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Review Article

Sodium Balance and Imbalance: A Review Linking Physiology with Pathophysiology

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Abstract

Sodium (Na+), one of the major extracellular cations in the body, exerts a significant role in regulating body fluid compartments and generating action potentials. It represents one of the most important and readily available biomarkers of fluid status. Disturbances of Na+ homeostasis are frequently observed in outpatient and inpatient settings and can be challenging to clinicians attempting to decipher the underlying aetiologies. Various disorders involving the renal, endocrine, and central nervous systems can lead to dysnatremias and imbalance in volume status. Understanding the diverse physiological mechanisms involved in normal Na+ regulation and the expected pathological outcomes when the normal processes are disrupted is crucial in assisting clinicians with coming up with reasonable differential diagnoses and targeted management plans for Na+ disorders. This review summarises the pathophysiology of Na+ disorders by linking it closely with normal Na+ homeostasis.

Key Words: sodium; hyponatraemia; hypernatraemia; physiology; pathophysiology

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Introduction

Sodium (Na^+) is one of the most critical minerals in maintaining cellular homeostasis and regulating water balance and blood pressure. Changes in the body's Na^+ content can significantly impact cellular and organ functions. Disturbances of serum Na^+ concentrations are the most frequently encountered electrolyte disorders by physicians, especially in inpatient settings.[1]. Diagnosing the underlying aetiology and instigating the correct management plan can be challenging and requires a thorough understanding of the normal Na^+ balance and common pathophysiological processes involved in dysnatremias.

Hyponatraemia represents a serum Na^+ concentration of <135 mmol/L and hypernatraemia represents a serum Na+ level of >145 mmol/L. Hyponatraemia, which is present in 15-30% of the inpatient population, presents with headache, nausea, vomiting, confusion, drowsiness, weakness, numbness, seizures and coma. It can be life-threatening in more severe cases.[2] Patients with hypernatraemia, which represents up to 5% of the inpatient population, can present with thirst, lethargy, weakness, focal neurological deficits, coma, and death if severe.[3] Prompt recognition and management is paramount to prevent adverse outcomes.

In most scenarios, the diagnosis of dysnatremias remains elusive in real-life settings. There are significant challenges because the clinical presentation is often non-specific, and it is not until more severe signs and symptoms of dysnatremias are present that patients are treated. Patients can initially be utterly asymptomatic during mild hyponatraemia or hypernatraemia stage before progressing into serious complications.[4] Compounding the picture is the multitude of differential diagnoses for hyponatraemia and hypernatraemia, which require an in-depth understanding of the patient's clinical picture and volume status and a thorough workup to recognise common causes before pursuing more complex investigations to determine the exact underlying aetiology.

This article aims to summarise the underlying physio-

logical and pathological mechanisms underpinning Na^+ homeostasis and imbalance, assisting clinicians with diagnosing and managing patients with Na^+ disorders.

Total body water and total body sodium

Water constitutes 50-60% of lean body weight in men and 45-50% in women. A healthy 70 kg man contains about 42L of total body water (TBW), which is primarily distributed into two main compartments: the intracellular fluid (ICF) and the extracellular fluid (ECF) compartments (Figure 1). Almost two-thirds (28L) of TBW is contained in the ICF compartment, and the remaining third (14L) is in the ECF, out of which about 9L constitutes interstitial fluid surrounding the cells and almost 5L is in intravascular space as plasma.[5] Water can freely move across the semi-permeable membranes, separating these major fluid compartments. However, the presence of osmotically active solutes, mainly Na^+ in the ECF and potassium (K+) in the ICF, prevents this free movement of water across membranes by exerting osmotic pressure, maintaining the water content of the two main fluid compartments at a relatively stable level.[5]

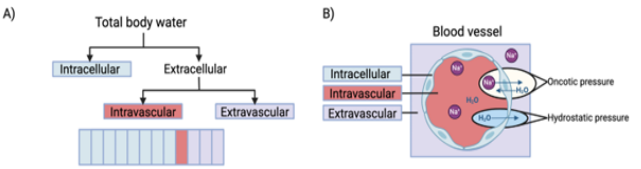

Figure 1: *Distribution and movement of total body water and sodium (created with biorender.com). (A) Total body water is distributed in a 2:1 ratio between the intracellular and extracellular compartments. The extracellular compartment can be further divided into the intravascular and extravascular compartments in a 1:3 ratio. (B) Water and sodium movement between the intravascular and extravascular compartments is driven by oncotic and hydrostatic pressure.*

ECF osmolality, defined as the number of particles of solutes per kilogram of solvents, is a significant factor in determining the movement of water to and from the cells and regulating the cellular volume. Water moves from areas of low osmolality to restore osmolar neutrality. The concentration of osmotically active solutes is primarily the same in plasma and interstitial fluid, and osmotic pressure generated by these solutes does not contribute to the regulation of plasma volume, which in turn is determined by the balance between the hydrostatic pressure in capillaries and oncotic pressure generated by plasma proteins. The body tightly regulates water distribution between these fluid compartments to maintain the homeostasis of TBW.[5]

A 70 kg adult male has around 92 g of Na+; almost half (46 g) is located in the extracellular fluid (ECF), about 35 g in the skeletal system, and around 11 g in the intracellular fluid (ICF) compartment. The Na^+-K^+ adenosine triphosphatase (ATPase) pump in the cell membranes maintains the concentration of Na^+ and K^+ in the ECF and ICF compartments, respectively, by moving Na+ out and K+ in the cells.[6]

Na^+ is the primary cation in the ECF and, along with the major anions, is responsible for almost 90% of the ECF and serum osmolality[7]. Both normal serum Na^+ concentration and serum osmolality are maintained within narrow limits of 135-145 mmol/L and 275-295 Osm/kg, respectively by various physiological mechanisms discussed in the subsequent sections of this article. Any changes in serum Na^+ concentration and serum osmolality can result in significant shifts in the body's fluid compartments and affect normal cellular function.[8]

Normal Water Regulation

Regulation of water balance during fluctuations in water intake and loss requires a delicate interaction between the hypothalamus, kidneys, and neurohypophysis.

Role of Antidiuretic hormone

Antidiuretic hormone (ADH) is synthesised in the hypothalamus and is the primary hormone that regulates water excretion. It increases aquaporin expression in the distal nephron segments and enhances water permeability and retention.[9] Changes in blood osmolality primarily regulate the release of ADH. Osmoreceptors in the anterior hypothalamus sense fluctuations in ECF osmolality, regulating ADH release.[10]

ADH levels are very low if the serum osmolality falls below 280 mOsm/kg, which can be seen after acute water load, such as consumption of large quantities of water or infusion of 5% dextrose. It causes almost complete cessation of water absorption in the distal nephron, resulting in dilute urine with < 100 mOsm/kg osmolality and excretion of excess water in the urine, thus restoring the normal serum osmolality. Conversely, the ADH secretion from vasopressinergic nerve endings in the neurohypophysis and, consequently, the serum level increases with the rise in serum osmolality above the normal physiological level of 290 mOsm/kg, such as in salt-free water loss with profuse sweating or water deprivation. This leads to water retention in the distal nephrons and the passage of concentrated urine, normalising serum osmolality. The rise in serum osmolality also stimulates thirst, which compels individuals to drink more water.[6]

In addition, changes in blood volume also regulate ADH release independent of ECF osmolality mediated by baroreceptors in the atria and carotid sinus.[10] These two mechanisms of ADH release are termed the osmotic and non-osmotic pathways, respectively (Figure 2). The osmotic pathway responds to a 1-2% change in

ECF osmolality, while the non-osmotic pathway requires a 5-10% decrease in blood volume to stimulate the release of ADH.[11]

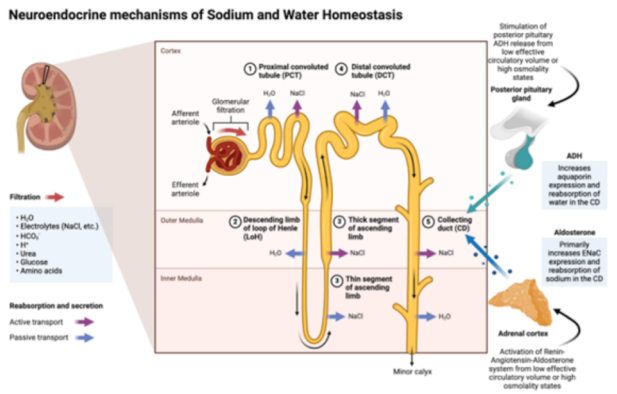

Figure 2: *Renal regulation of water and sodium balance*

Adapted from "Kidney Reabsorption and Secretion", by BioRender.com (2024).

Secondary hormones affecting antidiuretic hormone release

Secondary hormones indirectly involved in water homeostasis include atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) as well as angiotensin II (Ang II). ANP from cardiac atria and BNP from cardiac ventricles reduce the pituitary secretion of ADH and promote water excretion in response to increased myocardial wall pressure from an elevated ECF volume 12. Natriuretic action is affected through increased glomerular filtration rate (GFR)7.

Ang II promotes water retention by increasing ADH secretion and triggering central stimulation of thirst and salt appetite in periventricular circumventricular organs (CVOs), specifically the subfornical organ (SFO)[13,14].

Normal regulation of sodium balance

Extracellular Na^+ concentration is the chief determinant of the ECF volume. Various pathways, including renal excretion of Na^+, activation of the renin-angiotensin-aldosterone system, catecholamines, and the sympathetic nervous system, maintain the Na^+ balance (Figure 2). Effective arterial blood volume (EABV), also known as effective circulatory volume, which is almost 15% of the total plasma volume, plays a vital role in Na^+ hemostasis. The cardiac output and total peripheral arterial resistance determine EABV. A fall in EABV leads to increased Na+ and water absorption by the kidneys. Conversely, an expansion of EABV increases renal Na^+ and water excretion.[6]

Renal handling of sodium

The kidney plays a vital role in Na^+ homeostasis, achieved through three fundamental processes: glomerular ultrafiltration, reabsorption of solutes and water, and secretion of solutes into tubular fluid. The glomeruli filter 180 L of fluid in humans and reabsorb 178 L daily. Of the 24,400 mmol of Na+ that enter the nephron lumen daily, almost 24,300 mmol is reabsorbed, and about 100 mmol is excreted in the urine.[15]

While renal handling of Na^+ and water occurs throughout the entire nephron, the distal nephron is essential in making final adjustments to Na^+ and water reabsorption via a series of apical and basolateral transporters coordinated by complex endocrine and neural signalling pathways.[16] In brief, the nephron comprises the proximal convoluted tubule (PCT), loop of Henle (LOH), distal convoluted tubule (DCT), and the collecting ducts (CD). Most salt and water reabsorption occur in the PCT, which reabsorbs approximately two-thirds of filtered Na+ and water in addition to other solutes such as K^+, bicarbonate (HCO_3^-), glucose, and amino acids.[17]

In the first half of the PCT, Na^+ reabsorption is driven primarily through HCO_3^- reabsorption via Na_3^- hydrogen (H^+) antiporters (NHE_3) in the apical membranes and Na^+- K^+- ATPase and Na^+- HCO^3- cotransporter (NBC) in the basolateral membrane. In the second half of the PCT, Na^+ reabsorption depends mainly on chloride (Cl^-) reabsorption via NHE_3 and Cl^- base antiporters apically as well as Na^+- K^+- ATPase and K^+-Cl- cotransporter (KCC) in the basolateral membrane. Consequently, an osmotic gradient generated by the reabsorption of sodium chloride enhances free water reabsorption via osmosis in the PCT, which is highly permeable to water, given its high expression of aquaporin water channels (AQP1).[18]

In the LOH, approximately 25% of filtered NaCl and 15% of water are reabsorbed. Na^+ is reabsorbed through Na^+- K^+- 2Cl- symporters (NKCC) and NHE_3 in the ascending limb, while water is reabsorbed passively via aquaporin channels in the descending limb of the LOH. As the descending limb is permeable to water but impermeable to solutes, the concentration of NaCl in the tubular fluid increases as it progresses to the ascending limb, which is permeable to solutes but impermeable to water, resulting in the formation of a counter current multiplication system that enables energy-efficient reabsorption of water.[18,19]

Finally, the DCT and CD reabsorb <10% of filtered NaCl and a variable amount of water (8-17%). Na^+ reabsorption in the early DCT occurs primarily via the thiazide-sensitive NaCl cotransporter (NCC) in the apical membrane. In the late DCT and CD, principal cells are responsible for Na^+ and water reabsorption via apical epithelial Na^+- selective channels (ENaCs), as well as basolateral Na^+- K^+- ATPase and aquaporin channels.[20]

Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) is activated by various mechanisms, namely sympathetic nervous system stimulation, within the juxtaglomerular apparatus by the macula densa in response to decreased luminal NaCl concentration and by the granular cells in response to low EABV and reduced renal perfusion pressure. When RAAS is activated, renin is secreted by granular cells, which catalyses the conversion of angiotensin I to angiotensin II21. Angiotensin II stimulates the release of aldosterone from the adrenal cortex, which increases ENaC activity in the distal nephron in addition to minor actions on NCC and Na^+-K^+-ATPase that serves to increase Na+ reabsorption.[22] Ang II is also a potent vasoconstrictor, constricting the efferent arteriole more than the afferent renal arteriole, leading to increased filtration fraction and favourable Starling's forces, which encourage Na+ reabsorption in the PCT.[23]

Neurohormonal pathways

Catecholamines such as norepinephrine from sympathetic nerves and epinephrine from the adrenal medulla enhance Na^+ and water reabsorption throughout all nephron segments (Figure 3). In states of ECF volume contraction, the reduction in EABV is sensed by the volume receptors in the left atrium, aortic arch, carotid sinus, and the large thoracic veins, and sympathetic activity rises. This leads to the activation of RAAS and the non-osmotic release of ADH, which promotes salt and water retention by the kidneys. On the other hand, dopamine directly opposes Na^+ and fluid reabsorption in the PCT in states of increased ECF volume 7.

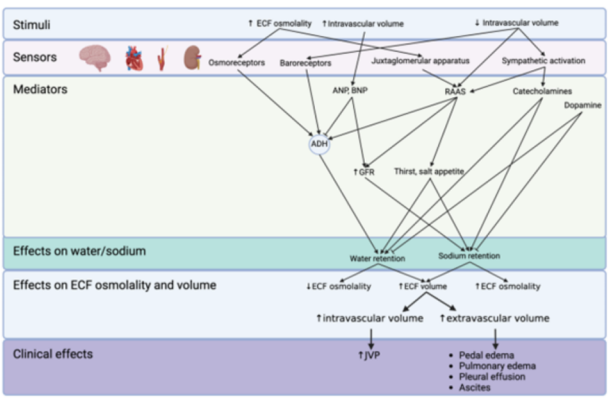

Figure 3: *Regulation of water and sodium balance (created with biorender.com)*

Effect of salt intake

Salt load, as seen in high Na^+ diets, increases ECF volume, which in turn increases EABV and renal perfusion pressure, inhibits the RAAS, and increases the release of ANP in response to an increase in a rise in atrial filling pressure. These responses lead to decreased DCT Na^+ reabsorption and promote urinary Na^+ excretion. On the other hand, a low salt diet and volume depletion, such as in vomiting and diarrhoea, leads to reduced EABV, increased RAAS activity, and decreased secretion of BNP, leading to increased Na^+ reabsorption in DCT[6].

Pathophysiology of sodium imbalance

Changes in Na+ are usually categorised as changes in volume or osmolality, and they can overlap (Table 1). Changes in volume, such as volume deficit or volume overload, are changes in the ECF volume, with no change to the salt-to-water ratio. Changes in osmolality imply a change in Na^+ or water content, leading to changes in the salt-to-water ratio.[21]

Abnormal serum Na^+ concentrations, namely hyponatraemia and hypernatraemia, are commonly a consequence of the patient's volume status.[24] Hyponatremia arises due to increased free water retention from the action of antidiuretic hormone or loss of Na^+ over water.[2,25] Common disorders resulting in hyponatremia include renal and extrarenal losses of sodium and water (hypovolemic hyponatremia), hypothyroidism, adrenal insufficiency, syndrome of inappropriate antidiuretic hormone secretion (SIADH) (euvolemic hyponatremia) as well as heart, liver and renal failure (hypervolemic hyponatremia).

In hypovolemic hyponatremia, patients are clinically dehydrated and often have a high blood urea nitrogen (BUN) to creatinine ratio. Loss of Na^+ and water from the intravascular space activates the release of ADH, which triggers thirst and renal retention of free water, thereby diluting ECF and causing hyponatremia. Urine Na^+ level helps distinguish between renal or extrarenal sources of Na^+ loss. High urine Na+ above 30 mmol/L signifies renal losses due to diuretics or mineralocorticoid deficiency. In contrast, low urinary Na^+ in dehydrated patients indicates extrarenal loss of salt and water, such as diarrhoea and vomiting. Regardless of the source of Na^+ losses, general principles for treating hypovolemic hyponatremia include fluid and salt replacement and targeted therapy to minimise further losses.[26,27]

If patients are clinically euvolemic, hypothyroidism and adrenal insufficiency must first be ruled out with a thyroid function test as well as serum cortisol level. Cortisol inhibits ADH secretion, so in hypercortisolism, ADH production and free water retention increase when this inhibitory effect is lost. Hypothyroidism has also been associated with increased ADH release as a result of decreased cardiac output and renal plasma flow.[25] After ruling out hypothyroidism and adrenal insufficiency, SIADH must then be considered. This is especially true in patients with disorders of the central nervous system, lung lesions, malignancy, or recent initiation of medications such as selective serotonin

receptor inhibitors or carbamazepine, which can result in inappropriately high ADH due to increased central secretion from the pituitary gland, ectopic ADH production such as in small cell lung cancers, or enhanced effects of ADH on the renal tubules.[28] The Schwartz and Bartter clinical criterion provides a guide for diagnosing SIADH, with serum and urine osmolality and Na^+ levels being important diagnostic tests.[29] Unlike hypovolemic hyponatremia, fluid restriction will be key to addressing SIADH.

In oedematous conditions such as congestive heart failure, hepatic cirrhosis, and nephrotic syndrome, salt and water are retained despite increased ECF volume. Reduced EABV due to reduced cardiac output or decreased peripheral arterial resistance is the key underlying pathology, activating the RAAS and sympathetic nervous system, stimulating the non-osmotic release of ADH, and causing hypervolemic hyponatremia from fluid retention.[30] Fluid restriction, diuretics, and therapy to address the underlying organ failure are the necessary management options.

Similarly, understanding the patient's fluid status is the first step for assessing hypernatremic states. Hypernatraemia is less common than hyponatraemia and is often seen in patients with impaired thirst mechanisms such as in altered mental status or elderly patients with advanced dementia.[31] Hypovolemic hypernatraemia occurs when there are free water losses over salt losses, such as in renal disorders and diuretic use, as well as gastrointestinal losses from vomiting and diarrhoea. Urine Na^+ levels can again be used to determine the source of water and Na^+ losses.[24] Free water replacement, for

Table 1: *Pathophysiology, etiology, and management principles of dysnatremias*

Causes	Pathophysiology	Primary management
Hyponatraemia		
Hypovolemic hyponatraemia		
▪ Renal losses (e.g. diuretics, salt wasting nephropathy) ▪ Extra-renal losses (e.g. vomiting, diarrhoea, burns, sweating)	Increase ADH release from pituitary due to hypovolemia	Fluid and salt replacement; minimize losses
Euvolemic hyponatraemia		
Hypocortisolism	Increase ADH release from pituitary	Treat hypocortisolism
Hypothyroidism	Increase ADH release from pituitary	Treat hypothyroidism
SIADH	▪ Increase ADH release from pituitary ▪ Ectopic ADH production ▪ Enhanced effects of ADH	Fluid restriction
Hypervolemic hyponatraemia		
▪ Congestive heart failure ▪ Cirrhosis ▪ Nephrotic syndrome ▪ Acute/chronic renal failure	Increased ADH release from pituitary from reduced effective circulating volume	Fluid restriction; diuretics; treat underlying causes
Hypernatraemia		
Hypovolemic hypernatraemia		
▪ Renal losses (e.g. diuretics) ▪ Extra-renal losses (e.g. vomiting, diarrhoea, burns, sweating)	Excess water loss > salt loss	Free water replacement
Euvolemic hypernatraemia		
Central/nephrogenic diabetes insipidus	Reduced or loss of effects of ADH	Desmopressin replacement in central diabetes insipidus; stop causative agents in nephrogenic diabetes insipidus
Hypervolemic hypernatraemia		
▪ Iatrogenic causes (e.g. hypertonic saline) ▪ Sea water ingestion ▪ Hyperaldosteronism ▪ Cushing's syndrome	▪ Excess sodium ingestion/infusion ▪ Excess sodium and water retention due to raised mineralocorticoid or glucocorticoid	▪ Stop causative agents; treat hyperaldosteronism or Cushing's syndrome

SIADH: Syndrome of inappropriate antidiuretic hormone secretion; ADH: antidiuretic hormone

instance, with intravenous 5% dextrose, coupled with therapy to address underlying losses, is needed to restore water and Na^+ balance.

One of the most common causes of euvolemic hypernatraemia is reduced ADH or insensitivity to ADH in diabetes insipidus, which may be central in origin, arising from central nervous system lesions, or nephrogenic in origin, such as arising from the use of nephrotoxic agents such as lithium. Diabetes insipidus can be diagnosed with a water test, which will result in continued low urine osmolality and Na^+ levels in diabetes insipidus due to the loss of ADH effects. The reversal of low urine osmolality and Na^+ levels with the administration of desmopressin can help distinguish central diabetes insipidus from nephrogenic causes.[31]

Hypervolemic hypernatraemia can result from iatrogenic hypertonic saline or Na^+ infusions, hypertonic haemodialysis, seawater ingestion in drowning patients, or as complications of hyperaldosteronism and Cushing's syndrome due to excess salt and water retention by the action of mineralocorticoids and glucocorticoids. Iatrogenic causes of hypernatraemia should be addressed by stopping the causative agent, while hyperaldosteronism or Cushing's syndrome needs specific treatment to restore Na^+ and water balance.[31]

Conclusion

Various body systems maintain normal Na^+ homeostasis, and Na^+ disorders are often inseparable from disturbances of one of these bodily functions. Understanding the roles of the kidney, the central nervous system, and the endocrine axes aids in understanding Na^+ disorders. When encountering Na^+ disorders of unknown aetiologies, volume status provides crucial clues to the investigating clinicians, along with a sound understanding of the role of ADH in Na^+ homeostasis.

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Authors' Contribution

HT, MMJ: Conceptualization of the project

SSYW, XRL: Design of the work.

WCEN, YXL, YTRH,: Data acquisition, analysis, or interpretation.

HT, WCEN, YXL, YT, RH: Draft the work.

SSYW, MMJ: Critical review of important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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