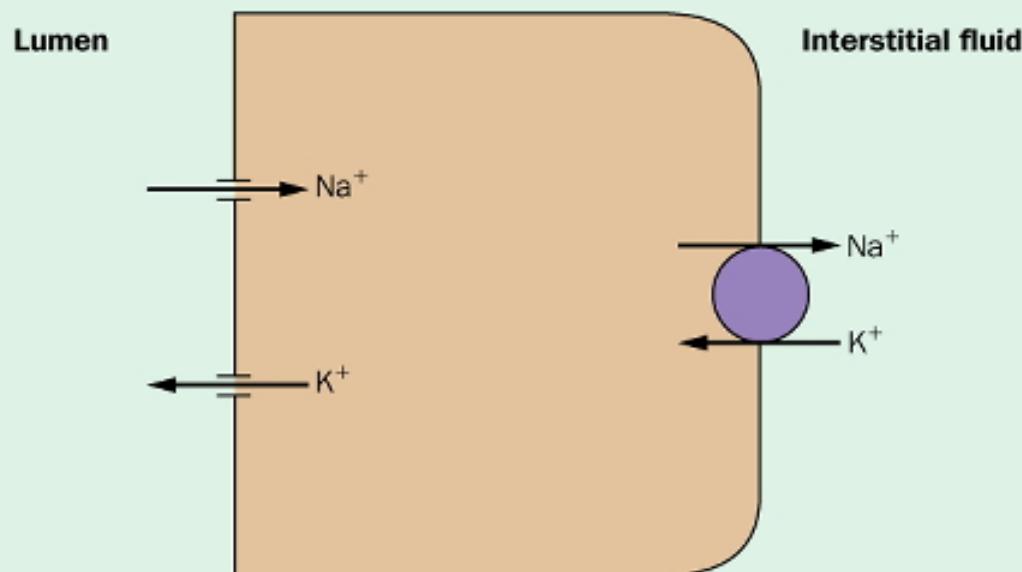
Countercurrent multiplication by the loop of Henle



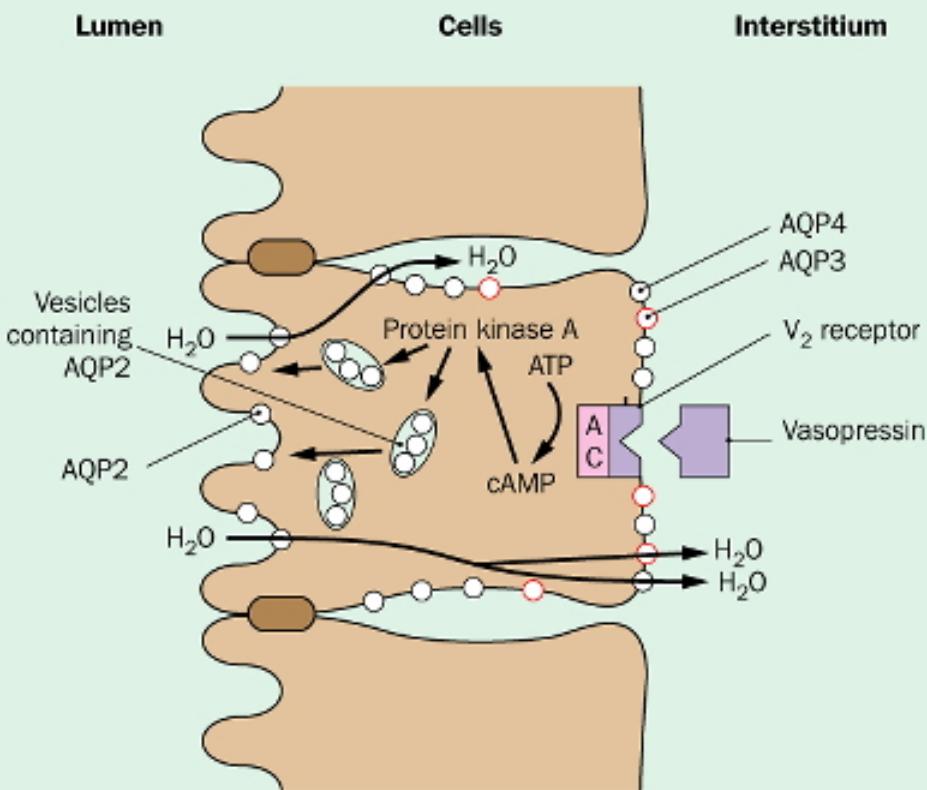
Countercurrent exchange



Principal cell



Action of vasopressin



VASOPRESSIN SECRETION

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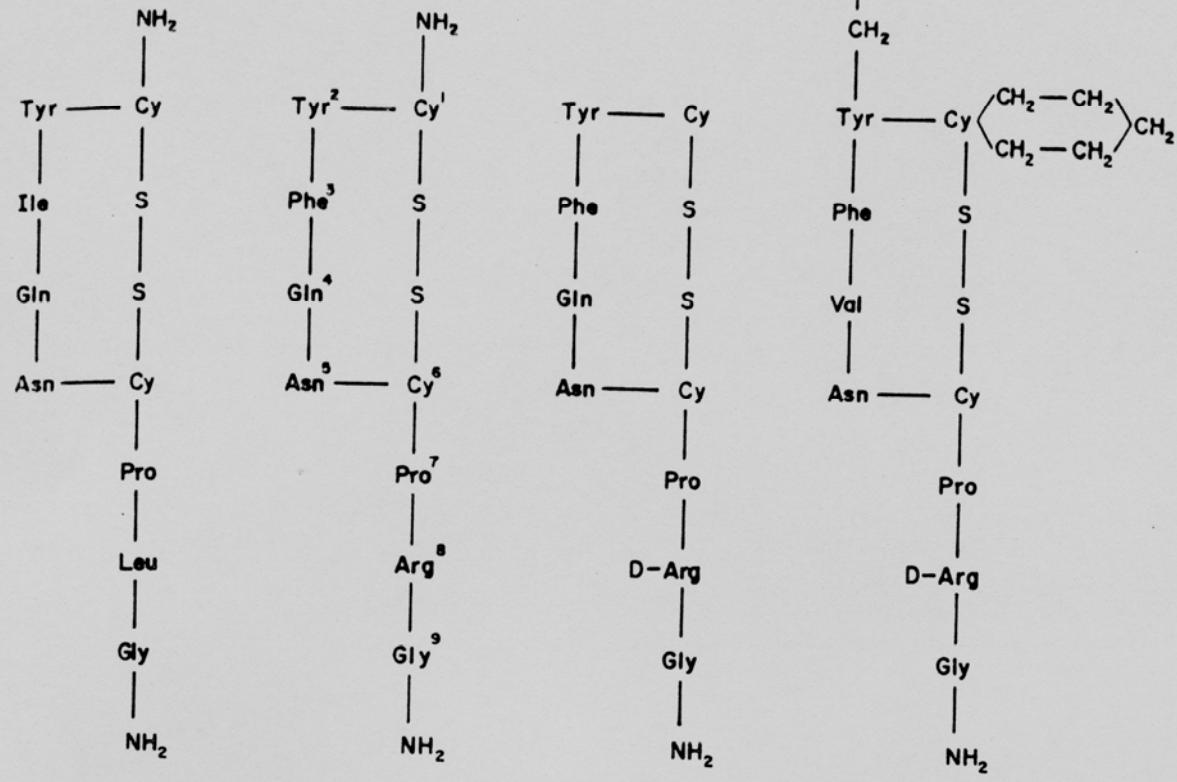
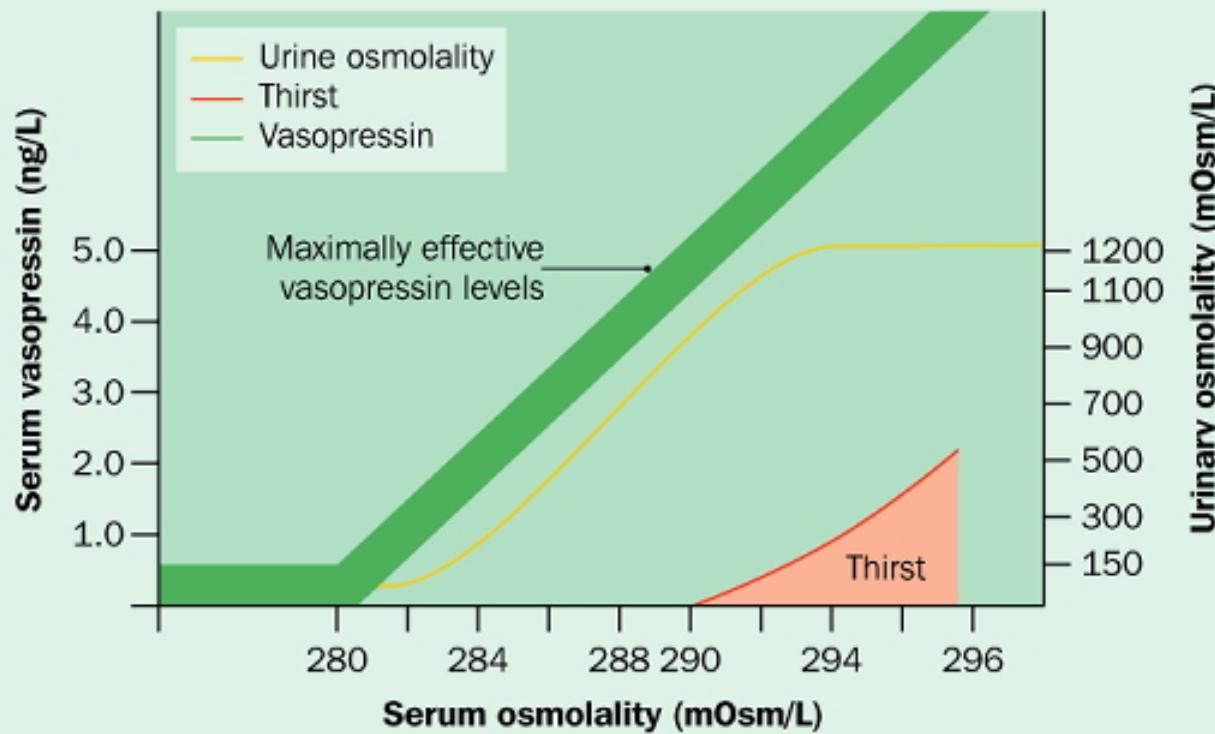
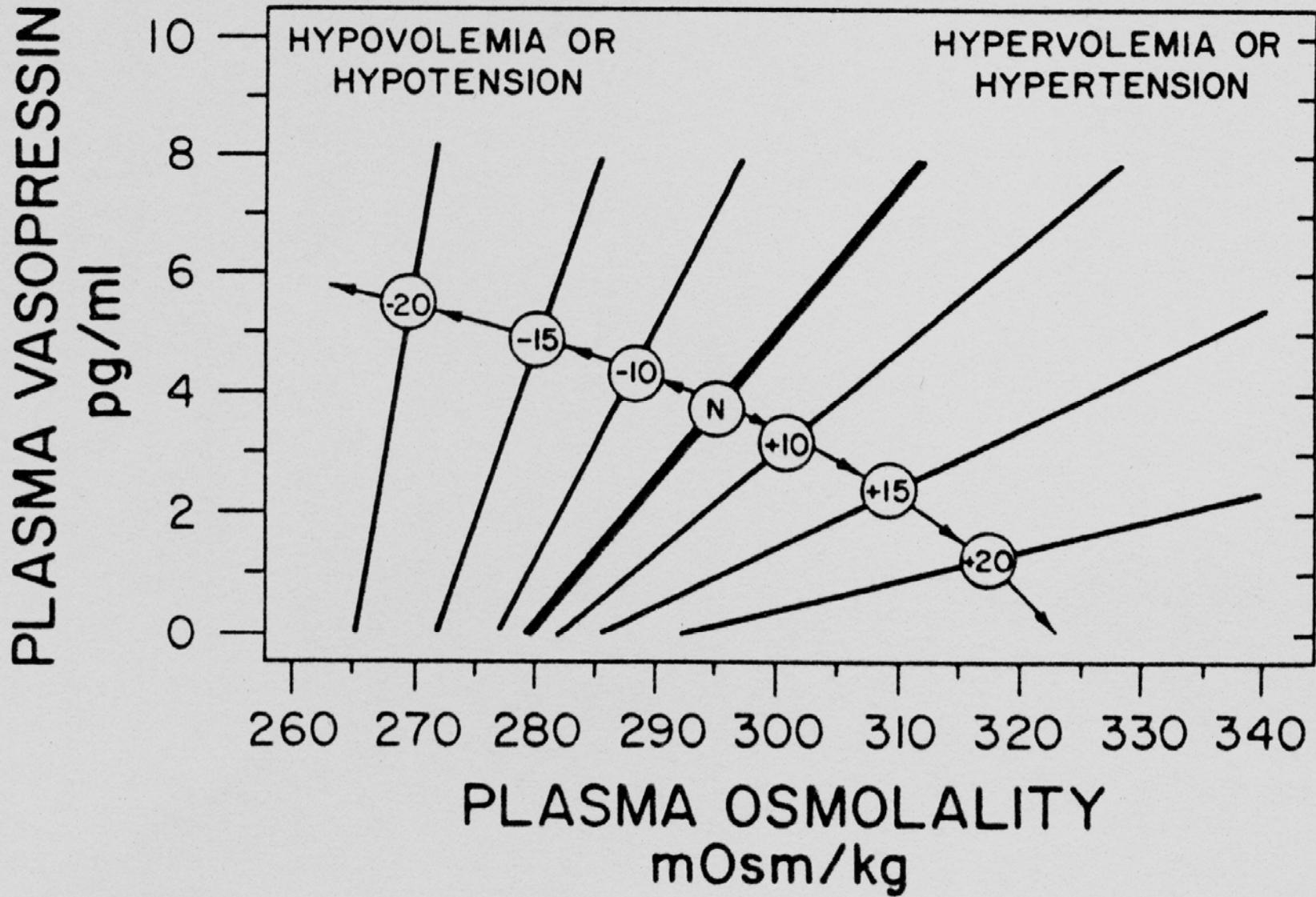


FIG. 2. Primary structures of arginine vasopressin and related peptides. Amino acid residues are abbreviated as follows: Cy, cysteine; Tyr, tyrosine; Phe, phenylalanine; Gln, glutamine; Asn, asparagine; Pro, proline; Arg, arginine; Gly, glycine; Ile, isoleucine; Leu, leucine; Val, valine.

Robertson GL, Ch 36, in
Seldin & Giebisch: The Kidney

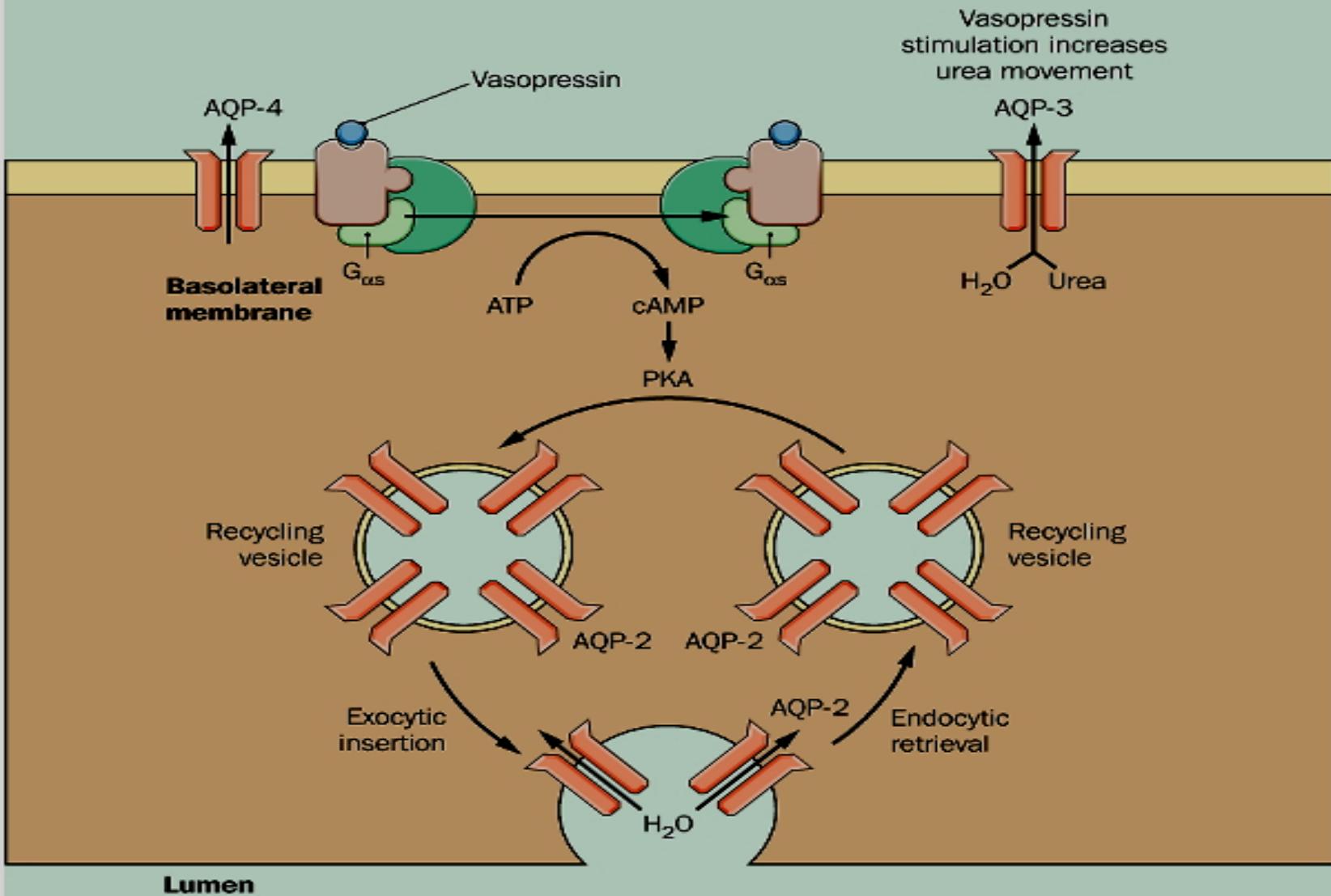
Response to changes in serum osmolality





Robertson GL Ch 36 in Seldin & Giebisch: The Kidney-Physiology-Pathophysiology

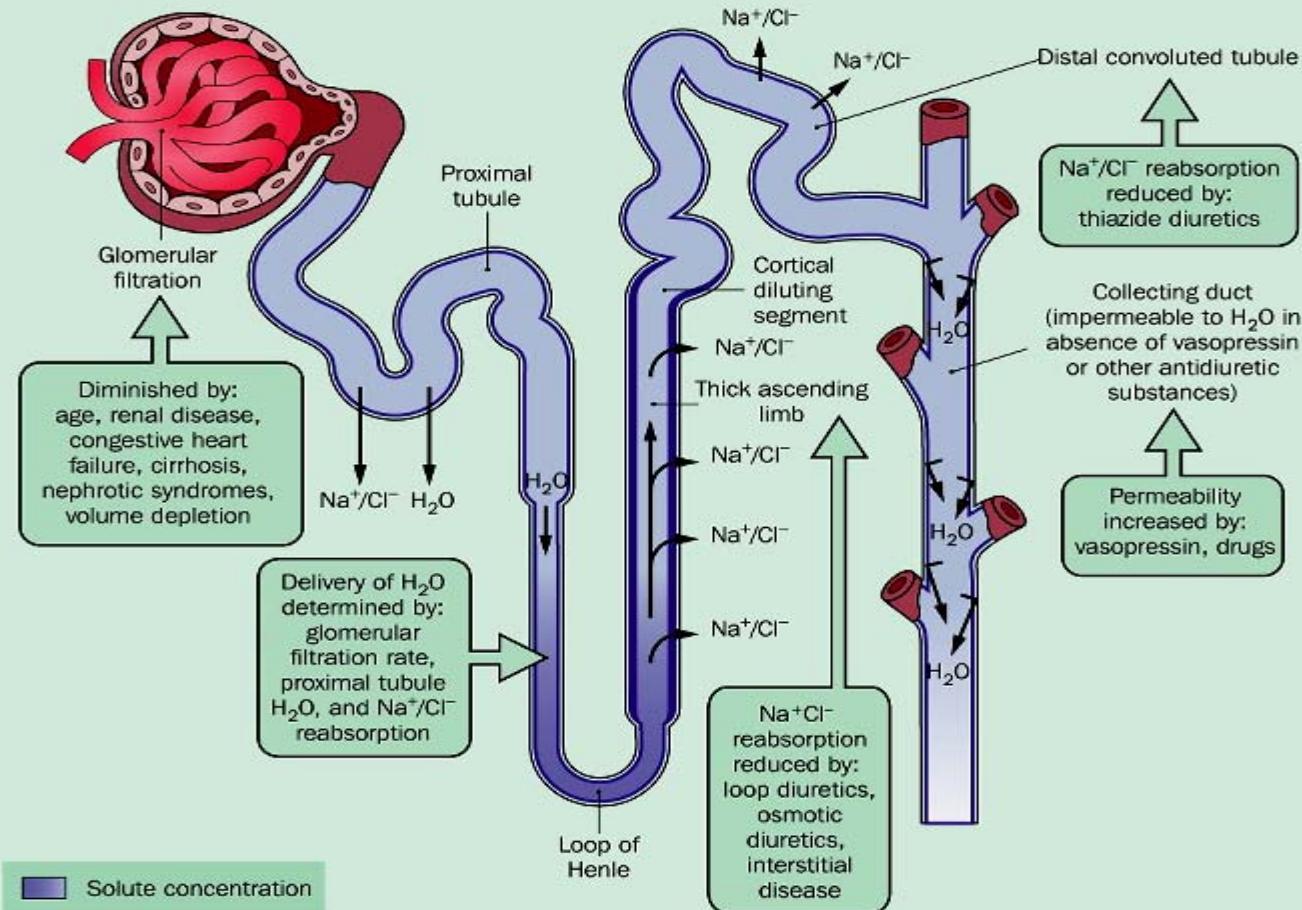
Aquaporins and vasopressin action



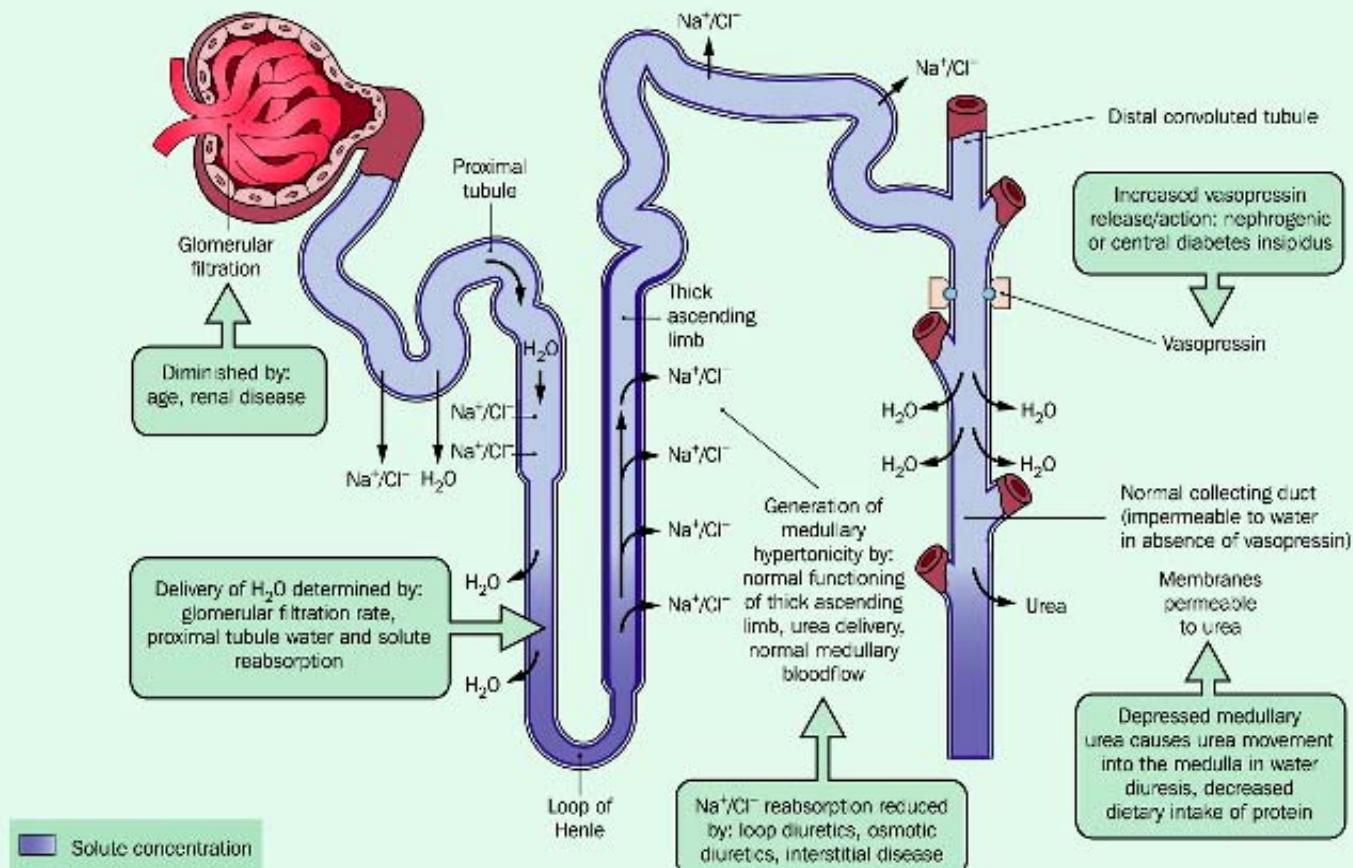
Characteristics of aquaporins (AQPs)

Characteristics	AQP-1	AQP-2	AQP-3	AQP-4	AQP-6	AQP-7	AQP-8
Size (amino acid residues)	269	271	285	301	282	269	263
Permeability to small solutes	No	No	Urea, glycerol	No	No	Glycerol, urea	Urea
Regulation by vasopressin	No	Yes	No	No	No	No	No
Site	Proximal tubules, descending thin limb	Collecting duct principal cells	Medullary collecting duct, colon	Hypothalamic, supraoptic and paraventricular nuclei; ependymal, granular, and Purkinje cells	Proximal tubules, collecting duct Intercalated cells	Testis, kidney	Kidney, pancreas, heart, liver, colon, brain
Cellular	Apical and	Apical membrane	Basolateral	Basolateral	Intracellular	unknown	Intracellular

Mechanisms of urine dilution



Mechanisms of urine concentration



Free Water Clearance

■ EQUATION 8.1

$$V = C_{\text{osm}} + C_{\text{water}}$$

$$C_{\text{water}} = V - C_{\text{osm}}$$

The term C_{osm} relates urine osmolality to plasma osmolality P_{osm} by

$$C_{\text{osm}} = \left(\frac{U_{\text{osm}} \times V}{P_{\text{osm}}} \right)$$

Therefore,

Free Water Clearance

■ EQUATION 8.2

$$C_{\text{water}} = V - \left(\frac{U_{\text{osm}} \times V}{P_{\text{osm}}} \right)$$

$$= V \left(1 - \frac{U_{\text{osm}}}{P_{\text{osm}}} \right)$$

Free Water (of electrolytes) Clearance

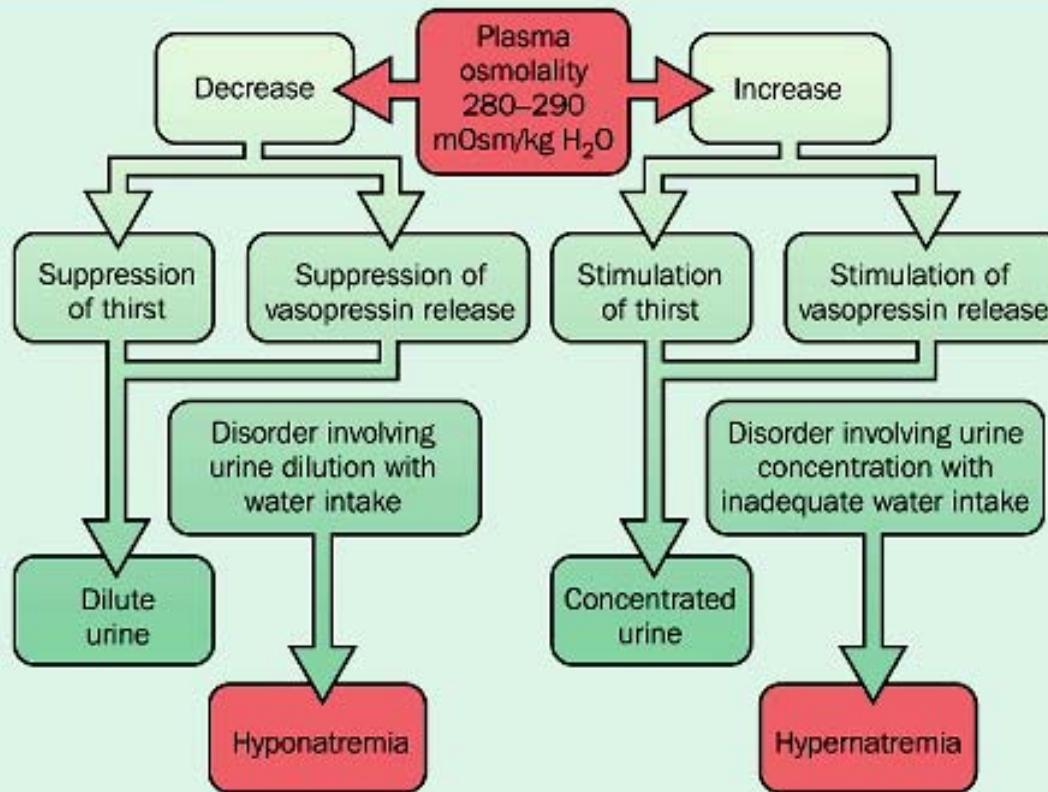
■ EQUATION 8.3

$$C_{\text{water}}(e) = V \left(1 - \frac{U_{\text{Na}} + U_{\text{K}}}{P_{\text{Na}}} \right)$$

Calculated serum Osmolality

- $2[\text{Na}^+ \text{mEq/L}] + \frac{\text{Urea mg/dL}}{6} + \frac{\text{Glucose mg/dL}}{18}$

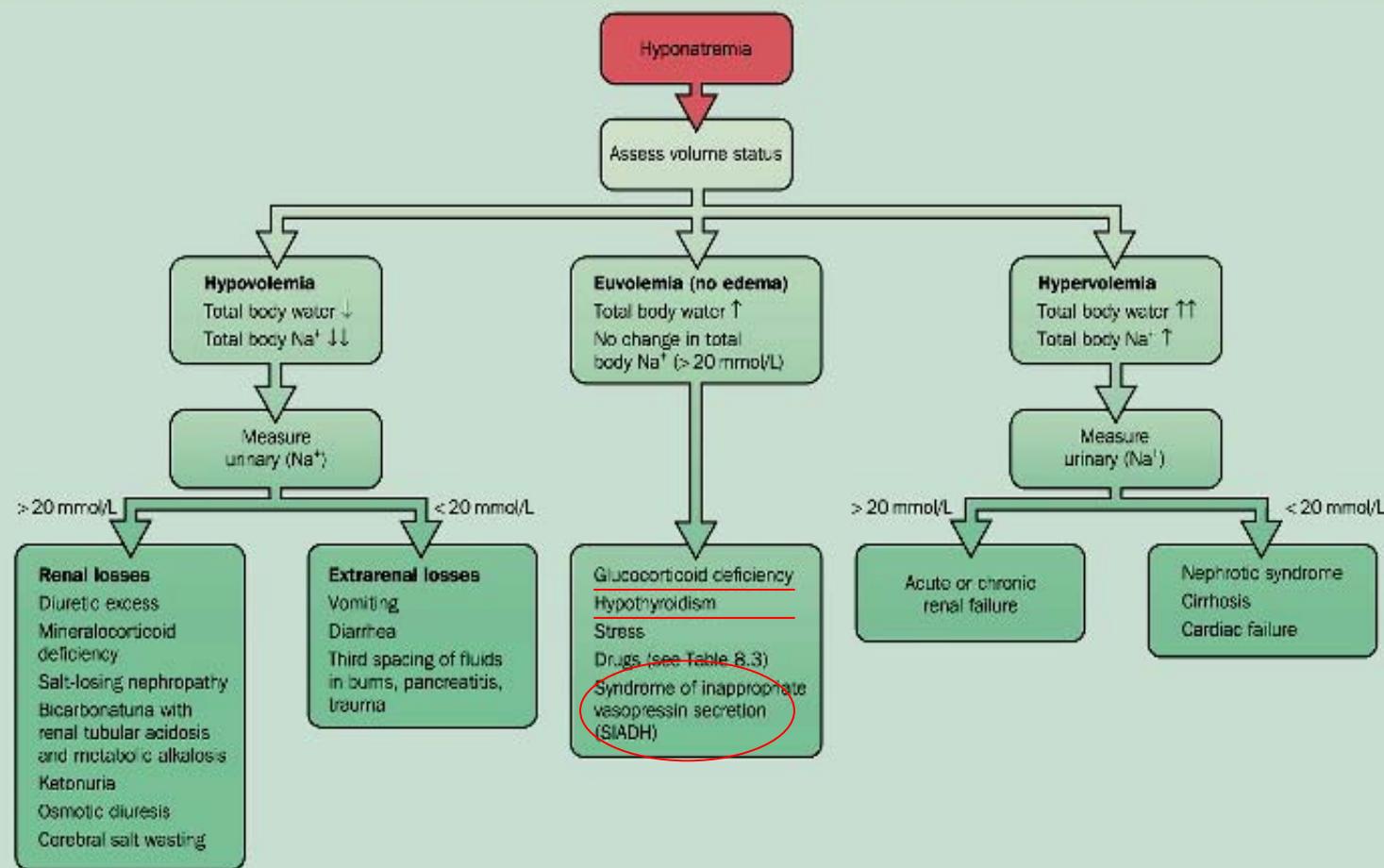
Plasma osmolality and dysnatremias



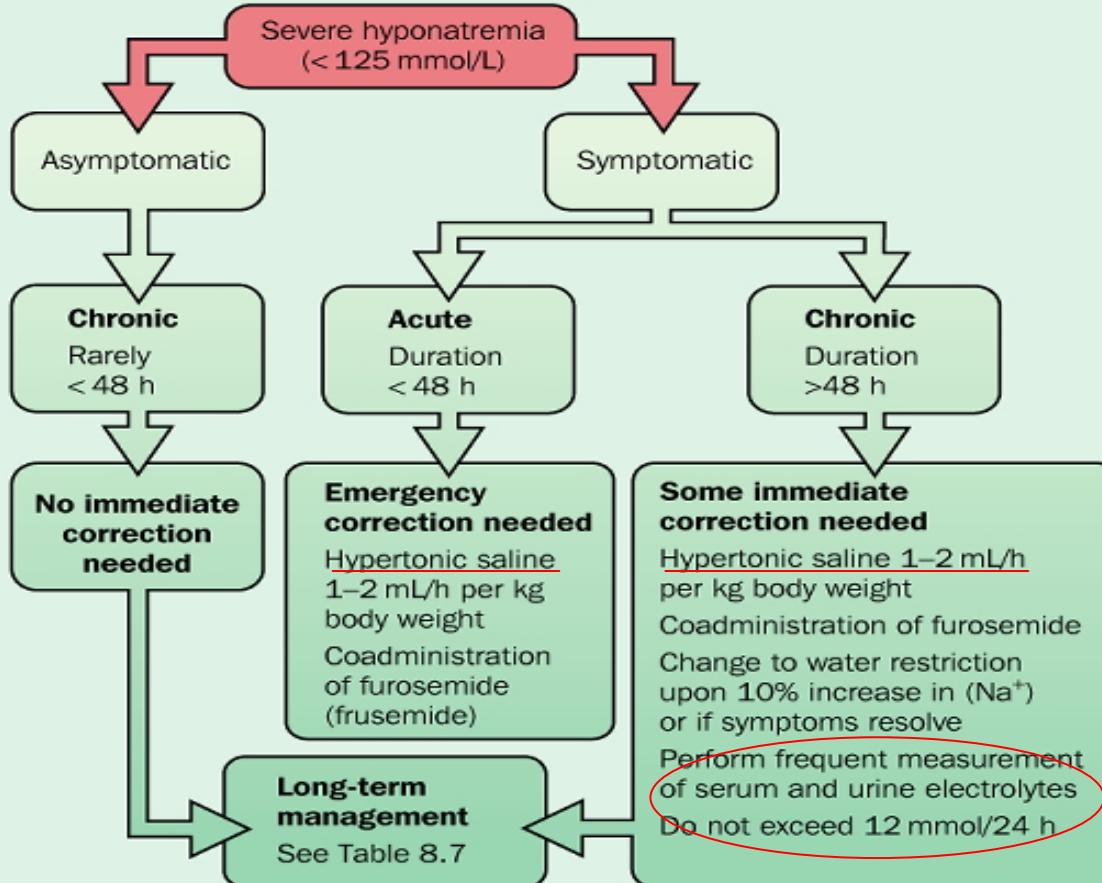
The effects of osmotically active substances on serum sodium levels

Substances that increase osmolality without changing serum Na⁺	Substances that increase osmolality and decrease serum Na⁺ (translocational hyponatremia)
Urea	Glucose
Ethanol	Mannitol
Ethylene glycol	Glycine
Isopropyl alcohol	Maltose
Methanol	

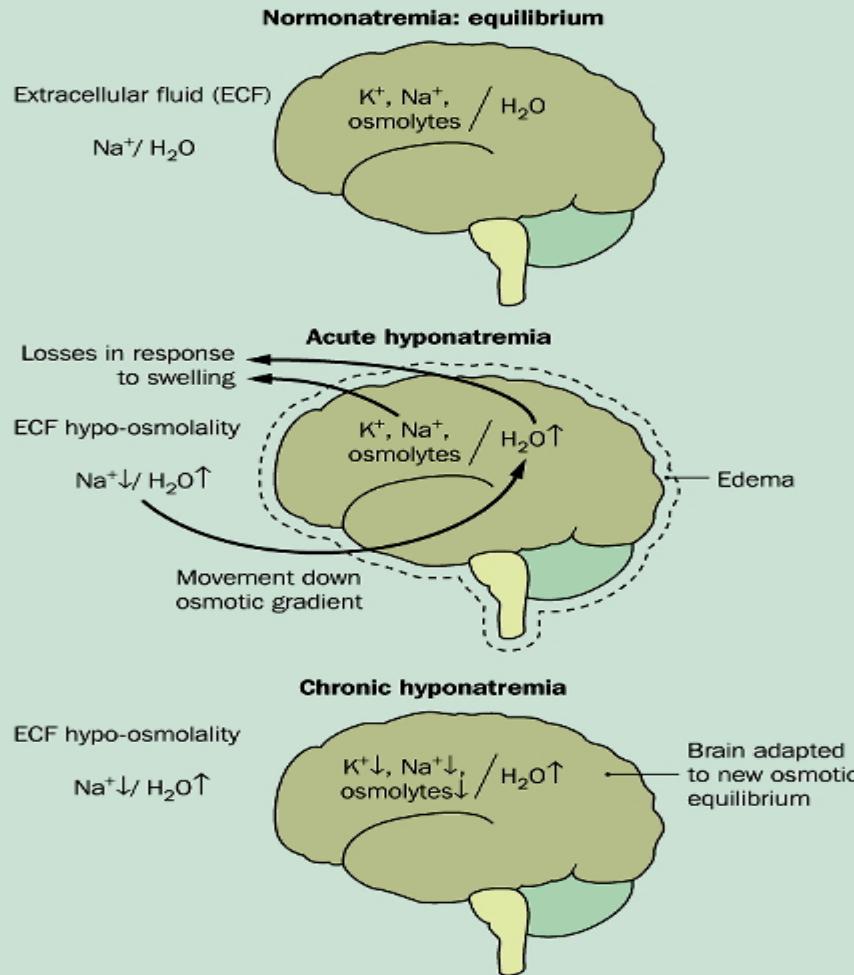
Diagnostic approach in hyponatremia

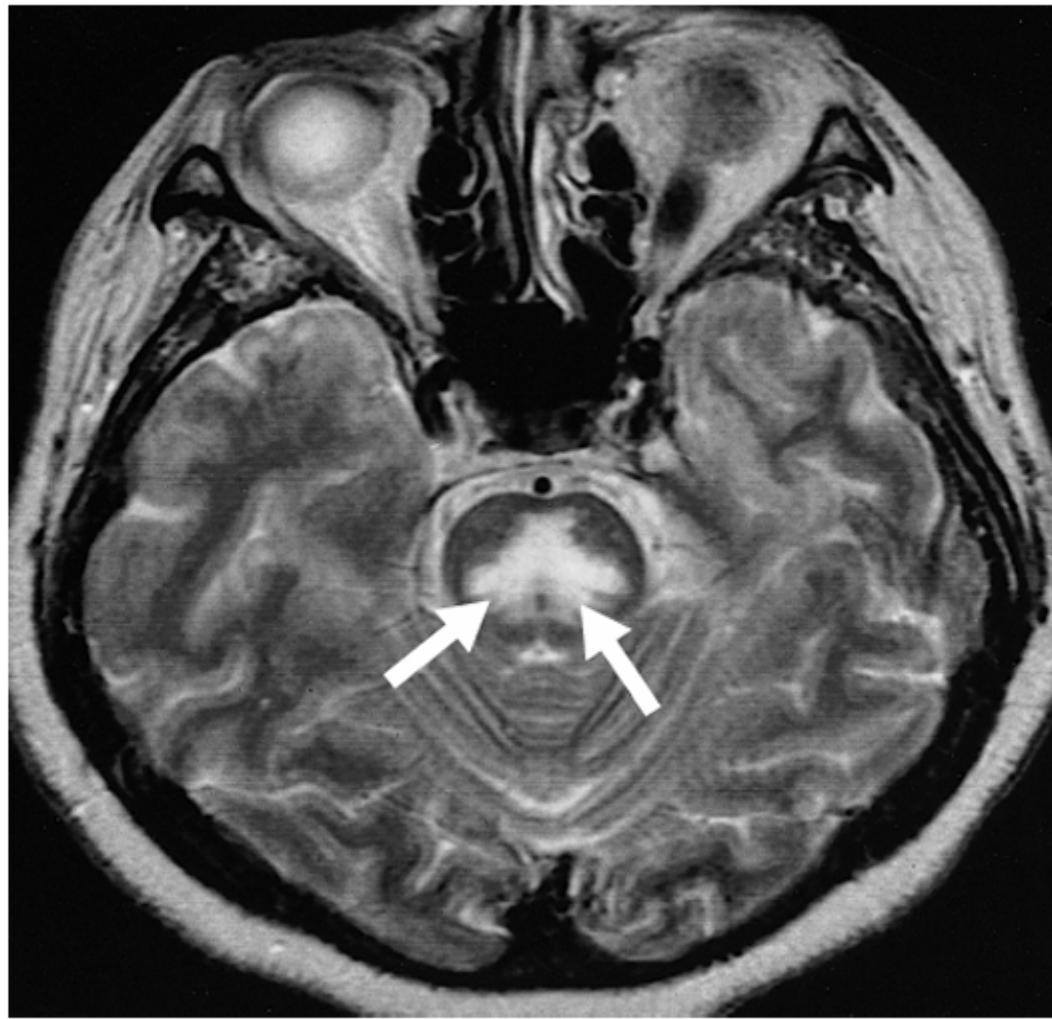


Symptomatic hyponatremia



Brain volume adaptation to hyponatremia





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Hyponatremic patients at risk for neurologic complications

Acute cerebral edema	Osmotic demyelination syndrome
Postoperative menstruant females	Alcoholics
Elderly women taking thiazides	Malnourished patients
Children	Hypokalemic patients
Psychiatric polydipsic patients	Burn victims
Hypoxemic patients	Elderly women on thiazide diuretics
	Hypoxemia

With permission from Lauriat and Berl²⁴

Drugs associated with hyponatremia*

Vasopressin analogs	Drugs that potentiate renal action of vasopressin
Desmopressin (DDAVP) Oxytocin	Chlorpropamide Cyclophosphamide Nonsteroidal anti-inflammatory agents Acetaminophen (paracetamol)
Drugs that enhance vasopressin release	Drugs that cause hyponatremia by unknown mechanisms
Chlorpropamide Clofibrate <i>Carbamazepine–oxycarbazepine</i> Vincristine Nicotine Narcotics <i>Antipsychotics/antidepressants</i> Ifosfamide	<u>Haloperidol</u> Fluphenazine Amitriptyline Thioradazine Fluoxetine <i>Metamphetamine (MDMA or Ecstacy)</i> Sertraline

*Not including diuretics

Modified with permission from Veis and Berl¹⁹

Italics: The common causes

Causes of the syndrome of inappropriate vasopressin release (SIADH)

Carcinomas	Pulmonary disorders	Nervous system disorders	Other
Bronchogenic carcinoma	<i>Viral pneumonia</i>	Encephalitis (viral or bacterial)	AIDS-HIV
Carcinoma of the duodenum	<i>Bacterial pneumonia</i>	Meningitis (viral, bacterial, tuberculous, and fungal)	Idiopathic (elderly)
Carcinoma of the pancreas	<i>Pulmonary abscess</i>	Head trauma	Prolonged exercise
Thymoma	Tuberculosis	Brain abscess	
Carcinoma of the stomach	Aspergillosis	Brain tumors	
Lymphoma	Positive pressure breathing	Guillain–Barré syndrome	
Ewing's sarcoma	Asthma	Acute intermittent porphyria	
Carcinoma of the bladder	Pneumothorax	Subarachnoid hemorrhage or subdural hematoma	
Prostatic carcinoma	Mesothelioma	Cerebellar and cerebral atrophy	
Oropharyngeal tumor	Cystic fibrosis	Cavernous sinus thrombosis	
Carcinoma of the ureter		Neonatal hypoxia	
		Hydrocephalus	
		Shy–Drager syndrome	
		Rocky Mountain spotted fever	
		Delirium tremens	
		Cerebrovascular accident (cerebral thrombosis or hemorrhage)	
		Acute psychosis	
		Peripheral neuropathy	
		Multiple sclerosis	

With permission from Berl and Schrier²⁰

Italics: the common causes.

Diagnostic criteria for the syndrome of inappropriate vasopressin release (SIADH)

Essential diagnostic criteria

Decreased extracellular fluid effective osmolality ($<270 \text{ mOsm/kg H}_2\text{O}$)

Inappropriate urinary concentration ($>100 \text{ mOsm/kg H}_2\text{O}$)

Clinical euolemia

Elevated urinary Na^+ concentration under conditions of a normal salt and water intake

Absence of adrenal, thyroid, pituitary, or renal insufficiency or diuretic use

Supplemental criteria

Abnormal water-load test (inability to excrete at least 90% of a 20 mL/kg water load in 4 h and/or failure to dilute urine osmolality to $<100 \text{ mOsm/kg}$)

Plasma vasopressin level inappropriately elevated relative to the plasma osmolality

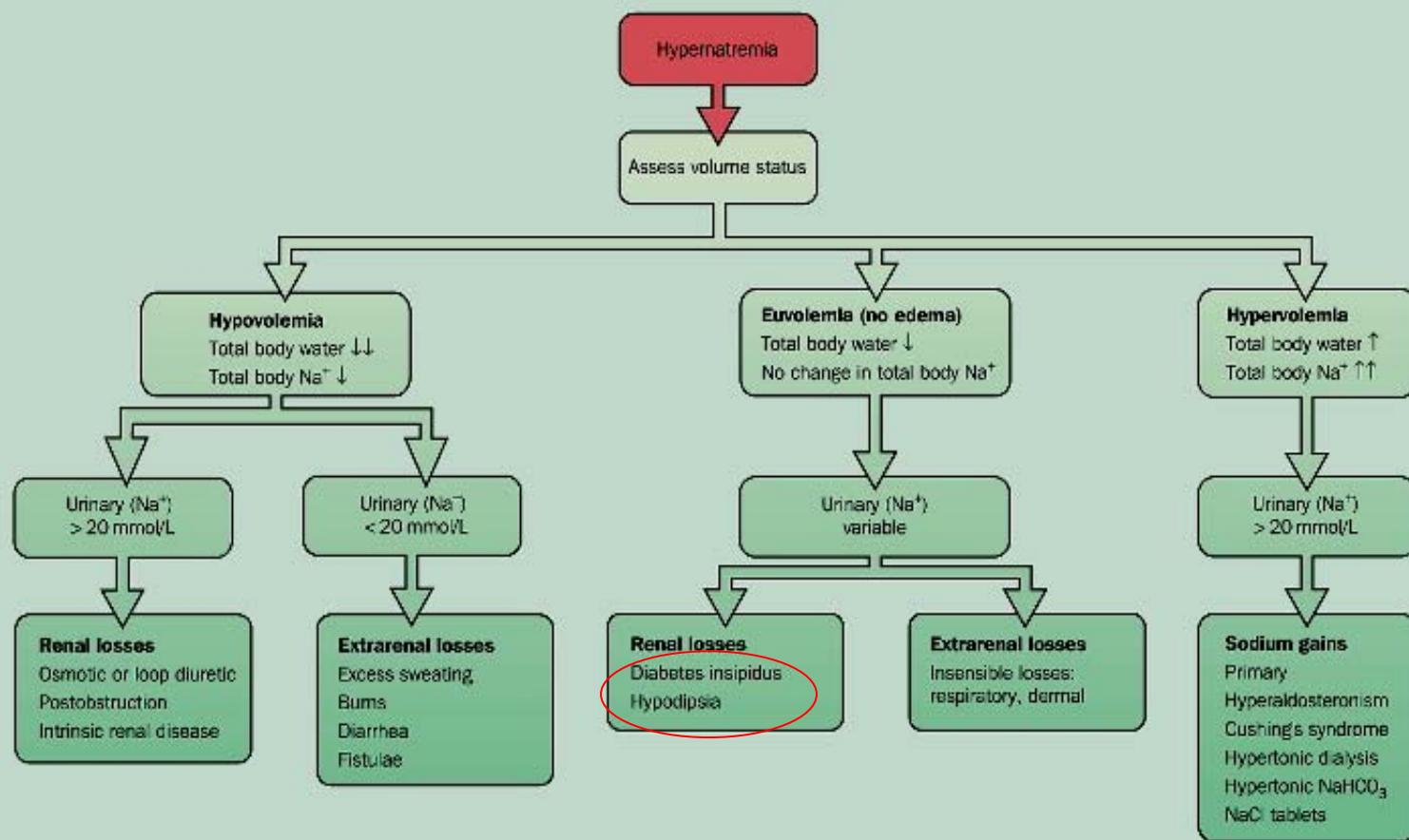
No significant correction of plasma Na^+ level with volume expansion, but improvement after fluid restriction

With permission from Verbalis²²

Treatment of chronic asymptomatic hyponatremia

Treatment	Mechanism of action	Dose	Advantages	Limitations
Fluid restriction	Decreases availability of free water	Variable	Effective and inexpensive Not complicated	Non-compliance
Pharmacologic inhibition of vasopressin action				
Lithium	Inhibits the kidney's response to vasopressin	900–1200 mg daily	Unrestricted water intake	Polyuria, narrow therapeutic range, neurotoxicity
Demeclocycline	Inhibits the kidney's response to vasopressin	300–600 mg twice daily	Effective; unrestricted water intake	Neurotoxicity, polyuria, photosensitivity, nephrotoxicity
V_2 receptor antagonist	Antagonizes vasopressin action	–	Ongoing trials	–
Increased solute (salt) intake with <u>furosemide (frusemide)</u>	Increases free water clearance	Titrate to optimal dose; coadministration of 2–3 g NaCl	Effective	Ototoxicity, K^+ depletion
with urea	Osmotic diuresis	30–60 g daily	Effective; unrestricted water intake	Polyuria, unpalatable, gastrointestinal symptoms

Diagnostic approach for the hypernatremic patient



Water deprivation test

Condition	Urinary osmolality with water deprivation (mOsm/kg H ₂ O)	Plasma vasopressin after dehydration (ng/L)	Increase in urinary osmolality with exogenous vasopressin
Normal	>800	>2	Little or no increase
Complete central diabetes insipidus	<300	Undetectable	Substantially increased
Partial central diabetes insipidus	300–800	<1.5	Increase of greater than 10% of urinary osmolality after water deprivation
Nephrogenic diabetes insipidus	<300–500	>5	Little or no increase
Primary polydipsia	>500	<5	Little or no increase
With permission from Lanese and Teitelbaum ³³ Test Procedure: Water intake is restricted until the patient loses 3–5% of his/her body weight or until three consecutive hourly determinations of urinary osmolality are within 10% of each other. (Caution must be exercised to ensure that the patient does not become excessively dehydrated.) Aqueous vasopressin (5 U subcutaneously) is given and urinary osmolality is measured after 60 min. The expected responses are given in the table.			

Causes of central diabetes insipidus

Congenital

Autosomal dominant

Autosomal recessive

Acquired

Post-traumatic

Iatrogenic (postsurgical)

*Tumors (metastatic from breast,
craniopharyngioma, pinealoma)*

Histiocytosis

Granuloma (tuberculosis, sarcoid)

Aneurysm

Meningitis

Encephalitis

Guillain–Barré syndrome

Idiopathic 50%

Italics: The common causes.

Treatment of central diabetes insipidus

Disease	Drug	Dose	Interval (h)
Complete central diabetes insipidus	Desmopressin (DDAVP)	10–20µg intranasally	12–24 12
	Desmopressin Acetate (DDAVP)	0.05–0.2mg oral	
Partial central diabetes insipidus	Desmopressin (DDAVP)	10–20µg intranasally	12–24
	Aqueous vasopressin	5–10U s.c.	4–6
	Chlorpropamide	250–500mg	24
	Clofibrate	500mg	6 or 8
	Carbamazepine	400–600mg	24

Acquired nephrogenic diabetes insipidus: causes and mechanisms

Disease state	Defect in generation of medullary interstitial tonicity	Defect in cAMP generation	Downregulation of aquaporin 2	Other
Chronic renal failure	Yes	Yes	Yes	Downregulation of V ₂ receptor message
Hypokalemia	Yes	Yes	Yes	—
Hypercalcemia	Yes	Yes	—	—
Sickle cell disease	Yes	—	—	—
Protein malnutrition	Yes	—	Yes	—
Demeclocycline therapy	—	Yes	—	—
Lithium therapy	—	Yes	Yes	—
Pregnancy	—	—	—	Placental secretion of vasopressinase

Patient groups at risk for development of severe hypernatremia

Elderly patients or infants

Hospitalized patients receiving hypertonic infusions, tube feedings, osmotic diuretics, lactulose, mechanical ventilation

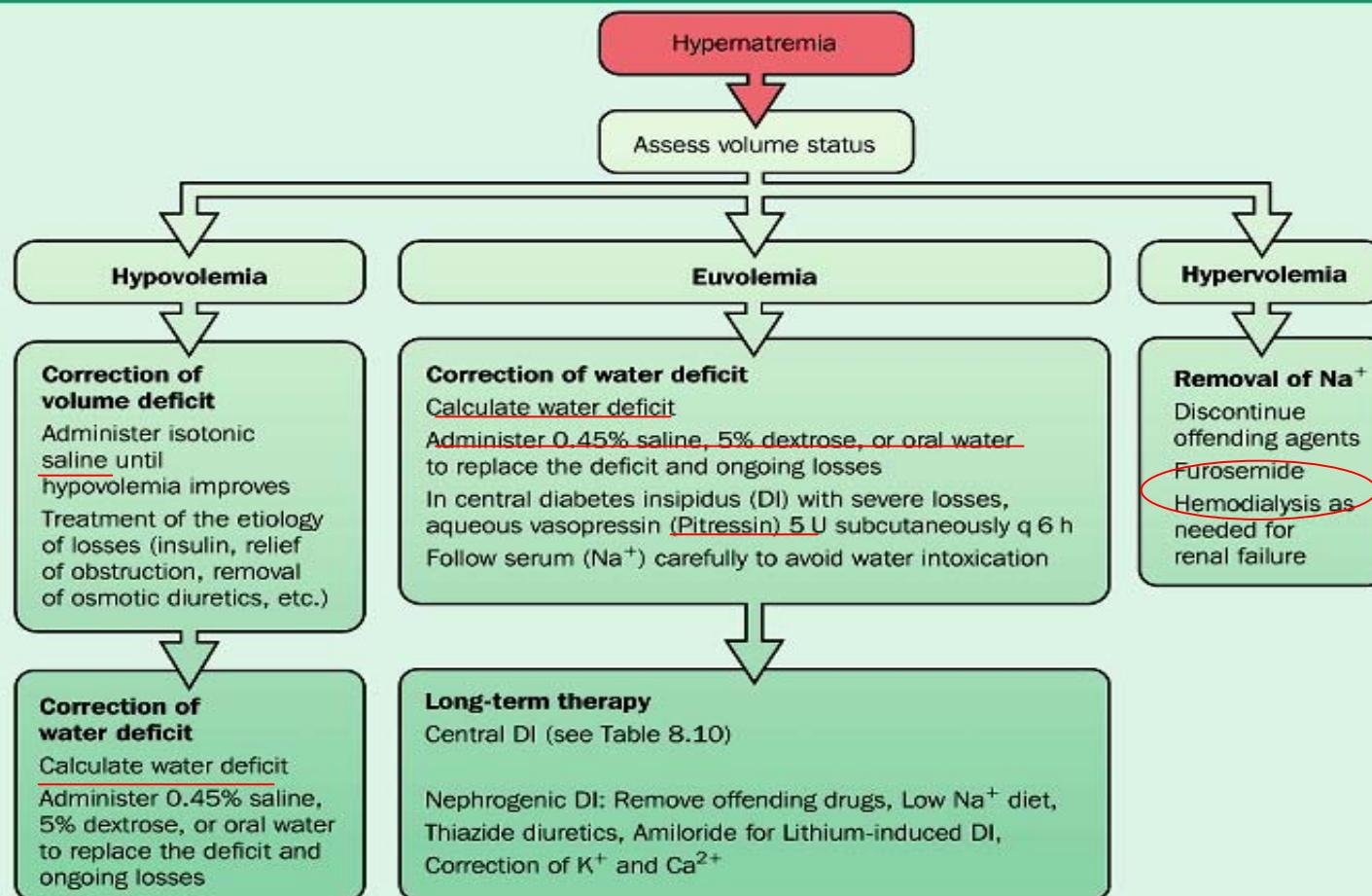
Altered mental status

Uncontrolled diabetes mellitus

Underlying polyuric disorders

With permission from Halterman and Berl⁵.

Management of hypernatremia



○

Sodium or Water correction

- Present $Na^*TBW = CorrNa^*NewTBW$
 - $Na_{pr}^*0.6^*BW = Na_{corr}^*NewTBW$
 - $120^*0.6^*70 = 140^*NewTBW$
 - $120^*42 = 140^*NewTBW$ $NewTBW = 36$
 - $160^*0.6^*70 = 140^*NewTBW$
 - $160^*42 = 140^*NewTBW$ $NewTBW = 48$

Daily Osmolar Load (OL) ~ 10mOsm/kg BW

- $OL(\sim 700) = U_v * U_{osm}$
- $OL = U_{vmax} * U_{osm \ min}$ $700 = 14 \text{ L} * 50$
- $OL = U_{vmin} * U_{osm \ max}$ $700 = 480 \text{ ml} * 1200$