Renal Regulation of Sodium and Volume

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Maintaining Volume

- Plasma water and sodium (Na^+) are regulated independently - you are already familiar with the regulation of plasma water.

  - Too much water – hyponatremia
  - Too little water – hypernatremia
  - Too much total Na^+ - hypervolemia and edema
  - Too little total Na^+ - hypovolemia and volume depletion

Aldosterone

- 21 carbon corticosteroid synthesized in the outermost area of the adrenal cortex, the zona glomerulosa.
- One of the major roles of aldosterone in renal function is to promote the reabsorption of Na^+ and the secretion of K^+ through the principal cells in the *late distal tubules and collecting ducts* of the kidney.
- Primarily stimulated via activation of the renin-angiotensin-aldosterone system (RAAS).

Atrial Natriuretic Peptide (ANP)

- A 28 amino acid polypeptide that is synthesized in the atria, and possibly the ventricular myocardial cells. Released in response to volume expansion / hypertension.
- ANP is a vasodilator, which lowers systemic blood pressure.
- ANP increases urinary Na^+ and water excretion through several mechanisms.
- ANP directly increases the GFR by vasodilating the afferent arterioles.

CEREBRAL SALT WASTING

- First described by Peters et al in 1950, cerebral salt-wasting syndrome (CSWS) is defined by the development of excessive natriuresis and subsequent hyponatremic dehydration in patients with intracranial disease.

- The exact mechanism underlying renal salt wasting in this syndrome remains unclear. However, one hypothesis states that the presence of abnormally high circulating natriuretic factors, including ANP, is important in producing the excess Na^+ loss seen in patients with CSWS.

Review of Renal Sodium Handling

- The **filtered load** for Na^+ is about 25,000 mEq's daily (assuming a GFR of 125 ml of plasma / min, this means about 180 liters of plasma is filtered every 24 hours, and normal plasma Na^+ concentration is about 140 mEqL).

- Average intake of Na^+ per day in U.S. is approximately 150 mEq (around 8 grams).

- Therefore, to stay in Na^+ balance, only about 150 mEq of the approximately 25,000 mEq of daily filtered Na^+ has to be excreted in the urine.

Renal Sodium Reabsorbtion

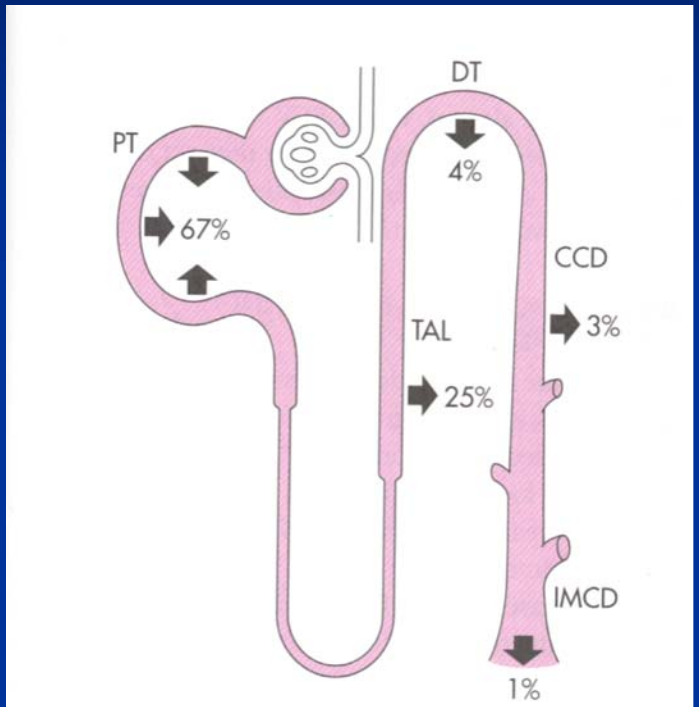
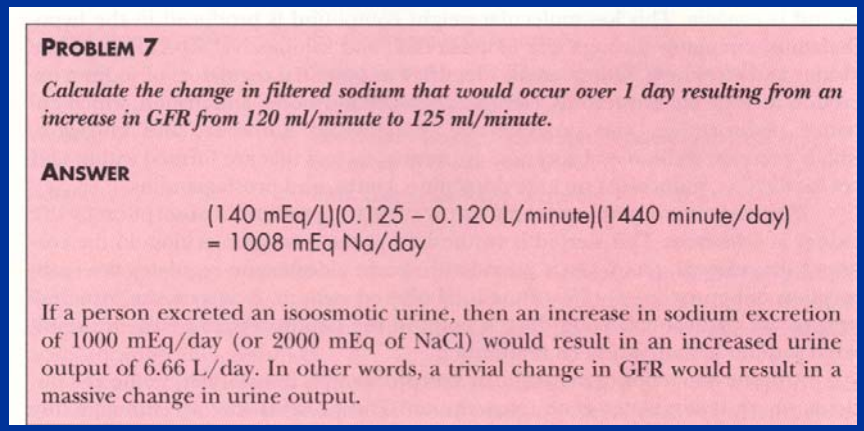


Figure 6-4 ■ Segmental Na^+ reabsorption. The percentage of the filtered load of Na^+ reabsorbed by each nephron segment is indicated. *PT,* Proximal tubule; *TAL,* thick ascending limb; *DT,* distal tubule; *CCD,* cortical collecting duct; *IMCD,* inner medullary collecting duct.

- About **two thirds** (67%) of the filtered load of Na^+ is isoosmotically reabsorbed in the proximal tubule (aldosterone not required).
- An additional 20 to 25% of the filtered Na^+ is reabsorbed in the thick ascending limb of Henles loop
- Around **8 to 13%** of the daily total filtered load of Na^+ actually makes it down to the **late distal tubules** and **collecting ducts**.

Renal Sodium Handling



PROBLEM 7

Calculate the change in filtered sodium that would occur over 1 day resulting from an increase in GFR from 120 ml/minute to 125 ml/minute.

ANSWER

(140 mEq/L)(0.125 – 0.120 L/minute)(1440 minute/day)
= 1008 mEq Na/day

If a person excreted an isoosmotic urine, then an increase in sodium excretion of 1000 mEq/day (or 2000 mEq of NaCl) would result in an increased urine output of 6.66 L/day. In other words, a trivial change in GFR would result in a massive change in urine output.

- The kidneys regulate urinary Na^+ loss is by changing the GFR (and thus the Na^+ filtered load), and changing rates of Na^+ reabsorbtion in the nephron.
- In the example at left, you can see how just a 5 ml/min increase in GFR can affect the total amount of Na^+ filtered in a day. This is what can happen in HYPERVOLEMIC states, making this Na^+ available for excretion into the urine.

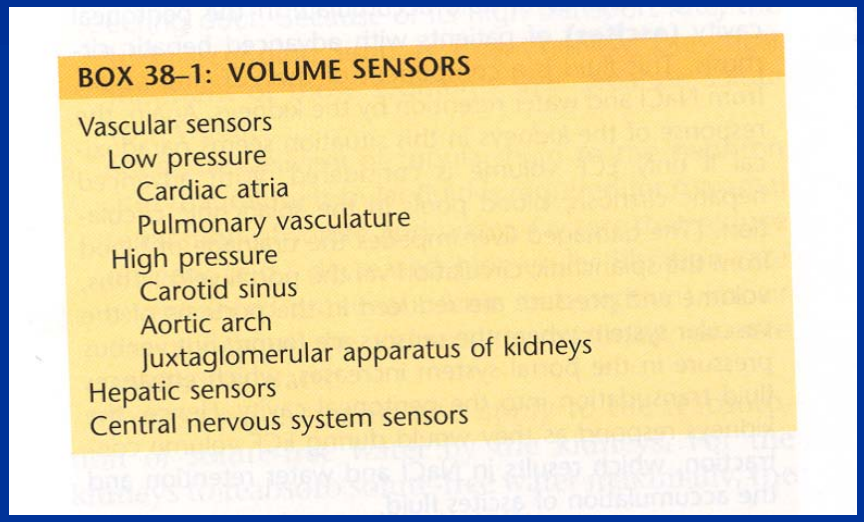
Effective Circulating Volume

- The ECV is not a measurable or distinct body fluid compartment, like the ECF. Instead, it is a concept related to the "fullness" and "pressure" within the large arteries.

- Therefore, unlike the ECF, which refers to the volume of fluid and solute in both the plasma as well as the interstitial fluid (ISF), ECV refers to the volume and pressure sensed *within the major arteries only*.

- In some disorders (CHF), the ECV and the ECF can differ markedly.

Low Pressure Sensors in the ECV



BOX 38–1: VOLUME SENSORS

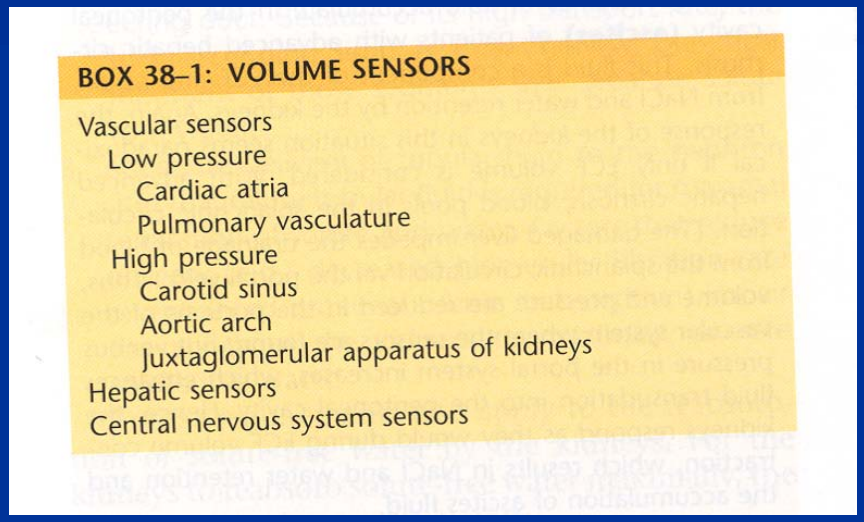
Vascular sensors
- Low pressure
  - Cardiac atria
  - Pulmonary vasculature
- High pressure
  - Carotid sinus
  - Aortic arch
  - Juxtaglomerular apparatus of kidneys

Hepatic sensors

Central nervous system sensors

- The ECV baroreceptors that lie within the low pressure side of the circulatory system - in the venous side - are located in the cardiac atria and pulmonary vasculature. These vascular sensors respond to changes in distension.
- If decreases in pulmonary vein filling or atrial distension is sensed, these baroreceptors send signals via the vagus nerve to the brainstem to activate increases in sympathetic outflow and ADH release. Increases in pulmonary vascular / atrial distension have the opposite effect.

High Pressure Sensors in the ECV



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Hepatic sensors

Central nervous system sensors

- The ECV sensors that lie within the high pressure side of the circulatory system - in the arterial blood - are located in the wall of the carotid sinus and aortic arch.
- A decrease in blood pressure causes these baroreceptors to send signals via both the vagus and glossopharyngial nerves to the brainstem to increase sympathetic outflow and ADH release.
- The afferent arterioles themselves also act as baroreceptors. A low ECV causes a decrease in stretch in these afferent arterioles, and this directly initiates renin release from their juxtaglomerular (granular) cells.

Major Sensors of Volume and Osmolality

Major Sensors and Effectors of the Osmoregulatory and Volume Regulatory Pathways

	Osmoregulation	Volume Regulation
What is sensed	Plasma osmolality	Effective tissue perfusion
Sensors	Hypothalamic osmoreceptors	Macula densa Afferent arteriole Atria Carotid sinus
Effectors	Antidiuretic hormone Thirst	Renin-angiotensin-aldosterone Atrial natriuretic peptide (ANP) ANP-related peptides Norepinephrine Antidiuretic hormone
What is affected	Urine osmolality Water intake	Urinary sodium Thirst

Renin Release due to Low ECV

- Renin release from granular cells is primarily determined by Na^+ intake in normal individuals, since dietary Na^+ will be the major factor that affects volume status in these individuals.

- Volume depletion / low ECV after prolonged decreased Na^+ intake or for any reason will increase renin release from juxtaglomerular cells in the afferent arterioles, and activate the renin-angiotensin-aldosterone system (RAAS). The three major factors which actually initiate renin release when a low ECV is present are:

1. Decreased perfusion of the afferent arterioles, which directly stimulates renin release.
2. Increased activation of the sympathetic nervous system, which stimulates beta adrenergic receptors on afferent arterioles and stimulates renin release.
3. Tubuloglomerular feedback (decreased delivery of NaCl to the macula densa cells in the thick ascending limb).

Renin Activates RAAS Cascade

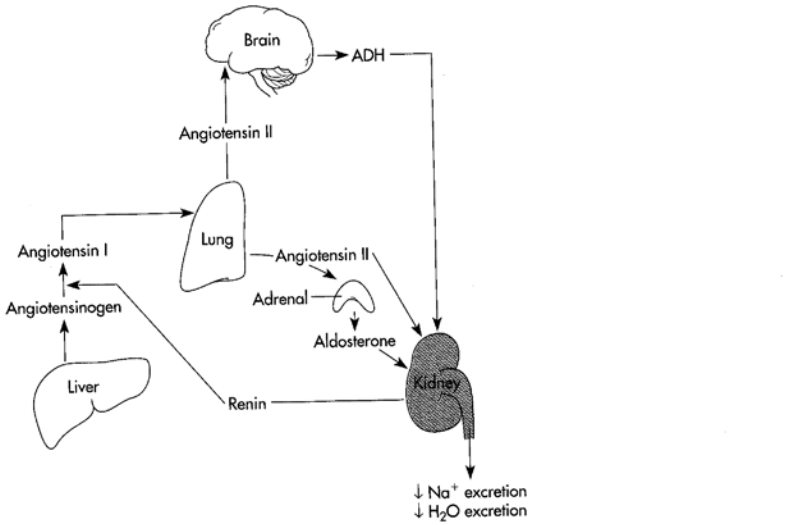


Figure 6-2 ■ Schematic representation of the essential components of the renin-angiotensin-aldosterone system. Activation of this system results in a decrease in the excretion of Na^+ and water by the kidneys. NOTE:Angiotensin I is converted to angiotensin II by an angiotensin-converting enzyme, which is present on all vascular endothelial cells. As shown, the endothelial cells within the lungs play a signficant role in this conversion process. *ADH,* Antidiuretic hormone. See text for details.

- Increases in plasma renin cleaves angiotensinogen to angiotensin I.
- Angiotensin I is cleaved to angiotensin II by ACE, primarily in the pulmonary vasculature.
- Angiotensin II has multiple effects including stimulation of aldosterone synthesis and release from the adrenal cortex, peripheral vasoconstriction, increasing ADH release, and directly enhancing Na^+ reaborbtion in the proximal tubule.
- Aldosterone directly enhances Na^+ reabsorbtion in the collecting tubules.

Summary of the RAAS Response to a Decreased ECV

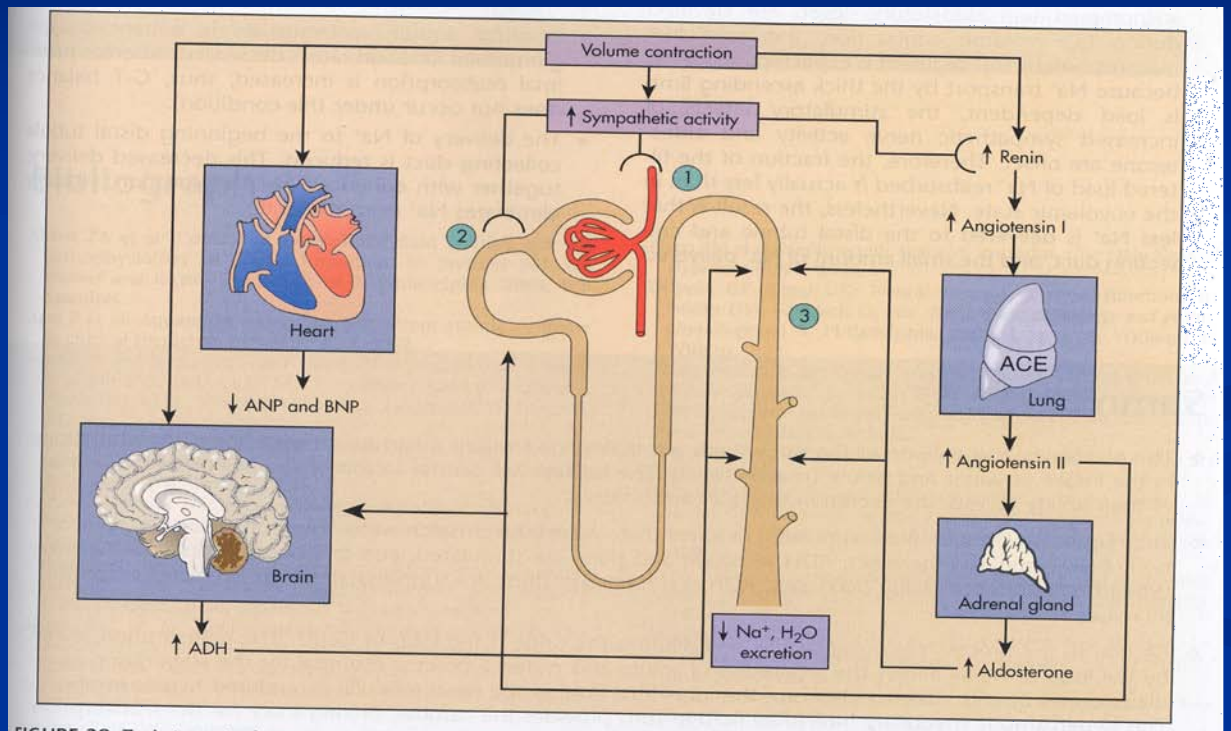
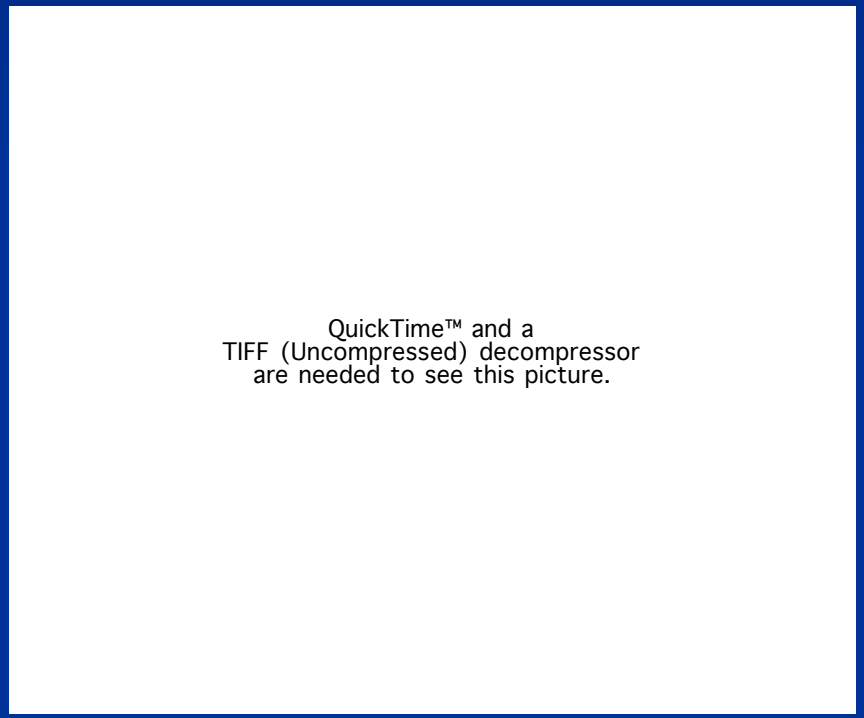


FIGURE 38–7. Integrated response to ECF volume contraction. Numbers refer to the description of the response in the text. Urodilatin levels are also decreased (not depicted). ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

Measuring Plasma Renin Levels

- There is NO FIXED NORMAL VALUE FOR PLASMA RENIN. It is very difficult to measure directly. Plasma renin activity can be estimated by mixing a patients plasma with a known amount of angiotensinogen, and measuring how much angiotensin I is produced per unit of time.

Renal Artery Stenosis



- Renal artery stenosis is a decrease in the diameter of the renal arteries. It is most often caused by atherosclerosis or fibromuscular dysplasia.
- The resulting restriction of blood flow to the kidneys may lead to impaired kidney function (renal failure) and high blood pressure, referred to as renovascular hypertension.
- The systemic hypertension occurs because the affected kidney(s) is being hypoperfused. This is interpreted as a low ECV, and renin is appropriately released.

Tissue Production of Angiotensin II

- In the past decade, research has shown that in addition to the classical circulating intermediates of the RAAS, many tissues are capable of producing their own RAAS intermediates, particularly angiotensin II.
- Several studies have strongly suggested that direct production of angiotensin II in tissues can occur by mechanisms other than conversion from angiotensin I by ACE. This means that ACE inhibitors would not be able to block tissue production of angiotensin II made in this fashion, during pathological states.
- This would help explain why ACE inhibitors seem to have limited effects on blocking the pathological changes mediated by angiotensin II in certain disease states, and why angiotensin receptor blockers (ARB's) may be more useful in these situations.

Mechanism For Aldosterone-Mediated Na^+ Reabsorbtion in Collecting Tubules

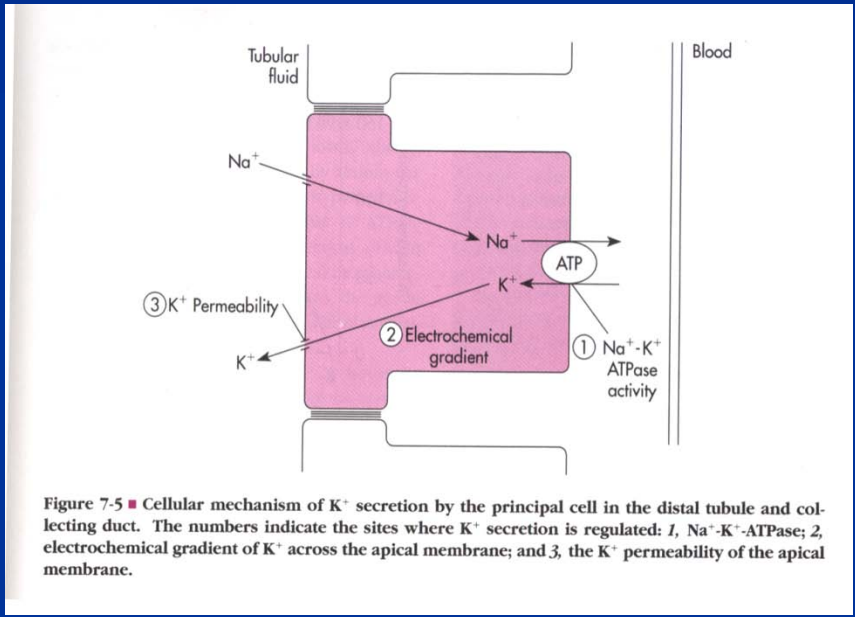
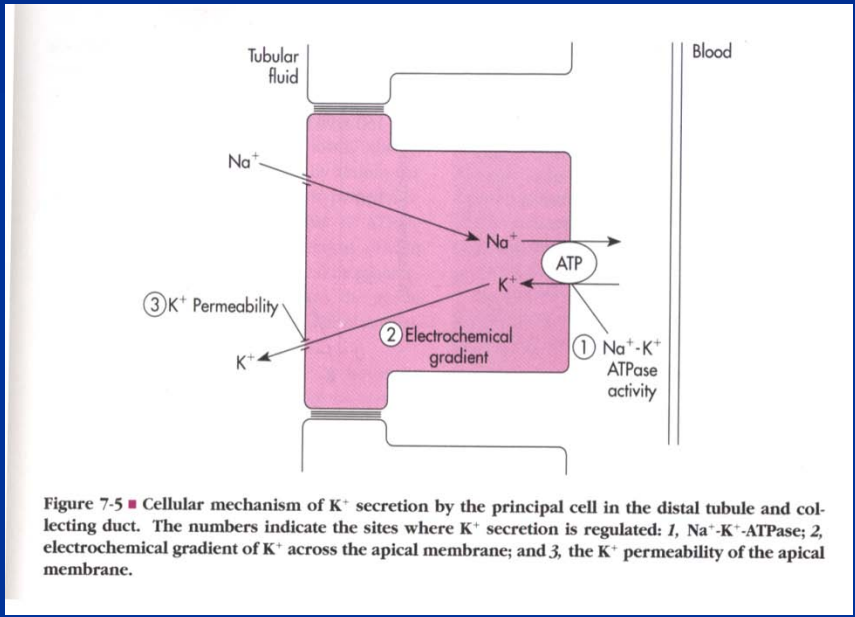


Figure 7-5 ■ Cellular mechanism of K^+ secretion by the principal cell in the distal tubule and collecting duct. The numbers indicate the sites where K^+ secretion is regulated: *1*, Na^+-K^+-ATPase; *2*, electrochemical gradient of K^+ across the apical membrane; and *3*, the K^+ permeability of the apical membrane.

- When plasma aldosterone levels rise, it binds it's cytosolic receptor in the principal cells and facilitates a number of processes, including:

1. Increased numbers of sodium channels on the apical membrane.
2. Increased numbers of Na^+/K^+ ATPases on the basolateral membrane, and increased activity of these Na^+/K^+ ATPases.

Aldosterone-Mediated Na^+ Reabsorbtion in Collecting Tubules



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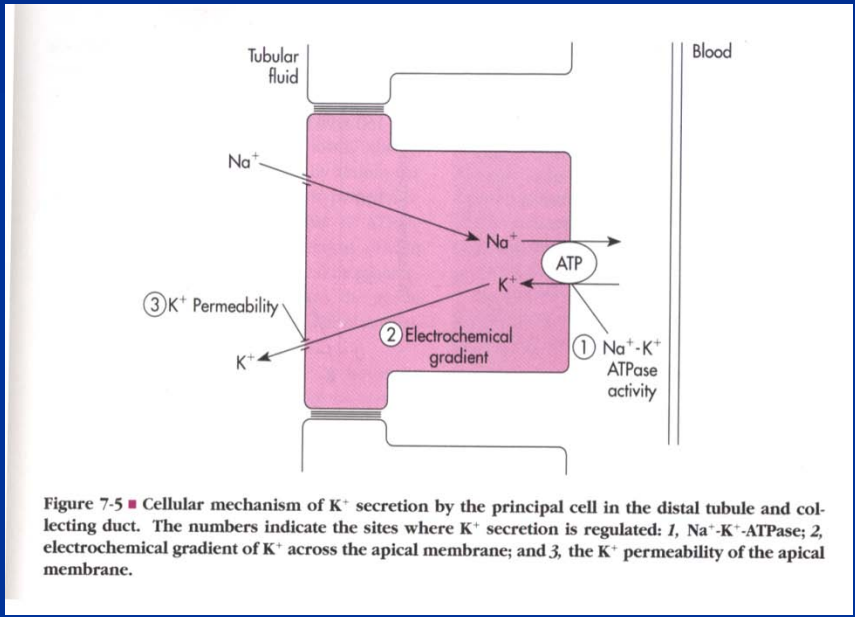
- Na^+ reabsorbtion here is coupled to K^+ secretion.
- Activity of the Na^+/K^+ ATPases keeps the cell Na^+ concentration low, allowing Na^+ to keep entering the cell through the apical membrane Na^+ channels, down it's concentration gradient.
- K^+ pumped into the cells will diffuse out of the cell and into the lumen of the nephron down it's concentration gradient, via passive apical membrane K^+ channels (intracellular $[K^+]$ around 150 mEq/L, while luminal $[K^+]$ is about 10 mEq/L).

Why Does K+ Exit the Principal Cells Primarily Though the Apical Membrane?



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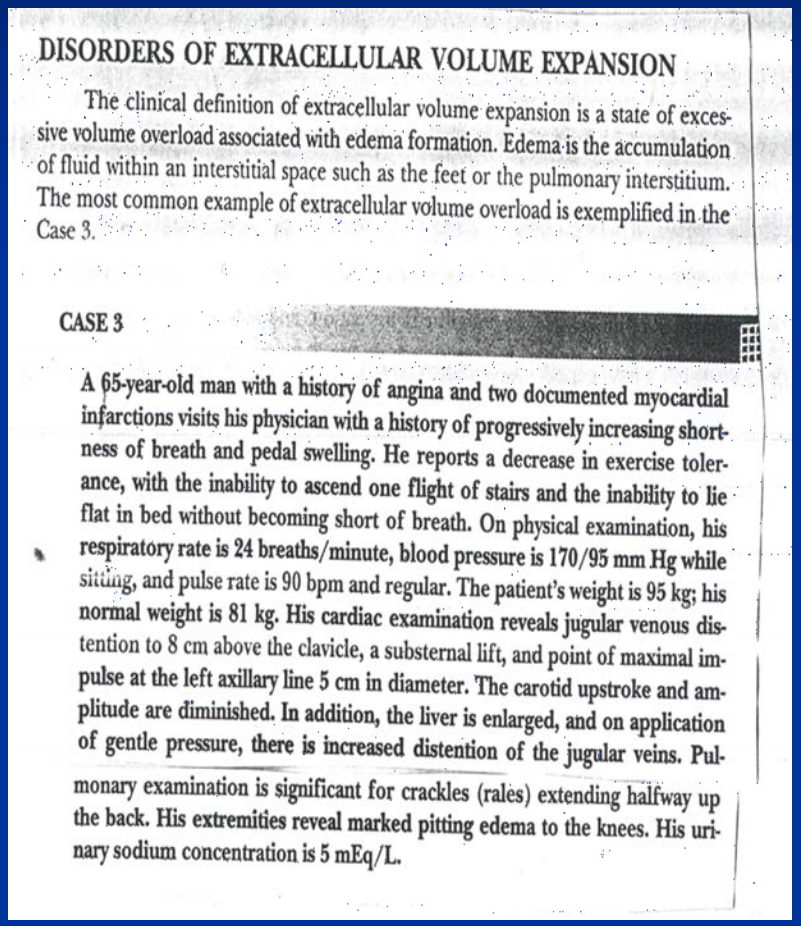
1. There are far more passive K^+ channels present on the apical membrane than on the basolateral membrane of principal cells.

2. The electrochemical gradient for K^+ across the apical membrane is greater than it is across the basolateral membrane.

3. This is especially true during volume depletion, when cationic Na^+ ions are being pulled from the filtrate, into the principal cells, making the filtrate even more electronegative.

Volume Expansion in CHF



DISORDERS OF EXTRACELLULAR VOLUME EXPANSION

The clinical definition of extracellular volume expansion is a state of excessive volume overload associated with edema formation. Edema is the accumulation of fluid within an interstitial space such as the feet or the pulmonary interstitium. The most common example of extracellular volume overload is exemplified in the Case 3.

CASE 3

A 65-year-old man with a history of angina and two documented myocardial infarctions visits his physician with a history of progressively increasing shortness of breath and pedal swelling. He reports a decrease in exercise tolerance, with the inability to ascend one flight of stairs and the inability to lie flat in bed without becoming short of breath. On physical examination, his respiratory rate is 24 breaths/minute, blood pressure is 170/95 mm Hg while sitting, and pulse rate is 90 bpm and regular. The patient's weight is 95 kg; his normal weight is 81 kg. His cardiac examination reveals jugular venous distention to 8 cm above the clavicle, a substernal lift, and point of maximal impulse at the left axillary line 5 cm in diameter. The carotid upstroke and amplitude are diminished. In addition, the liver is enlarged, and on application of gentle pressure, there is increased distention of the jugular veins. Pulmonary examination is significant for crackles (rales) extending halfway up the back. His extremities reveal marked pitting edema to the knees. His urinary sodium concentration is 5 mEq/L.

- In congestive heart failure, ECV is low to ⇓ cardiac output, activating the RAAS, which then promotes reabsorbtion of Na^+ and water, overfilling the ECF.

- Venous pressure is ⇑ due to ⇓ cardiac output. The ⇑ venous pressure will ⇑ peripheral capillary hydrostatic pressure, and promote movement of fluid out of these capillaries and into the ISF (edema).

Case Discussion

- Why does cardiac failure increase the extracellular fluid volume?
- The urinary Na^+ excretion in this patient is very low (5 mEq/L; normal is around 40 mEq/L in a euvolemic patient). Is that appropriate?
- What would his GFR be if you measured it (high or low?).
- Although not provided, his plasma Na^+ *concentration* would likely be very low. Can you think of a reason why?