Molecular Mechanisms of Body Water Homeostasis

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Molecular Mechanisms of Body Water Homeostasis
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www.morganclaypool.com

ISBN: 9781615047321 paperback

ISBN: 9781615047338 ebook

DOI: 10.4199/C00144ED1V01Y201610ISP067

A Publication in the

COLLOQUIUM SERIES ON INTEGRATED SYSTEMS PHYSIOLOGY: FROM MOLECULE TO FUNCTION TO DISEASE

Lecture #68

Series Editor: D. Neil Granger, LSU Health Sciences Center, and Joey P. Granger, University of Mississippi Medical Center

Series ISSN

ISSN 2154-560X print

ISSN 2154-5626 electronic

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ABSTRACT

This book discusses our intimate relationship with and dependence on water, how the body regulates its water levels, and various pathophysiological states associated with impairments in body water homeostasis. The human body consists of 70–80% water. Therefore, concise control of water homeostasis is essential to survival and involves coordination of several systems, but primarily the brain and kidney systems. Water requirements of the average healthy human range between 2–4 L/d, and a major portion of this can come from food sources. The major hormonal regulator of water balance is the anti-diuretic hormone, vasopressin. Vasopressin, a 9–amino acid peptide, is produced in the hypothalamus, stored in the posterior pituitary, and secreted when plasma osmolality rises. Vasopressin acts on the kidney to conserve water. The kidneys filter ~180 L of blood per day, consisting of about 50–65% water, and reabsorb around 99% of this in the proximal tubule, distal tubule, and collecting duct, producing only 1–2 L of urine. The vasopressin-sensitive distal tubule and collecting duct are responsible for fine-tuning water reabsorption. Conditions exist, however, where urine cannot be concentrated effectively. This is known as diabetes insipidus and can lead to dehydration and failure to thrive. At the other extreme, hyponatremia (low serum sodium) is the inability to adequately dilute urine or get rid of free body water in excess of body needs, a serious and sometimes fatal condition.

KEYWORDS

water homeostasis, total body water, kidney, hydration, aquaporin, diabetes insipidus, hyponatremia, vasopressin, osmolality.

Contents

CHAPTER 1

Water, Water Everywhere

1.1 CHAPTER OVERVIEW

About 71% of the earth's surface is water-covered [1]. The most primitive of life forms are waterborne species. As organisms on the phylogenetic tree became more complex, including various land-dwellers, evolutionary pressure increased to develop the means to conserve water. Water is essential for survival, not only for humans, but for all species in the five kingdoms of biology: plantae, protista (algae, mold), monera (eubacteria and archeobacteria), fungi, and animalia. *Homo sapiens* cannot survive if their water content decreases by about 12% [2]; thus homeostasis of water is perhaps the most critical of physiological functions. The balance between water intake and excretion must be strictly maintained. Water intake is largely regulated through the control of thirst, while excretion is controlled through urinary dilution and concentration.

Among anthropologists, there exists a highly disputed and controversial theory, known as the Aquatic Ape Theory, which posits that the early ancestors of modern man spent a large amount of time in the water, while they continued to evolve, as opposed to in a more terrestrial or forested environment [3]. The basis for the theory originated in 1960, as the result of a publication by Sir Alister Hardy [4]. The hypothesis lost traction in the 1990s [3], and has somewhat re-emerged in the early part of this century [5]. The Aquatic Ape Theory holds that many features distinctive to humans (as opposed to primates), e.g., hairlessness, a descended larynx that closes up under water, a large brain, a fair amount of subcutaneous fat, and walking upright, appear as adaptations that would provide an advantage (or at least not be disadvantageous) in a semi-aquatic environment. Opponents to the idea argue that there is no clear proof in support of the hypothesis. Nonetheless, few would dispute that humans need and have a great affinity for water. Nearly 44% of the world's population lives within 150 km of an ocean or sea [6]. In this first chapter, we discuss: (1) water composition and compartmentalization in the human body and how it may vary by sex, age, and body leanness; (2) dehydration and its effects on physiological functioning; and (3) common environmental modulators of body water composition, such as changes in heat and humidity, altitude, and diet.

1.2 BODY WATER COMPOSITION

Water, i.e., H_2O, is the most abundant molecule (chemical) in the human body. Water provides a means to transport nutrients and oxygen via the stream of blood in the vasculature. It also provides a way to cool the body by dissipating heat through sweating and evaporative cooling. Interstitial water bathes cells and provides a medium for a number of essential hormones, proteins, and immunoglobulins. The percentage of water in a human can vary anywhere from 50% to close to 80% (by weight) [7]. Other mammalian species have been reported to have similar percentages of total body water (TBW) [8]. Variability in TBW between healthy individuals is primarily due to differences in body composition, i.e., degree of adiposity. Lean tissue is about 73% water, while adipose tissue is about 10% water [7]. Age is also a primary determinant of TBW. Within the human population, infants have the highest percentage of TBW, at around 75–78%. This is followed by children, then adult men, then adult women. An adult woman may be near 55% TBW, while an elderly woman may be nearer to 50%. Women typically have a lower percentage of body water than men, as they generally have a greater percentage of body fat, and less lean muscle. However, this is clearly not true for all women or all men. This reduction in TBW with aging and in females can affect the distribution and, thus efficacy of medications, the cooling of the body (in hot temperatures), and the distribution of nutrients and oxygen.

1.2.1 Changes in Water Homeostasis Over the Lifespan

There are a number of reasons why TBW declines with aging, e.g., body composition changes with age so there is reduced lean muscle, relative to adipose tissue. Second, the thirst apparatus may not function as efficiently in aging, leading elderly persons to either overhydrate or under-hydrate. Third, a number of medications are associated with diuresis and natriuresis, which can affect body fluid status, and elderly persons are more likely to be prescribed these medications. Finally, the kidneys are not as effective at concentrating or diluting urine with age, affecting the fine-tuning of whole-body water homeostasis. Hyponatremia, due to excessive water retention in the plasma space, is extremely common (~40%) in hospitalized elderly subjects [9]. We have devoted Chapter 4 to hyponatremia.

At the other end of the spectrum, infants, especially those born premature, are likewise relatively more susceptible to dehydration or over-hydration than adults. Infants cannot effectively communicate their level of thirst; furthermore, the kidneys are still developing. Both renal blood flow (RBF) and glomerular filtration rate (GFR) are low at birth, although GFR increases markedly over the first two weeks of life. RBF, on the other hand, matures more slowly, with developmental changes occurring up to 24 months of life [10].

In infants, over-hydration is most likely to occur in an inpatient setting, where it can be difficult to estimate fluid requirements (discussed in Chapter 4). Dehydration can occur rapidly in infants, especially, e.g., in cases where they suffer from one of the various genetic disorders of urine concentration known as nephrogenic diabetes insipidus (NDI, see Chapter 5). These are often unbeknownst to their parents at least at birth. Diarrhea is the leading cause of morbidity and mortality worldwide among children under 5 years of age in low-income and middle-income countries [11]. Dehydration is the primary and most immediate cause of death in infants with diarrhea. In a meta-analysis, Munos et al. [12] determined that if dehydration were managed, for example with oral rehydration fluids containing small amounts of sodium and glucose or "home fluids" consisting of rice water and sugar solution, 93% of diarrheal deaths in children under 5 could be prevented.

1.2.2 Body Water Intake Requirements

The Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine have suggested that an average, healthy adult male living in a temperate climate requires about 3.7 L of total beverages each day [13]. An average woman, in comparison, requires about 2.7 L. On average, about 80% of any one person's total water intake comes from drinking water and beverages and the other 20% comes from food sources [13]. While no higher limit has been set on an acceptable level of water intake by this agency, it is currently recognized that excessive water intake can be dangerous, i.e., lead to water intoxication, morbidity, and even death. This subject is covered in more detail in Chapter 6.

There has been a commonly held belief that individuals should aim to drink about 8 cups of water per day [14, 15]. This concept was probably loosely based on a 1945 recommendation by the Food and Nutrition Board that suggested each person consume 1 ml of water for each calorie consumed (based on little solid evidence); thus an average intake of 1,900 kcal would equate to 1,900 ml (or about 8 cups) of water per day [14, 16]. However, this recommendation was probably meant to include water contained in food sources and other beverages, not just pure water. Pregnancy and lactation represent addition special conditions in which water requirements are increased. The Institute of Medicine recommends 2.3 L of beverages (or fluid from other sources including food) per day during pregnancy and 3.1 L during lactation [13].

However, there is no solid evidence that drinking somewhat less than the recommended amounts results in dehydration. There is a pervasive belief that many of us are chronically dehydrated or at least partially dehydrated and would benefit from consuming more water on a daily basis, if for nothing else than to purge our bodies of toxins. However, no clear proof exists that consuming extra water helps to eliminate toxins or provide any other health benefit. What many people fail to realize is that the kidney and AVP system act as a buffer against dehydration. We are not just wet towels drying in the wind; our kidneys are able to adapt to lower water intake to keep TBW fairly constant (see Chapter 3), and there is no clear evidence that this adaptation is pathological. The current recommendation regarding water intake by the majority of medical professionals is that one should drink when one feels thirsty, not be compelled to consume a certain number of cups of liquid a day. This rule of thumb seems to be quite adequate for most healthy adults who have a suitably functioning thirst perception [14, 17]. However, having said this, one needs to be aware of one's thirst and need for rehydration, especially in hot and humid environments, and when exercising for long periods of time.

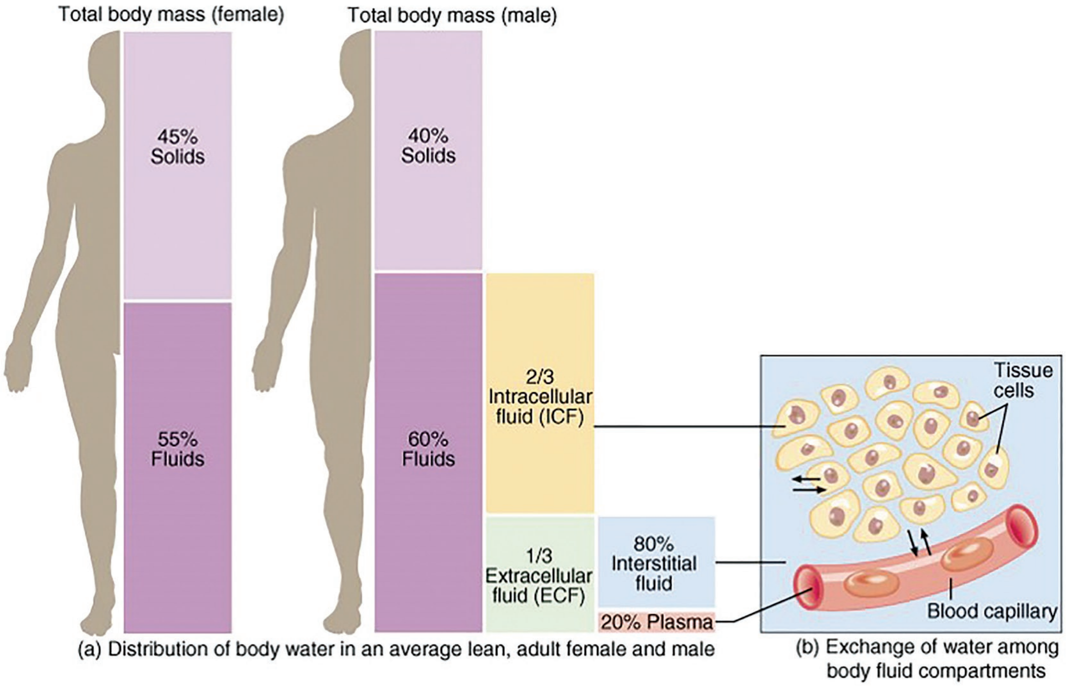
1.3 MEASUREMENT OF TOTAL BODY WATER (TBW)

TBW can be estimated in a number of ways. Theoretically, examination of a substance that behaves like water but can be easily measured in urine or plasma is ideal. One approach is to utilize tritium or deuterium oxide water. This is water made with heavier isotopes of hydrogen that can be measured by mass spectroscopy. The labeled water can be administered to the subject in a known volume and after it has equilibrated with unlabeled body water, blood is sampled and urine collected. Assuming the label has distributed evenly through all body compartments, the degree to which the label is diluted can be used to estimate TBW. Another method to measure TBW is to measure dilution of a deuterium-labeled water molecule in breath samples collected from individuals who have ingested a known volume of D_2O [18]. Flowing afterglow mass spectrometry can be utilized to measure deuterium abundance. This non-invasive approach was found to agree remarkably with dilutional isotope approaches, and can be more easily employed for large study populations [18].

One of the more recent means used to gauge TBW is bioelectrical impedance analysis (BIA). This approach involves applying electrodes to the bare hands or feet of the individual; then a weak, single-frequency current is introduced of about 50 kHZ. This alternating current waveform allows the creation of a current inside the body [19]. The degree to which this current is impeded is inversely proportional to TBW. The current is able to travel through water/lean tissue unimpeded, but undergoes resistance when traveling through adipose tissue. Many modern scales in the home estimate TBW utilizing this approach. Clinically BIA can be used to estimate relative leanness in an individual to assess metabolic fitness, and has an advantage over using simply body mass index, which takes into account only measures of height and weight. Bioimpedance spectroscopy (BIS) is a unique BIA approach that allows for differentiation of intracellular versus extracellular fluid [20]. This approach can be applied clinically to determine cell mass, an important indicator of nutritional status. Estimation of TBW by bioimpedance technology can also be beneficial in assessing fluid overload in dialysis patients [19].

1.3.1 Body Water Compartmentalization

Total body water is distributed into two main compartments: 1) extracellular fluid (ECF) and 2) intracellular fluid (ICF). The ICF and ECF contain about 65% and 35% of total body water, respectively [21]. Figure 1.1 displays estimates of the composition of the fluid and solid compartments in an average-sized human male and female. A 70 kg male has about 42 liters (L) of TBW; therefore the ICF contains ~28 L and the ECF, 14 L water. The ECF is composed of plasma (fluid of the blood surrounding blood cells) and interstitium (fluid that bathes the cells, but is not in the



(a) Distribution of body water in an average lean, adult female and male

(b) Exchange of water among body fluid compartments

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FIGURE 1.1: Compartmentalization of fluids and solids in human females and males. Image from [292]. Reprinted with permission of John Wiley & Sons, Inc.

vasculature). The plasma of a 70 kg male contains about 3.2 L water and the interstitium about 10.8 L. Body water can move from compartment to compartment mainly via membrane channels (aquaporins, described in detail in Chapter 3). Within the course of normal daily activities, a person loses on average 2.4 L of water per day (5–10%). Sources of water loss include ~1.4 L in urine, 200 ml in feces, and 100 ml in sweat. The remaining 700 ml or so are lost through what is known as insensible losses. This occurs via diffusion directly through the skin or through pores, as well as from the lungs via respiration.

In addition to methods used to measure TBW (deuterium oxide, bioimpedence), there are a number of ways to estimate the water in each of the body compartments. Plasma volume (PV) can be estimated by measuring the dilution of a radiolabeled circulating protein such as albumin or ferritin. Evan's blue dye is a tracer that has traditionally been used to estimate PV. In addition, in the short term, hematocrit can provide an index of water retention in the vascular space [22]. ECF can be estimated either by ionic or crystalloid tracers [23]. Ionic tracers include radiolabeled bromide, sulfate, and chloride. These electrolytes diffuse rapidly but may over-estimate ECF because they can partially enter cells. Crystalloids such as mannitol and inulin, on the other hand, do not distribute as well, and may under-estimate ECF. Red blood cell (RBC) volume can be estimated by radio-chromium. Chromium can enter red blood cells and the amount of labeled chromium per RBC can be used as an estimate of the size of the RBC. Interstitial fluid (IF) is estimated by calculating the difference between ECF and PV. Finally, intracellular fluid can be estimated by radiolabeled potassium or estimated by the difference between TBW and ECF. Maw and colleagues [24] have developed a simultaneous radioisotope dilution approach to estimate plasma volume (PV) by administration and eventual measurement of dilution of radioiodinated human serum fibrogen, red cell (erythrocyte) volume by radiochromated autologous erythrocytes, ECF by radiobromide, and TBW by tritiated water. In addition to the variety of dilutional approaches to estimate the size of various fluid compartments, bioimpedence has been improved from single frequency to bioimpedance spectroscopy (BIS) to allow for estimation of both ECF and ICF. The approach (or algorithm employed) is based on the different conductance properties of the fluids ECF (primarily saline) and ICF (high-potassium based), taking into account the capacity for membranes to hold charge [25].

1.4 DEHYDRATION

Dehydration (also known as hypohydration) is a condition when body water content is lower than what is needed for normal bodily functions. Reduced body water content can result from disease, injury or trauma, inappropriate water intake, or inappropriate water expulsion. Dehydration is one of the 10 most frequent diagnoses responsible for hospital admission in the elderly in the United States [26]. Recently, chronic dehydration has been linked to kidney disease [27]. This may be especially pervasive in warm climates where migratory workers toil for many hours in the hot sun, do not rehydrate often enough, and when they do, they often consume sugary beverages. The high osmolality of the serum apparently increases AVP production and activates the polyol-fructokinase pathway, which produces endogenous fructose [28]. Fructokinase knockout mice were protected from dehydration-induced renal injury [29]. Fructose ingestion has been shown to increase inflammation and fibrosis in the kidney, at least in rodents [30–32].

1.4.1 Exercise and Water Requirements

Body water perturbations are common when performing strenuous exercise over relatively long periods of time, especially when the weather is hot, cold, or during extremes in altitude [21]. Sweat losses during various sports have been reported to range from 455–3,630 ml/day [21], based on the temperature, humidity, and intensity of the exercise (Figure 1.2). Body water losses of greater than 2% are clinically defined as hypohydration. With hypohydration, there have been reports of mood changes, fatigue, and loss of general alertness [33]. Acute changes in hydration status due to extreme exertion can be best assessed by weighing. Whether or not one should consume water (or other liquid replacement) in excess of thirst during exercise to stave off dehydration has been a subject of some debate. A recent study evaluated treadmill performance in young men and women allowed drinking water either on a voluntary basis or at prescribed amounts and set intervals. The investigators determined that the prescribed regimen actually reduced performance (time to exhaustion). The authors speculated that drinking water when not thirsty and at higher volumes may have led to gastrointestinal distress and diversion of blood flow away from muscle toward stomach and intestine [34]. Voluntary consumption, in this particular study, did prove to be lower than the prescribed volume.

With improper rehydration, there is a loss of water in each of the body's compartments; however, the percent lost from each compartment can vary. Nose and colleagues [35] exposed rats to a hot, dry environment and found the fluid deficit was apportioned as such: 41% in the ICF, 47% from interstitial fluid, and 12% from plasma volume. Thus plasma volume was relatively maintained at the expense of cellular and interstitial water. In regard to organ fluid loss, 40% came from muscle, 30% from skin, 14% from viscera, and 14% from bone. Neither the brain nor liver lost a significant amount of water. The brain consists of about 80% water, which is higher than the body, as a whole [36]. Most of the intracellular water in the central nervous system is found in astrocytes (star-shaped glial cells).

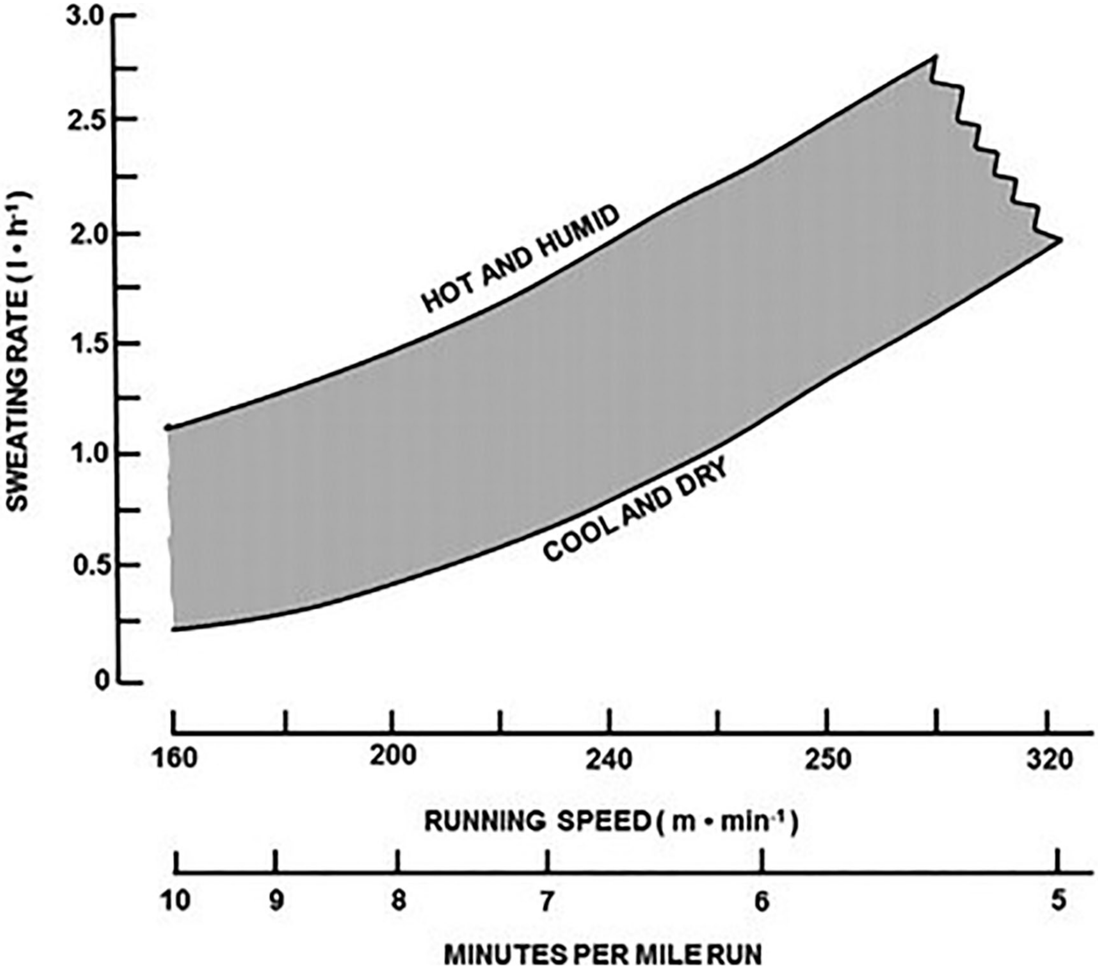

FIGURE 1.2: Approximation of hourly sweating rates for runners in different environments. From [293]. Reprinted with permission from Springer.

Other studies evaluating the effect of dehydration on the brain have demonstrated impaired cognitive functioning [33, 37, 38]. A recent study examined the cognitive effects of 4 hours in a 30°C room with or without access to drinking water in 101 young adults (18–24-year-olds). The study showed that body water losses as low as 1% were correlated with impaired memory and focus [38], challenging the conventional wisdom that slight dehydration is of little physiological consequence. Older adults are particularly susceptible to dehydration encephalopathy, and thus, to cognitive impairment as a result of reduced TBW, thirst acuity, and renal function (as discussed above). Astrocyte density declines with age, as do brain reserves of water. Dehydration has also been demonstrated to accelerate the progression of Alzheimer's disease [39].

1.5 ENVIRONMENTAL MODULATORS OF BODY WATER COMPOSITION

A number of environmental factors can influence TBW and even the distribution of water within the body. Some of the common factors that an ordinary person may encounter during their life span include: 1) high-altitude exposure; 2) extremes in temperature or humidity; 3) changes in dietary habits.

1.5.1 High Altitude

High-altitude-related health problems that involve alterations in fluid dynamics include: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE) [40]. Edema is the pooling of inappropriate levels of body water in the interstitial space. It is fundamentally due to changes in the Starling forces and pressure in vessels versus that in the interstitium (Figure 1.3). Edema will form when the interstitial osmolality is high, relative to that in the vessels (pulling force), and the pressure is high in the vessels (pushing force). HACE and HAPE require immediate medical attention as they can be quite serious and lead to loss of consciousness or death, although these developments are quite rare. Edema that results from high altitude is mainly due to the drop in barometric pressure leading to capillary leakage. Capillary leakage will increase the volume of water in the interstitial space, and can potentially increase overall TBW, if water intake is increased due to activation of thirst mechanisms with the reduction in vascular volume. Cerebral edema is characterized by ataxic gait, severe lassitude, and altered consciousness, including confusion and impaired mental function [41]. Pulmonary edema is characterized by difficulty breathing. Both HACE and HAPE are thought to result from reduced bioavailability of nitric oxide (NO), increases in reactive oxygen species (ROS), and inflammatory cytokines [42]. One mechanistic explanation for cerebral edema is increased activity of the water channel, aquaporin-4 (AQP4, discussed further in Chapter 3) [43, 44].

Acute mountain sickness (AMS), on the other hand, is quite common in about 25% of persons traveling to or above 2,500 meters above sea level [45]. AMS is characterized by nausea, vomiting, light-headedness, and modest swelling of the hands and feet. Susceptibility to AMS seems to

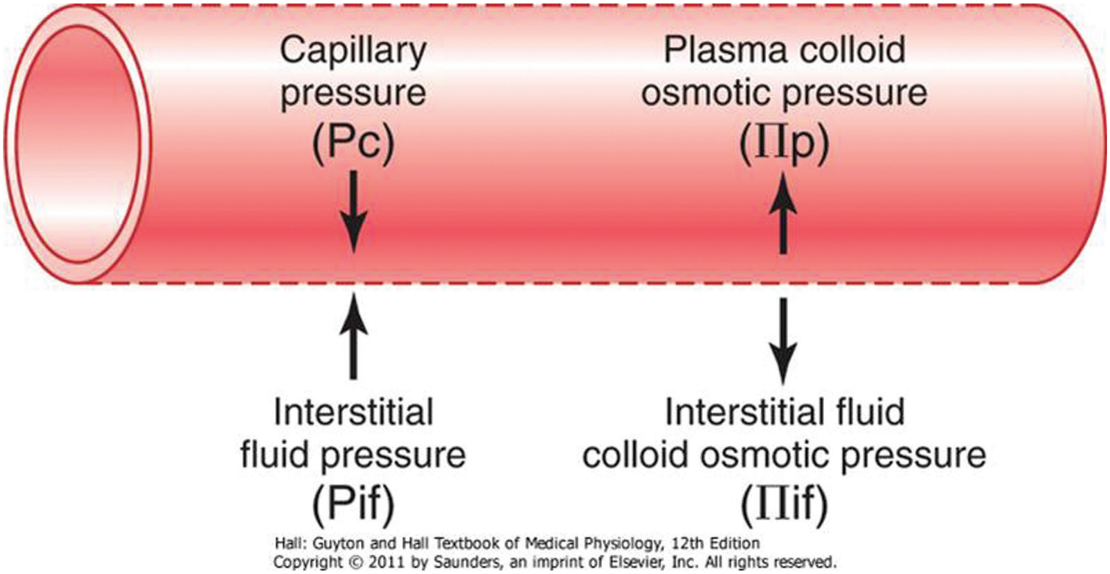

FIGURE 1.3: Starling and osmotic forces affect fluid flow into and out of capillaries. From [305]. Reprinted with permission from Elsevier.

be at least partly determined by the sensitivity of the chemoreceptors to hypoxia [40]. Hypoxia initially leads to a ventilatory response. Those individuals who have the strongest ventilatory response appear to also exhibit high diuretic and natriuretic responses to altitude [40].

In addition, chronic exposure to high altitude can lead to adaptations in the kidney and circulatory system, including polycythemia (increased concentration of hemoglobin in the blood), systemic hypertension, reduced renal plasma flow, glomerular hypertrophy, microalbuminuria, and hyperuricemia. However, in most instances, GFR appears to be relatively preserved [46]. In addition, chronic high-altitude exposure can lead to hypovolemia, due to insensible fluid losses as a result of low humidity and tachypnea (abnormally rapid breathing), and reduced fluid intake due to decreased thirst and reduced appetite [40, 47]. The diuretic response to altitude has been reported to involve decreased vasopressin release with a concomitantly increased atrial natriuretic peptide (ANP) release. ANP would then act on sites in the renal tubule to increase sodium excretion, while a drop in AVP would result in water diuresis. Additional studies show transient hypoxia (as would be encountered at altitude) triggers coordinated humoral responses involving norepinephrine, renin, and vasopressin [48].

1.5.2 Extremes in Temperature or Humidity

It is not surprising that extremes in temperature or humidity can affect TBW and body water compartmentalization. Maw et al. [24] investigated the effects of short-term modification of skin temperatures in which core temperature changes were minimized. Seven males participated in hot (36.2°C), moderate (22.0°C), and cold (14.4°C) trials separated by 28 days. Each subject underwent each treatment for a 30-minute period, after which body fluid compartments were estimated using a simultaneous radionucleotide dilution approach [24]. Plasma volume contracted under the cold temperature (~205 ml) and expanded under the hot (~108 ml), while ECF and TBW remained virtually unchanged. It was assumed that ICF fluid contracted slightly in the heat and expanded slightly in the cold (as the source and the sink for the changes in plasma volume); however, changes in this compartment were not detected.

1.5.3 Dietary Alterations

In general, TBW, and its distribution in the body, is carefully controlled by a complex network of regulatory pathways (see Chapters 2 and 3); however, acute changes in dietary habits can affect fluid distribution especially in the short term. Ingestion of unusually high amounts of water (polydipsia) can be considered a psychiatric disorder termed "compulsive water drinking" and is covered under pathological conditions in Chapter 6. However, what is a normal body response to high (within reason) versus low consumption of water or water-containing beverages? A high water intake under normal, healthy conditions will not expand any body fluid compartments. As blood (and thus water) is filtered by the kidney, it becomes urine. Under these conditions less of the filtered water is reabsorbed. In contrast, under low water intake, the kidneys work hard to reabsorb as much water as possible and concentrate the urine.

One dietary chemical that has been demonstrated to affect urine concentration is caffeine (a methylxanthine). The most common caffeinated beverage consumed in the United States is coffee, and the average daily intake of caffeine is around 300 mg. Fifty-four percent of Americans over the age of 18 consume caffeine on a daily basis [49]. Caffeine is a diuretic in that it attenuates the ability of the kidney to reabsorb water especially in the proximal tubule (the first part of the renal tubule). Studies have shown that caffeine's effects are primarily the result of antagonism of the adenosine (A1) receptor [50]. A diet high in caffeine or caffeinated beverages, however, does not usually result in dehydration, as reported by Zhang et al. in a recent meta-analysis [51]. Persons usually compensate for the mild diuretic action of caffeine by consuming more fluid. Furthermore, caffeine does not appear to affect TBW or compartmentalization of body water. Silva et al. [52] conducted a double-blind, randomized, cross-over study where 30 men were assigned to caffeine (5 mg/kg/d) or placebo treatments for 4 days, with a 3-day wash-out period, followed by the opposite treatment. TBW and ECF were assessed by deuterium oxide and sodium bromide dilution, respectively, while ICW was determined by subtraction of ECW from TBW. No significant differences in TBW, ECF, or ICF were observed between the caffeinated versus the placebo periods.

An extremely low-protein diet can also cause diuresis and potentially dehydration due to a reduction in the ability of the kidney to concentrate the urine. The mechanism underlying this effect is due to low dietary levels of urea, which is one of the main determinants of a renal urinary concentrating capacity [53] (see Chapter 3). Protein-calorie malnutrition is one of the leading causes of morbidity and mortality in the developing world [54]. It has been shown to impair urine concentrating capacity and reduce glomerular filtration rate and renal plasma flow [55].

Diets high in sodium are also associated with water retention (increase in TBW), in particular in sodium-sensitive subjects [56]. The study of salt sensitivity on water retention has mostly been conducted in the context of salt-sensitive hypertension (which is covered in Chapter 6). The conventional wisdom is that salt-sensitive individuals retain excessive sodium when consuming a high-sodium diet, while those who are salt-resistant tend to excrete excess sodium, and therefore their blood volume (ECF) remains normal. Water is reabsorbed relatively passively (through water channels) in the kidney due to the osmotic gradient created by the NaCl in the renal interstitium. However, an alternative hypothesis which has garnered support is that TBW and ECF undergo similar or even greater volume expansion in salt-resistant versus salt-sensitive individuals [57]. The difference in blood pressure between the two groups results because salt-resistant individuals have greater capacity to vasodilate, thus the pressure in vessels is reduced [57].

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