

### Objectives

1. Understand the importance of homeostasis.
2. Review how body fluids are compartmentalized.
3. Review the concept of the steady state.
4. Understand how the steady state is monitored.
5. Review the compensatory responses to perturbations of the steady state.

### Readings

Rose and Rennke, pages 29-64.  
Rennke and Denker, pages 31-67.

### I. Homeostasis

- A. Homeostasis is the process of maintaining a relatively stable chemical, electrical, and osmotic internal environment in the setting of wide ranges of intake, loss, and metabolic demand. It involves carefully sensing the composition of plasma, and adjusting excretory patterns accordingly. The result is a milieu that optimizes cellular function.
- B. The Reason for Life – The currency for *cellular* homeostasis is sodium and charge. The ocean has a salinity of approximately 30 parts per thousand (or 3%). Cells are distinguished from the sea by a phospholipid bilayer membrane that allows for independent adjustments of the internal environment. **The Na<sup>+</sup>/K<sup>+</sup> ATPase is the most important protein that has ever evolved.** It is capable of externalizing 3 Na<sup>+</sup> molecules in exchange for internalizing 2 K<sup>+</sup> molecules. The resulting differential in Na<sup>+</sup> and K<sup>+</sup> concentrations (low Na<sup>+</sup> and high K<sup>+</sup> internally), and the charge imbalance (net negative charge internally), drives many cellular functions. The compositions of both the intra-cellular and extra-cellular compartments are critical components of this relationship.

- C. The Cellular Environment – The composition of the intra-cellular milieu is tightly regulated. Proteins on the cell membrane function as pumps and channels to create and utilize chemical and electrical gradients for cellular function. Examples of the importance of the intra-cellular milieu include:
1. Enzyme function is optimized within a narrow range of ion concentrations and pH.
  2. Membrane potentials are linked to the internal concentration of  $K^+$ .
  3.  $Ca^{++}$  concentrations are important mediators of membrane excitability and second-messenger trafficking.
- D. The Internal Ocean – As life graduated to land, the ocean was brought with it. The plasma assumed the high  $Na^+$  and low  $K^+$  foil to the cellular concentrations. The critical job of maintaining the plasma has fallen to the kidney.
- E. The Role of the Kidney
1. Unlike the composition of the vast ocean, the smaller confines of the body are far more susceptible to disturbance from environmental factors, variable needs, and limited resources. The separation of life from the abundant and readily available resources of the ocean has forced the development of adaptive skills to handle bingeing and deprivation. These skills, present in even the simplest organisms, allow for life to exist.
  2. The kidney is uniquely capable of controlling the internal milieu. It processes large volumes of blood, responds to a variety of hormones that indicate perturbations in the internal environment, and has the capacity to retain or excrete  $Na^+$ , electrolytes, water, acid/base, and an abundance of other molecules accordingly.
  3. You are **not** what you eat. You are what your body (most notably your kidneys) retains.

## II. The Distribution of Fluid and Solute

- A. The body can be thought of as two principal compartments with distinct electrolyte compositions separated by a semi-permeable cellular membrane. These compartments are the *intracellular space* and *extracellular space*.

|                           |       |      |
|---------------------------|-------|------|
| Weight                    | 70 Kg | 100% |
| Body Water                | 42 L  | 60%  |
| Intracellular Fluid (ICF) | 28 L  | 40%  |
| Extracellular Fluid (ECF) | 14 L  | 20%  |
| Plasma Volume (PV)        | 3.5 L | 5%   |

Table 1

- B. As the cellular membrane is freely permeable to water, the osmolality of the intracellular and extracellular compartments are always equal. However, the cellular membrane is impermeable to electrolytes, with  $K^+$  being the principal intracellular cation and  $Na^+$  the principal extracellular cation.

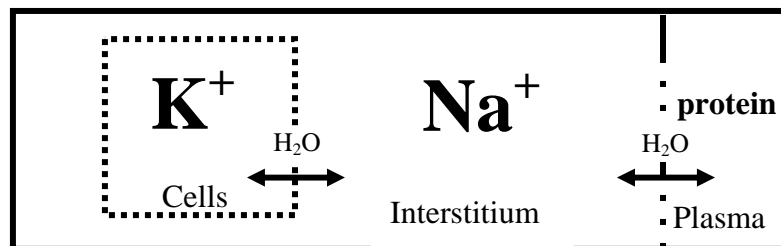


Figure 1

- C. Extracellular Compartment – The extracellular compartment is divided by the capillary wall into the interstitium and plasma. Water and electrolytes pass freely across the capillary wall, but a predominance of intravascular proteins maintain the integrity of this space.

| Compartment | Osmotically Active Solute | Physiologic Process Regulating Solute Content | Osmolality (mOsm/kg) | Oncotic Pressure (mOsm/kg) |
|-------------|---------------------------|---|----------------------|----------------------------|
| ICF         | $K^+$                     | $Na^+ - K^+$ ATPase (active transport)        | 290                  | ?                          |
| ECF         | $Na^+$                    | Kidney sodium handling                        | 290                  | $\approx 0.75$             |
| PV          | Protein (albumin)         | Albumin metabolism                            | 290                  | $\approx 1.5$              |

Table 2

### III. The Steady State

- A. The steady state occurs when there is minimal fluctuation in content or concentration.  $H^+$  concentration remains between 37 and 43 nEq/L (pH 7.37 to 7.43),  $Na^+$  concentration is constant between 137 and 143 mEq/L, and other molecules including creatinine, urea (BUN), hemoglobin, etc... have the same level from one day to the next. In the steady state, input and output are equal.

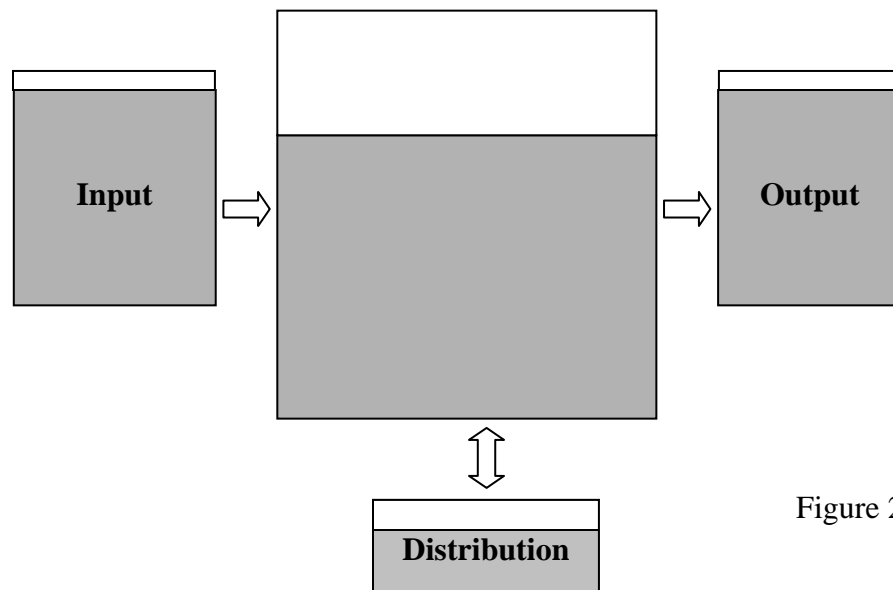


Figure 2

- B. Input – Input is comprised of oral and intravenous food and fluid, as well as released and produced substances.
- C. Output – Output is comprised of losses in the urine, stool, sweat, or exhaled air. It also includes consumption or metabolism that leads to the removal of a molecule from the internal environment.
- D. Distribution – Cellular distribution plays a large role in regulating solute and solvent content. The buffering of a  $K^+$  load by intracellular sequestration before it can be completely excreted plays an important role in minimizing large swings in the extracellular  $K^+$  concentration. Distribution does **not** affect net balance.
- E. The Steady State can be summarized as:

$$\text{Intake} + \text{Production} = \text{Excretion} + \text{Consumption} \pm \text{Distribution} \quad \text{Equation 1}$$

- F. A rise or fall in any molecule's content or concentration can be directly traced to a disturbance in the above equation.

#### IV. Perturbations of the Steady State

Perturbations to the steady state can come in many forms. Regardless of the form of the perturbation, the body's response is similar (i.e. a rise in  $K^+$  from an enteric load, an intravenous load, or trans-cellular shift from rhabdomyolysis all induce similar compensatory responses). Mechanisms of perturbations includes:

A. Input

1. Intake
  - a. Enteric
  - b. Intravenous
2. Production
  - a. Catabolism
  - b. Cellular destruction

B. Output

1. Excretion
  - a. GI losses
  - b. Kidney losses
    - i. Glomerular filtration
    - ii. Tubular handling (secretion vs. reabsorption)
  - c. Insensible losses (sweat)
  - d. Respiratory losses ( $CO_2$ )
2. Consumption
  - a. Metabolism (glucose, nitrogen)
  - b. Cellular growth (phosphate, potassium)

C. Re-Distribution

D. Examples

1. Hyperkalemia could be related to a  $K^+$  load, impaired excretion of  $K^+$  from the kidney, or release from intra-cellular stores (i.e. tissue destruction as in rhabdomyolysis).
2. Metabolic acidosis can be a manifestation of an acid load (i.e. lactic acidosis), bicarbonate loss (i.e. diarrhea), or impaired  $H^+$  excretion by the kidney (i.e. renal tubular acidosis).
3. Hyponatremia can reflect water intoxication (i.e. psychogenic polydipsia) or impaired water excretion (inability to dilute). **It does not reflect  $Na^+$  status!!!**
4. A rise in the serum concentration of creatinine could reflect ingestion (steaks at Abe & Louie's), production (release from muscles after running a marathon or crush injury), or impaired excretion from a drop in glomerular filtration or depressed tubular secretion.

## V. Recognizing and Responding to Perturbations of the Steady State

Sensors throughout the body closely monitor the internal milieu.

### A. Sodium

1. **Sodium is the only electrolyte whose content is not monitored by its plasma concentration.** Sodium status is assessed by the *effective circulating volume*, and handling of  $\text{Na}^+$  occurs in response to hemodynamic sensors. A  $\text{Na}^+$  load results in volume expansion (**not hypernatremia!!!**), and induces a natriuresis by the kidney. Volume depletion indicates a  $\text{Na}^+$  deficit and results in  $\text{Na}^+$  retention by the kidney.
2. Sensors of sodium content (i.e. effective circulating volume) include the carotid bodies, the cardiac stretch receptors, and the kidney.
3. Mediators of volume status include renin/angiotensin/aldosterone from the kidney and adrenal glands, sympathetic tone from the carotid bodies, atrial natriuretic peptide from the myocardium, and ADH from the hypothalamus/posterior pituitary.
4. These mediators, many of which oppose each other's action, balance. A preponderance of activity dictates how  $\text{Na}^+$  will be handled.

| Sodium Handling |   |
|-----------------|---|
| What is sensed  | Effective tissue perfusion  |
| Sensors         | Afferent arteriole<br>Atria<br>Carotid sinus  |
| Mediators       | Renin-angiotensin-aldosterone<br>Atrial natriuretic peptide<br>Norepinephrine<br>Antidiuretic hormone |
| Effectors       | Urinary sodium<br>Thirst  |

Table 3

### B. Potassium

1. Potassium concentration is sensed by every cell in the body. The overwhelming majority (98%) of potassium is located intracellularly. Rises and falls in serum potassium concentration are buffered by trans-cellular shift.
2. Aldosterone is released by the adrenal glands in response to hyperkalemia, and results in potassium secretion from the collecting tubule.

3. Reduced aldosterone secretion in times of hypokalemia (and suppressed renin/angiotensin activity) leads to reduced loss of potassium in the urine. ACE inhibitors are associated with reduced potassium excretion in the urine, and elevated plasma potassium concentrations.
4. Bowel mucosa also increases potassium secretion in response to aldosterone, but this is a minor homeostatic mechanism (except in advanced chronic kidney disease).

### C. Water

1. Water content is sensed by osmoreceptors in the hypothalamus. **Serum sodium concentration is the major contributor to plasma osmolality and the best indicator of water status.**
2. As osmolality rises above 280 mOsm/kg, a graded release of ADH occurs from the posterior pituitary.

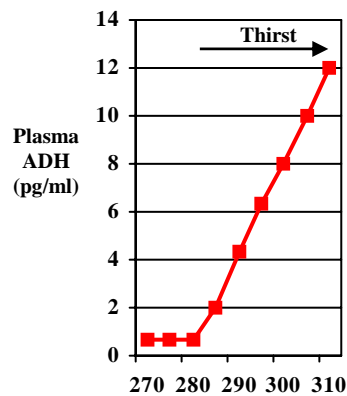


Fig. 3: Plasma Osmolality (mOsm/kg)

3. ADH leads to retention of water by kidney, as concentrated urine is produced.
4. Thirst is also triggered as serum osmolality rises

| Water Handling |                                  |
|----------------|----------------------------------|
| What is sensed | Plasma osmolality                |
| Sensors        | Hypothalamic osmoreceptors       |
| Mediators      | Antidiuretic hormone<br>Thirst   |
| Effectors      | Urine osmolality<br>Water intake |

Table 4

**D. pH**

1.  $H^+$  loads are buffered by plasma  $HCO_3^-$  according to the equation:



2. Increased  $pCO_2$  results in cerebral acidosis, which stimulates minute ventilation and  $CO_2$  excretion.
3. pH is also sensed by all cells, and  $H^+$  is buffered in exchange for intra-cellular  $K^+$ .
4. Cellular acidosis in the kidney stimulates  $NH_3$  production by the tubule. This up-regulates excretion of titratable acid. This is the main adaptive response to an acid load.
5.  $H^+$ -ATPase in the intercalated cells of the collecting tubule are up-regulated by acid loads, and down-regulated by alkalosis. This plays a minor role.
6. In chronic acidoses, the acid load is buffered by bone leading to demineralization.

**E. Calcium**

1. Calcium is stockpiled in bone. It is accessible by regulation of osteoblast and osteoclast activity.
2. Ionized calcium is sensed by the parathyroid glands, which release parathyroid hormone as calcium level falls.
3. Parathyroid hormone stimulates:
  - a. release of  $Ca^{++}$  and phosphate from bone by increasing osteoclast activity greater than osteoblast activity
  - b.  $Ca^{++}$  reabsorption from the glomerular filtrate
  - c. 1,25-hydroxylation of Vitamin D by the kidney, which then stimulates  $Ca^{++}$  absorption from the gut

**VI. Solute and Solvent Handling by the Kidney**

- A. Variable Filtration – The filtered load of a particle is related to its plasma concentration and the GFR. Small molecules and uncharged solutes have a sieving coefficient close to 1. As the plasma concentration is altered by loads or deficits, the filtered load is increased or reduced accordingly.



- B. Tubular Handling – Altered tubular handling of solute and water is the major mechanism for responding to perturbations in the steady state. There is no normal or abnormal value for urine  $\text{Na}^+$  or  $\text{K}^+$  concentration, pH, or osmolality. When sodium is maximally reabsorbed from the filtrate during periods of volume depletion, the  $U_{\text{Na}^+}$  will fall to 10-15 mEq/L. After a salt load (i.e. MacDonald's french fries),  $U_{\text{Na}^+}$  will rise to as much as 100 mEq/L. Similarly, where water deprivation will increase  $U_{\text{osm}}$  above 1200 mOsm/kg as water retention and urinary concentration occurs, water loading may drop  $U_{\text{osm}}$  to less than 50 mOsm/L in an attempt to excrete the bolus as dilute urine.

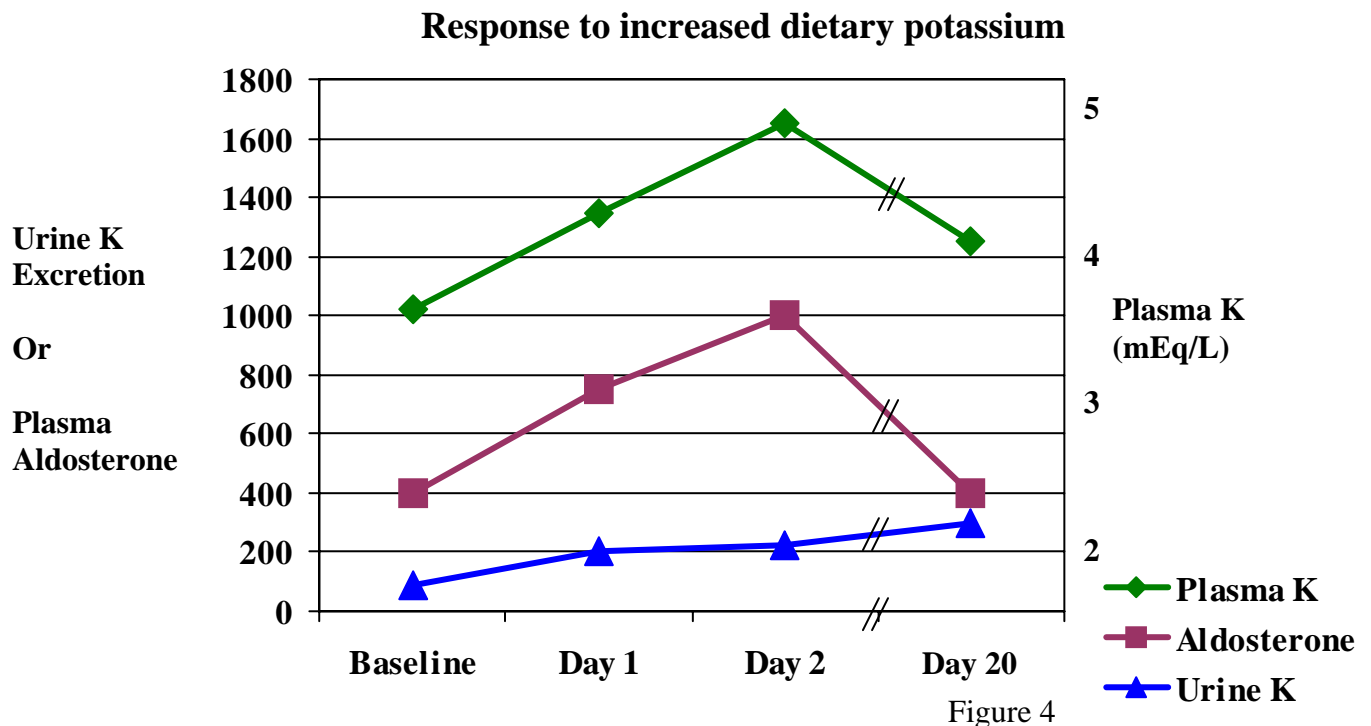
Some examples of how electrolytes are handled by the tubular mechanisms include:

1. Tubular Flow Rate – The proximal tubule and the loop of Henle constitutively reabsorb sodium, with modest up-regulation induced by angiotensin II. During times of volume depletion when  $P_{\text{GC}}$  and GFR fall, slower tubular filtrate flow allows for a greater amount of the filtered sodium load to be reabsorbed.
2. Tubular Secretion – There is minimal potassium in the tubular filtrate after the distal tubule. Excretion of potassium relies solely on tubular secretion in the collecting tubule, which is governed by aldosterone.
3. Tubular Reabsorption – Bicarbonate is filtered in large quantities by the glomerulus, and then nearly completely reabsorbed by the tubule. The bulk of  $\text{HCO}_3^-$  reabsorption occurs in the proximal tubule where  $\text{Na}^+$  and  $\text{H}^+$  are counter-transported across the luminal membrane ( $\text{Na}^+$  is reabsorbed as  $\text{H}^+$  is secreted). The remainder of  $\text{HCO}_3^-$  reabsorption occurs as the intercalated cells secrete  $\text{H}^+$  in the collecting tubule.

## **VII. Reestablishing the Steady State**

- A. With a water or electrolyte load, the steady state will be disrupted as input exceeds output. The excess will trigger the counter-regulatory mechanism describes above until the load has been excreted, then return to baseline levels.
- B. Similarly with a deficit, counter-regulatory mechanisms will limit further losses until dietary (or other) intake replete the loss. When stores have been replaced, counter-regulatory mechanism again return to baseline.
- C. What if a load continues? What happens when subjects who ingest 100 mEq of potassium per day increase their intake to 400 mEq per day? As the steady state has been disrupted, potassium will begin to accumulate. First, potassium will be taken up by cells, and then the plasma concentration will rise. The higher plasma concentration will stimulate the release of aldosterone, which will increase potassium excretion by the kidney. As the load continues, potassium may continue to accumulate, plasma levels will continue to rise, and aldosterone secretion will continue to increase. Eventually, a new steady state will develop.

- D. A new steady state develops when input again equals output. When the steady state is restored, urinary potassium loss has risen from 80 to 330 mEq/day, GI potassium loss has risen from 15 to 50 mEq/day, and sweat loss is up from 5 to 20 mEq/day. The increased output is a result of higher aldosterone levels. The higher aldosterone level is a reflection of the higher serum potassium level.



- E. Over time, the kidney, gut, and sweat glands become more efficient as excreting potassium (possibly from hypertrophy of potassium secreting tissue and up-regulation of potassium channels). Plasma potassium levels and aldosterone levels may fall slightly, as less aldosterone is required to achieve an equivalent potassium loss and maintain the steady state.
- F. When potassium intake returns to its prior level, a reverse process will occur. A reduced input with a constant output will place the patient in negative balance and lower plasma potassium levels. The lower potassium level will reduce stimulation for aldosterone secretion, which will then lower potassium excretion. A new steady state will develop when intake again equals excretion, and the plasma potassium concentration will level off where it stimulates aldosterone secretion just right.
- G. Similar interactions between intake, output, plasma levels, and counter-regulatory mechanisms exist for all electrolytes and water (note: for sodium this is manifested as volume overload and hypertension).

**VIII. Summary**

1. Homeostasis is critical for maintaining a stable chemical, electrical, and osmolar environment to optimize cellular function.
2. Despite wide fluctuations in intake, excretion, production, and consumption, the body's internal milieu changes very little.
3. The body is compartmentalized into an intracellular space and an extracellular space by the cellular membrane. Each compartment has a unique chemical composition.
4. The capillary membrane further divides the extracellular space into the interstitium and the plasma. The plasma is maintained by plasma proteins, which produce a higher oncotic pressure.
5. The steady state exists when input equals output, and is readily identified by stable plasma content and concentration.
6. Perturbations to the steady state are rapidly sensed, and compensatory measure initiated to restore balance.
7. Balance is restored, but often at a different plasma concentration (or volume status for sodium) and a new level of counter-regulation.