Chapter 21 –Fluid, Electrolyte, and Acid-Base Balance

Objectives

Given the synopsis in this chapter, competence in each objective will be demonstrated by writing short essays, drawing diagrams, and responding to multiple choices or matching questions, at the level of 85% or greater proficiency for each student.

A. To explain how the sympathetic nervous system, the posterior pituitary, and the renin-angiotensin system controls filtration and reabsorption.
B. To explain how baroreceptor reflexes regulate fluid and electrolyte balance in response to low blood volume.
C. To explain how osmoreceptor reflexes regulate fluid and electrolyte balance in response to low water intake (increased blood osmolarity.
D. To explain how the kidney controls acid secretion and bicarbonate reabsorption and participates in the regulation of acid base balance.
E. To explain how the kidney controls potassium secretion and participates in the regulation of potassium balance.
F. To explain how the kidney controls calcium and phosphate reabsorption and participates in the regulation of calcium and phosphate balance.

Fluid and Electrolyte Balance

Blood volume and blood osmolarity are maintained at constant levels consistent with supplying the needs of the body. Blood volume is regulated at about 7% of body weight (4.9L in a 70 kg person), and blood osmolarity is regulated at about 290 mOsm.

Vascular and osmotic information

Together, the cardiovascular, renal, endocrine, and nervous systems are able to maintain appropriate levels of blood volume and blood osmolarity by using information about systemic arterial pressure, cardiac filling, blood osmolarity, renal blood flow, tubular filtrate flow, and plasma concentration of sodium and potassium.

- Baroreceptors in the carotid sinus and aortic arch measure systemic arterial pressure
- Stretch receptors of the veins and cardiac atria measure venous and atrial pressure and changes in blood volume and atrial filling
- Osmoreceptors of the hypothalamus and liver measure the osmolarity of blood
- Juxtaglomerular cells of the renal afferent arterioles measure changes in renal arterial pressure and flow
- Macula densa cells of the renal tubules, measure tubular filtrate flow and/or sodium reabsorption
- Specialized cells in the central nervous system measure sodium concentration
- Specialized cells of the adrenal cortex measure potassium concentration

Neural and hormonal responses

As we saw earlier, there are many neural and hormonal reactions that affect the cardiovascular system and kidneys that play a critical role in the control of fluid balance.

- Sympathetic stimulation
  - Constricts systemic arterioles, lowers capillary pressure, and moves fluid into the vascular space.
  - Constricts renal afferent arterioles and lowers filtration pressure and glomerular filtration rate.
  - Increases renal reabsorption of sodium and chloride ions.
  - Increases renin secretion from the kidney.
- Angiotensin II generated through the renin – angiotensin system
  - Stimulates directly, renal reabsorption of sodium and chloride ions.
  - Stimulates production of Aldosterone.
  - Constricts systemic arterioles, lowers capillary pressure, and moves fluid into the vascular space.
  - Stimulates secretion of vasopressin from the posterior pituitary and increases thirst.

- Aldosterone
  - Stimulates renal reabsorption of sodium and chloride ions
  - Stimulates renal secretion of potassium ions.
- Vasopressin
  - Stimulates renal reabsorption of water.
  - Constricts systemic arterioles, lowers capillary pressure, and moves fluid into the vascular space.
- Atrial Natriuretic Hormone inhibits renal reabsorption of sodium ions and water.

Reflexes

When blood volume or blood osmolarity become too low or too high, reflexes generate neural and hormonal responses to restore the volume or osmolarity to normal. Some of these reflexes can become rather complex, and for this reason we will examine them in segments.

Blood volume

In response to decreased blood volume (decreased atrial filling) the objective, of course, is to restore the blood volume. This can be achieved by conserving water and electrolytes by renal reabsorption, moving fluid into the circulation by increased capillary absorption, and moving fluid into the body by drinking.

The regulation of water reabsorption in response to low blood volume is relatively simple and is illustrated first in Figure 21.1.

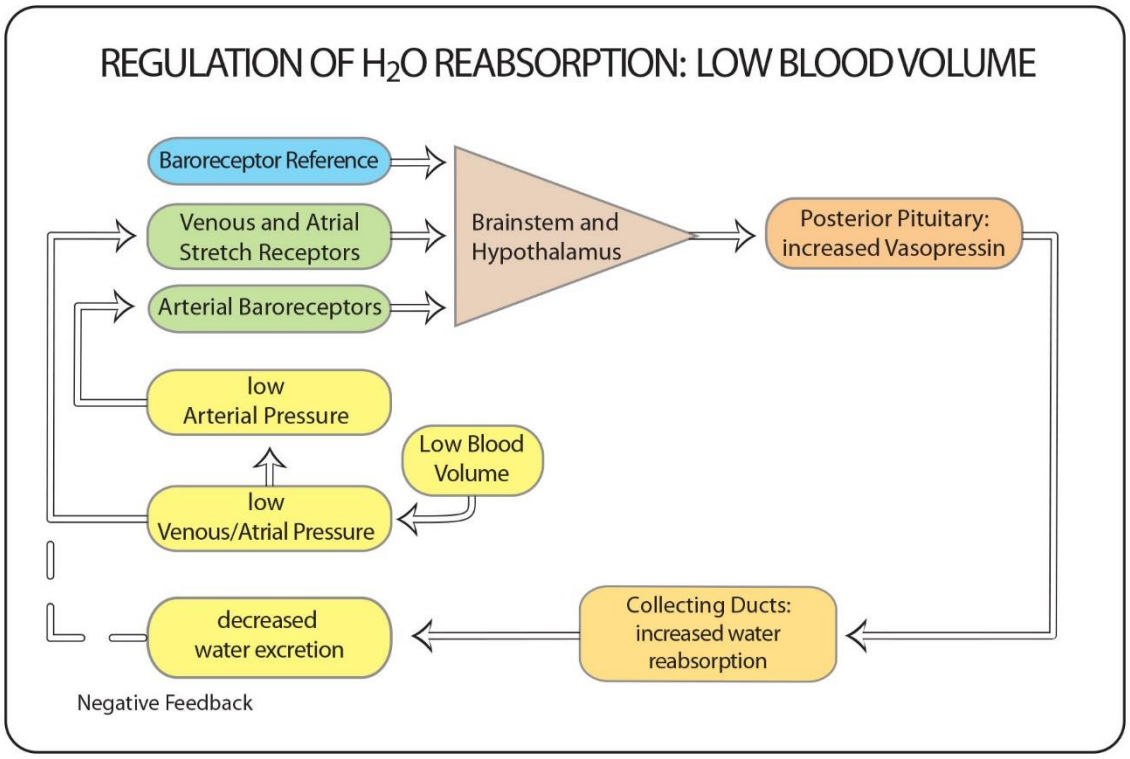

Figure 21.1 © 2014 David G. Ward, Ph.D.

- Low blood volume causes low venous/atrial pressure and low arterial pressure (arterial pressure decreases minimally with small decreases in blood volume).
- The changes in volume and pressure are detected by venous and atrial stretch receptors and by arterial baroreceptors.
- Signals from the stretch receptors and baroreceptors travel to the brainstem and hypothalamus and stimulate, in part, increased secretion of vasopressin from the posterior pituitary.
- Vasopressin acts, in part, on the collecting ducts to increase the number of water channels and thus increase water reabsorption.
- Vasopressin also constricts systemic arterioles which increases fluid absorption from the interstitial spaces into the capillaries (refer to chapter 18, Figure 18-9).

The regulation of sodium ion (Na^+) reabsorption in response to low blood volume is more complex and is illustrated next in Figure 21.2.

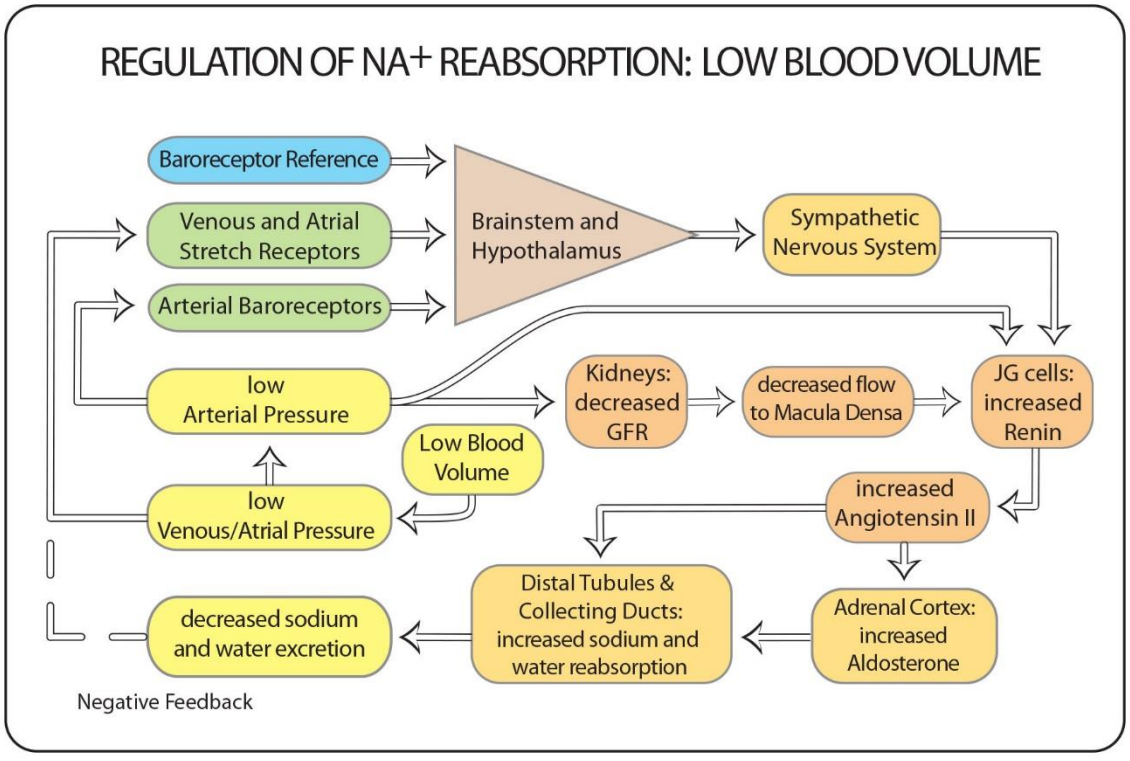

Figure 21.2 © 2014 David G. Ward, Ph.D.

- Low blood volume causes low venous/atrial pressure and low arterial pressure (arterial pressure decreases minimally with small decreases in blood volume).
- The changes in pressure are detected by venous and atrial stretch receptors and by arterial baroreceptors.
- Signals from the stretch receptors and baroreceptors travel to the brainstem and hypothalamus and, in part, increase sympathetic nerve activity that stimulates the juxtaglomerular cells (JG cells) and increases secretion of renin.
- Low renal arterial pressure directly stimulates JG cells and increases secretion of renin.
- Low renal arterial pressure decreases glomerular filtration rate (GFR) which in turn leads to decreased tubular flow to the macula densa that in turn stimulates JG cells and increases secretion of renin.
- Renin causes increased production of angiotensin I and thus angiotensin II.
- Angiotensin II
    - Stimulates the adrenal cortex to increase production of Aldosterone.
    - Directly acts on the proximal and distal tubules to increase sodium, chloride and water reabsorption.
    - Constricts systemic arterioles which increase fluid absorption from the interstitial spaces into the capillaries.
    - Stimulates thirst; and secretion of vasopressin.
- Aldosterone acts on the late distal tubules, and collecting ducts to increase sodium and water reabsorption

Together, the reabsorption of water and sodium by the kidney, the increased absorption of fluid from the interstitial spaces into the capillaries, and the increased fluid intake stimulated by thirst, lead to the restoration of blood volume.

In response to <u>increased</u> blood volume (increased atrial filling) the objective is to lower the blood volume. This can be achieved by excreting water and electrolytes by <u>inhibiting</u> renal reabsorption, moving fluid <u>out</u> of the circulation by <u>inhibiting</u> capillary absorption, and <u>inhibiting</u> thirst. The mechanisms responsible for lowering blood volume operate opposite to those for restoring blood volume and include one additional hormone. Increased blood volume increases atrial filling and stimulates the secretion of atrial natriuretic hormone (ANH) from cardiac atrial myocytes.

- Atrial natriuretic hormone (ANH)
    - Acts directly on the collecting ducts to inhibit sodium and water reabsorption.
    - Inhibits secretion of vasopressin from the posterior pituitary.
    - Inhibits secretion of renin from the juxtaglomerular cells (JG).
    - Inhibits production of aldosterone from the adrenal cortex.
    - Increases glomerular filtration rate (GFR) by dilating the renal afferent arteriole and constricting the efferent arteriole.

Blood osmolarity

In response to low water intake, and the accompanying increase in blood osmolarity, the objective is to lower the blood osmolarity. This can be achieved best by increasing renal water reabsorption and increasing fluid intake by drinking, as shown in Figure 21.3.

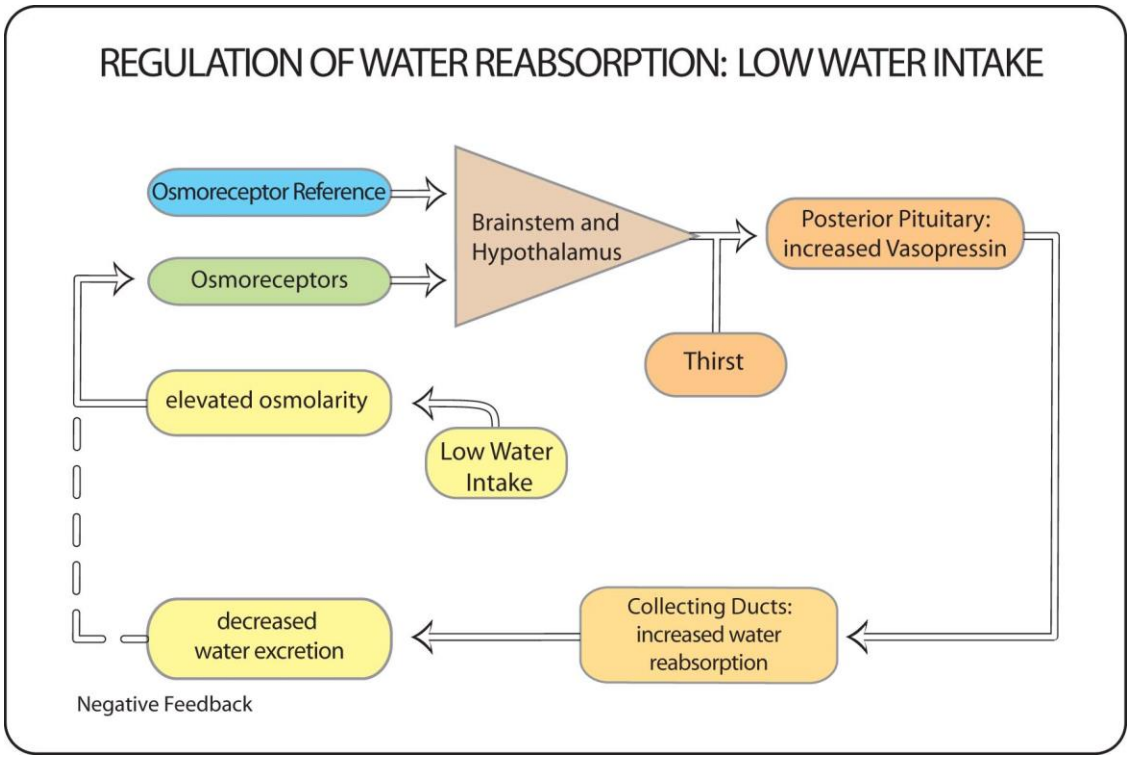

Figure 21.3 © 2010 David G. Ward, Ph.D.

The regulation of water reabsorption and thirst in response to low water intake (and the accompanying increased blood osmolarity) is relatively simple.

- Low water intake causes an increase in blood osmolarity (and probably a decrease in blood volume see also Figure 21.1).
- The changes in blood osmolarity are detected by osmoreceptors in liver and hypothalamus.
- Signals from the osmoreceptors travel to the brainstem and hypothalamus and stimulate, in part,
    - Increased thirst and fluid intake.
    - Increased secretion of vasopressin from the posterior pituitary
- Vasopressin acts, in part, on the collecting ducts to increase the number of water channels and thus increase water reabsorption.
- Vasopressin also constricts systemic arterioles which increases fluid absorption from the interstitial spaces into the capillaries (refer to chapter 18, Figure 18-9).

Acid-Base Balance

As we saw in chapter 19 the respiratory system plays a critical role in the control of acid base balance by managing the removal of CO_2. Carbon dioxide (CO_2) and water (H_2O), carbonic acid (H_2CO_3), and bicarbonate ions (HCO_3^-) and hydrogen ions (H^+) are in equilibrium in a reversible reaction in the blood. Carbonic anhydrase (CA) is necessary to catalyze the reaction between carbonic acid and carbon dioxide and water.

$$CO_2 + H_2O \xleftrightarrow{CA} H_2CO_3 \longleftrightarrow HCO_3^- + H^+$$

Increasing the removal of CO_2 will decrease the H^+ concentration and raise the pH of the blood. Conversely, decreasing the removal of CO_2 will increase the H^+ concentration and lower the pH of the blood. This process provides a mechanism to rapidly adjust the pH of the blood.

As shown in in Figure 21.4, the kidney also plays a critical role in the control of acid base balance by managing the removal of hydrogen ions (H^+) and the reabsorption of bicarbonate ions (HCO_3^-). Hydrogen ions (H^+) are secreted into the tubular fluid and bicarbonate ions (HCO_3^-) are reabsorbed. Reabsorbing all of the bicarbonate ions and increasing the removal of hydrogen ions through the urine will decrease the H^+ concentration in the blood and raise the pH of the blood. Conversely, decreasing the reabsorption of bicarbonate ions will increase the H^+ concentration in the blood and lower the pH.

This process is slow and takes hours to days to adjust the pH of the blood. Starting at the glomerular capillaries, bicarbonate ions (HCO_3^-), phosphate ions (HPO_4^{2-}), and ammonia (NH_3) are filtered out of the blood and enter the tubular fluid. There are about 25 times more bicarbonate ions (HCO_3^-) than there are phosphate ions (HPO_4^{2-}) and ammonia (NH_3).

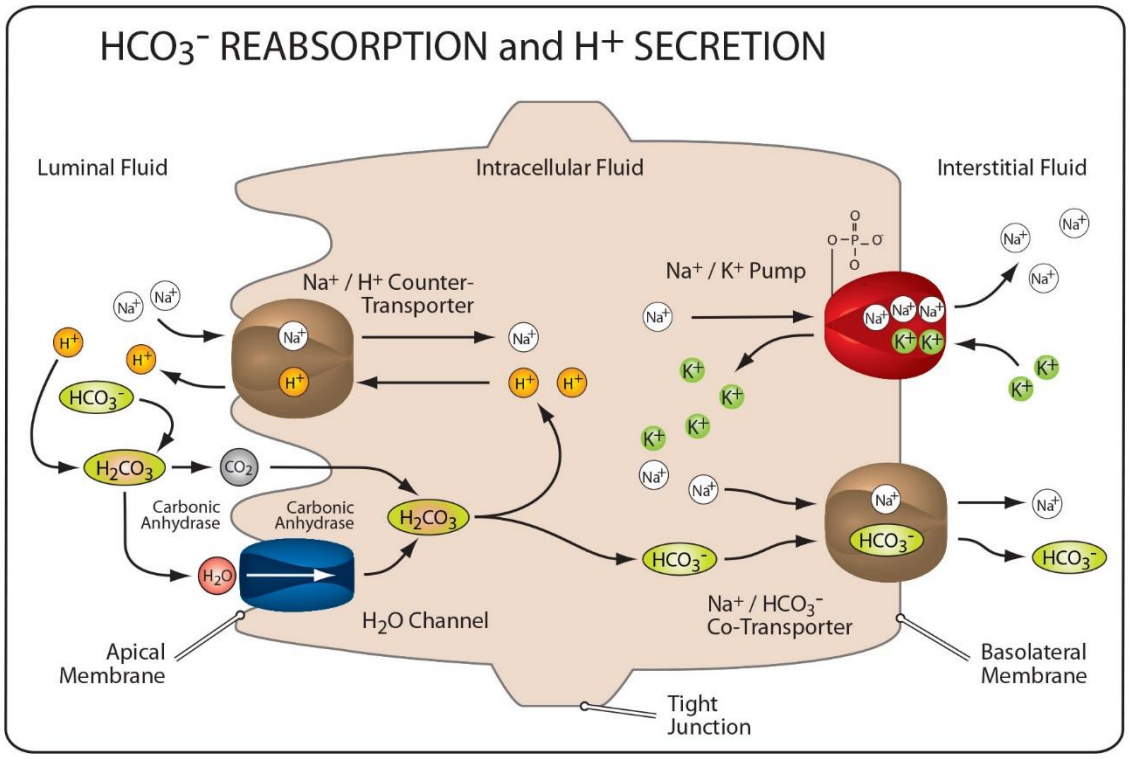

Figure 21.4 © 2014 David G. Ward, Ph.D.

Starting in the proximal tubule

- Hydrogen ions (H^+) re-associate with bicarbonate ions (HCO_3^-) to form carbonic acid (H_2CO_3), that in turn is converted to carbon dioxide (CO_2) and water (H_2O) by carbonic anhydrase (CA) on the apical membrane of the tubular cells.
- The carbon dioxide (CO_2) and water (H_2O) diffuses through the apical membrane into the tubular cell where they are synthesized back to carbonic acid (H_2CO_3) by carbonic anhydrase (CA).
- The carbonic acid (H_2CO_3) dissociates into bicarbonate ions (HCO_3^-) and hydrogen ions (H^+).
- The hydrogen ions (H^+) are secreted by counter-transport coupled with the movement of sodium ions (Na^+) across the apical membrane.
- Bicarbonate ions (HCO_3^-) are reabsorbed through the basolateral membrane, in part, by co-transport with sodium ions (Na^+).
- This process will cycle and reabsorb bicarbonate ions (HCO_3^-) as long as there are bicarbonate ions in the tubular fluid.

As more and more bicarbonate ions (HCO_3^-) are reabsorbed, it becomes more likely that secreted hydrogen ions (H^+) will re-associate with mono-hydrogen phosphate ions (HPO_4^{2-}) or ammonia (NH_3) and form di-hydrogen phosphate ions ($H_2PO_4^-$) or ammonium ions (NH_4^+) (not illustrated). These ions allow hydrogen ions to be removed through the urine.

In order to reabsorb more bicarbonate ions (HCO_3^-), glutamine (an amino acid) is transported from the peritubular capillaries into the tubular cells and catabolized into ammonium ions (NH_4^+) and bicarbonate ions (HCO_3^-). The ammonium ions (NH_4^+) are secreted by counter-transport coupled with the movement of sodium ions (Na^+) across the apical membrane. Bicarbonate ions (HCO_3^-) are reabsorbed through the basolateral membrane, in part, by co-transport with sodium ions (Na^+). Some ammonia (NH_3) diffuses across the apical membrane and re-associates with hydrogen ions (H^+) to form ammonium ions (NH_4^+), removing even more hydrogen ions.

- Renal adjustment for a low blood pH (high H^+ concentration) depends on reabsorbing all of the filtered bicarbonate ions (HCO_3^-) and excreting excess hydrogen ions (H^+) through the urine.
- Renal adjustment for a high blood pH (low H^+ concentration) depends on reabsorbing only a portion of the filtered bicarbonate ions (HCO_3^-).

Potassium, Calcium, and Phosphate Balance

Potassium

Although most potassium (K^+) is found intracellular, imbalance of extracellular K^+ can have adverse effects on membrane potentials and especially on the function of nerve and muscle. Recall how K^+ concentration is a major determinant of membrane potential and how abnormal plasma K^+ can cause cardiac arrhythmias and even cardiac arrest.

As we saw earlier in this chapter, sodium ions (Na^+) are actively transported out of tubular cells and into interstitial fluid and potassium ions (K^+) are transported out of interstitial fluid and into tubular cells, by Na^+ / K^+ pumps in the basolateral membrane. In the proximal tubules and in the thick ascending limb of the nephron loop, large amounts of the potassium ions (K^+) are reabsorbed through the basolateral membrane by diffusion through channels, or by co-transport with other ions.

In contrast, in the late segment of the distal tubule and in the collecting ducts, K^+ ions may be secreted through the apical membrane by diffusion through K^+ channels.

Potassium secretion is controlled by local factors and by hormones. Locally, increased plasma K^+ concentration directly increases K^+ uptake by the Na^+ / K^+ pumps in the basolateral membrane, and thus increases secretion by diffusion through K^+ channels in the apical membrane. Conversely, decreased potassium concentration decreases secretion. The secretion of potassium is also controlled by aldosterone.

- Elevated plasma potassium concentration directly stimulates the synthesis and release of aldosterone by the cells of the zona glomerulosa of the adrenal cortex.
- Aldosterone acts on tubular cells of the late distal tubule and cortical collecting duct to increase the number of K^+ channels in the apical membrane, thus the secretion of potassium into the tubular fluid.
- Aldosterone acts on tubular cells of the late distal tubule and cortical collecting duct to increase the number of Na^+ / K^+ pumps in the basolateral membrane, and thus to increase the uptake of potassium and its secretion by diffusion through the apical membrane.

Calcium and phosphate

As we have seen in previous chapters, calcium (Ca^{2+}) is critical for intracellular signaling, nerve and endocrine secretion, and muscle contraction. Low plasma Ca^{2+} can increase the excitability of muscle and nerve membranes. High plasma Ca^{2+} can cause cardiac arrhythmias and depressed neuromuscular excitability.

Gastrointestinal Tract

In contrast to water, sodium, and potassium which are almost completely absorbed from the gastrointestinal tract, a considerable amount of ingested calcium and phosphate is not absorbed. The gastrointestinal absorption of calcium and phosphate is controlled by hormones and provides a major means for regulating calcium balance. After absorption, about 99% of calcium and phosphate is stored in bone.

Kidneys

Calcium is transported in the blood either as free Ca^{2+} or bound to protein. In the kidneys free Ca^{2+} is filtered at the glomerular capillaries and enters the tubular fluid. Most of the filtered Ca^{2+} is reabsorbed by diffusion through Ca^{2+} channels in the apical membrane of tubular cells and by counter-transport with Na^{+} ions in the basolateral membrane.

The renal reabsorption of calcium and phosphate is controlled by hormones. Parathyroid hormone and calcitriol (1, 25- $(OH)_2$ D) are the dominant hormones controlling calcium and phosphate balance. Parathyroid hormone is produced by the chief cells of the parathyroid glands. 1,25(OH)2D is metabolized from vitamin D, first in the liver, and then in the kidneys. (See Appendix A, Table A.5 and Table A.9).

Overall control

The regulation of blood Ca^{2+} in response to low blood Ca^{2+} is shown in Figure 21.5 on the next page.

- Low blood calcium stimulates the chief cells of the parathyroid gland and increases the secretion of parathyroid hormone (PTH)
- PTH acts on bone to increase calcium and phosphate movement into blood (resorption) and to stimulate breakdown of bone by osteoclasts.
- PTH acts on the kidney to
  - increase calcium reabsorption and phosphate excretion.
  - increase calcitriol [1,25(OH)2D] production.
- 1,25(OH)2D acts on the intestine to increase calcium and phosphate absorption.

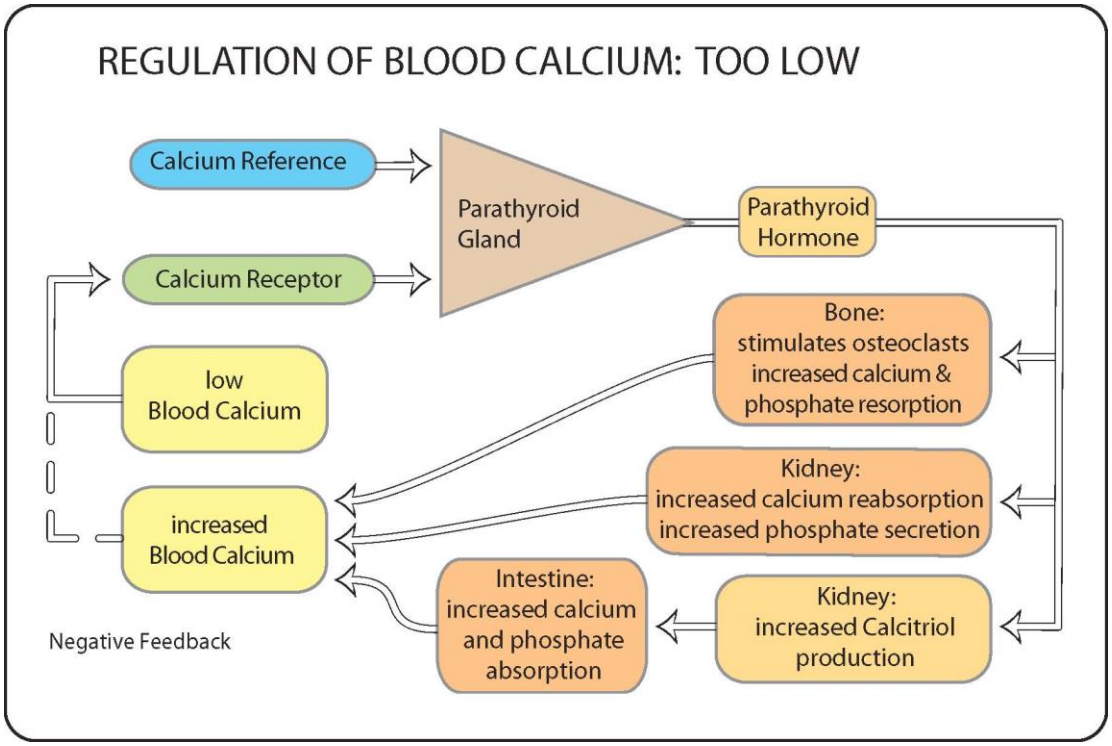

Figure 21.5 © 2007 David G. Ward, Ph.D.

Parathyroid hormone increases the movement of both calcium and phosphate from bone into blood (resorption), even when phosphate is normal. To compensate for this, parathyroid hormone increases calcium reabsorption, but increases phosphate excretion by the kidney. This combination of responses allows parathyroid hormone to increase blood calcium without increasing phosphate. Calcitriol [1,25(OH)2D] on the other hand increases the absorption of both calcium and phosphate from the gastrointestinal tract. In addition, 1,25(OH)2D may decrease secretion of both calcium and phosphate by the kidney (not shown in Figure 21.5). This later combination of responses could allow 1,25(OH)2D to increase phosphate and well as calcium.

The regulation of blood calcium in response to elevated blood calcium is the opposite of what we just described. However, if blood calcium becomes very high another hormone, calcitonin (not calcitriol) is secreted from interfollicular cells of the thyroid gland. Calcitonin acts mainly on bone to inhibit osteoclasts and decrease release of calcium and phosphate from bone into blood.

Quiz Yourself

1-5. Matching

A)	Glomerulosa cells of adrenal cortex	Produce aldosterone	1) _____
B)	Cardiac stretch (volume) receptors	Detect osmolarity of blood	2) _____
C)	Juxtaglomerular cells of kidney	Are stimulated by angiotensin II	3) _____
D)	Osmoreceptors	Detect changes in blood volume and cardiac filling	4) _____
		Are stimulated by sympathetic NS and produce renin	5) _____

6-10.

A)	Atrial natriuretic hormone	Stimulates aldosterone	6) _____
B)	Converting enzyme	Causes renal excretion of sodium	7) _____
C)	Angiotensin II	Causes renal conservation of water	8) _____
D)	Vasopressin	Causes renal conservation of sodium	9) _____
E)	Aldosterone	Converts angiotensin I to angiotensin II	10) _____

11-15. Matching

A)	$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$	Secreted into renal tubules	11) _____
B)	$CO_2 + H_2O \leftarrow H_2CO_3 \leftarrow H^+ + HCO_3^-$	Seen in systemic capillaries	12) _____
C)	HCO_3^-	Seen in pulmonary capillaries	13) _____
D)	H^+	Reabsorbed out of renal tubules	14) _____
		Occurs in cytoplasm of renal tubular cells	15) _____

16-20. Matching

A)	Parathyroid hormone	Increases phosphate excretion by kidney	16) _____
B)	Calcitriol [1,25(OH)2D]	Increases calcium reabsorption by kidney	17) _____
		Increases calcium absorption by intestines	18) _____
		Increases phosphate absorption by intestines	19) _____
		Increases resorption of calcium and phosphate from bone	20) _____

Fill in

21. Low blood volume will stimulate a reflex _____ (change) in _____ (hormone).

22. Low osmolarity will stimulate a reflex _____ (change) in _____ (hormone).

23. _____ (hormone) is inhibited by excess water consumption.

24. Sodium reabsorption from the renal tubules is stimulated largely by _____.

25. Calcium & phosphate absorption from the intestines is stimulated largely by _____.

Study Questions

1. Compare and contrast the homeostatic control of acid-base balance by the lungs and the kidney.
2. Explain the homeostatic control of fluid and electrolyte balance following loss of blood volume or low water intake. Emphasize the role of the kidney.
3. Explain the homeostatic control of blood calcium and phosphate. Include the role of parathyroid, renal, and thyroid hormones.