The Secret Stories of Sodium How Infants, Athletes, Psychotics, And Otherwise Healthy People Die from Sodium Imbalance

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LEARNING OBJECTIVES

1. Define the normal blood sodium concentration and the definitions of hypo- and hypernatremia.
2. Summarize how extracellular sodium and intracellular potassium drive tonicity balance
3. Describe the roles of hormones in sodium balance.
4. Explain how plasma osmolality and plasma volume are monitored within the body.

ABBREVIATIONS: [Na^+] – sodium concentration, ADH - anti-diuretic hormone, AVP – arginine vasopressin, CVO - circumventricular organs, ECF – extracellular fluid, ICF – intracellular fluid, IV – intravenous, K^+ - potassium, RAAS - renin-angiotensin-aldosterone system

INDEX TERMS: Fluid homeostasis, sodium balance, hyponatremia, hypernatremia

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INTRODUCTION

Every number tells a story. As such, clinical laboratory science empowers modern medicine with a vast yet growing repertoire of analytes, which subsequently guide the diagnosis, treatment and prognosis of most – if not all - medical conditions. The body's integrated response to dynamic perturbations in homeostasis creates an elusive trail of biochemical footprints, each providing clues to where pathophysiology began and how far the body has strayed off course (i.e. severity of the insult and appropriateness of the response). The ubiquitous cation, sodium, is one of the main markers of whole body homeostasis. The sodium concentration ([Na^+]) within the extracellular fluid space is essential for maintaining cellular size and adequate tissue perfusion. As such, the inherent regulation of water and sodium balance is strict, precise, and fiercely protected by the body. Therefore, when blood sodium levels venture outside of the heavily guarded trails of normonatremia (normal blood [Na^+]), into hyponatremia (low blood [Na^+]) or hypernatremia (high blood [Na^+]), each deviation foretells tales of health and disease - and in rare cases, of abuse and neglect.

Water and sodium within the exterior milieu is essential to life. However, within the interior milieu, it is the *balance* between the two that is critical for individual human survival. We refer to this balance, between water and sodium within the internal milieu, as "fluid homeostasis." The physiological mechanisms that govern fluid intake (thirst) and output (urine), as well as sodium intake (sodium palatability) and output (urine) have been well-described.[1-3] Of historical note, the ancestral gene encoding for the hormone serving to conserve total body water - clinically described as anti-diuretic hormone (ADH) and biochemically referred to as arginine vasopressin (AVP) - has been verified in vertebrate and some invertebrate species which date back over 700 million years.[4] Even the nematode, *Caenorhabditis elegans*, expresses a vasopressin-like neuropeptide (nematocin), which modulates salt chemotaxis as a learned response.[5] Such archaic

examples highlight strong evolutionary pressures towards the development and maintenance of species-specific mechanisms designed to defend fluid homeostasis that are deeply rooted within our DNA. Thus, in most cases, the small percentage of people who actually die from derangements in blood [Na^+] do so largely because of human error or impending failure of the system to cope with any additional internal or external stressors.

In humans, the normal blood sodium concentration ([Na^+]) ranges between 135 mmol/L and 145 mmol/L (sodium ions per liter of water within the vascular space). The actual numerical threshold that defines normonatremia may vary slightly according to the laboratory performing the test. But irrespective of the actual numerical cut-off, a blood [Na^+] below the normal biochemical range (typically <135 mmol/L) defines a diagnosis of hyponatremia (low blood sodium) while a blood [Na^+] above the normal biochemical range (>145 mmol/L) defines a diagnosis of hypernatremia.

The physiological significance of abnormally low or high blood [Na^+] relates to tonicity balance, which drives water in and out of cells via changes in osmotic pressure and determines cellular size. Sodium ions are primarily sequestered within the extracellular fluid (ECF) space while potassium (K^+) ions are located largely within the intracellular fluid (ICF) space. Neither sodium nor potassium ions can passively cross the cell membrane barrier, but each functions as an effective osmole, which attracts water molecules across semi-permeable cellular membranes. Through this process of osmosis, hyponatremia (low sodium content in the ECF) causes water to flow into the cells while hypernatremia (high sodium content in the ECF) causes water to flow out of the cells (Figure 1).

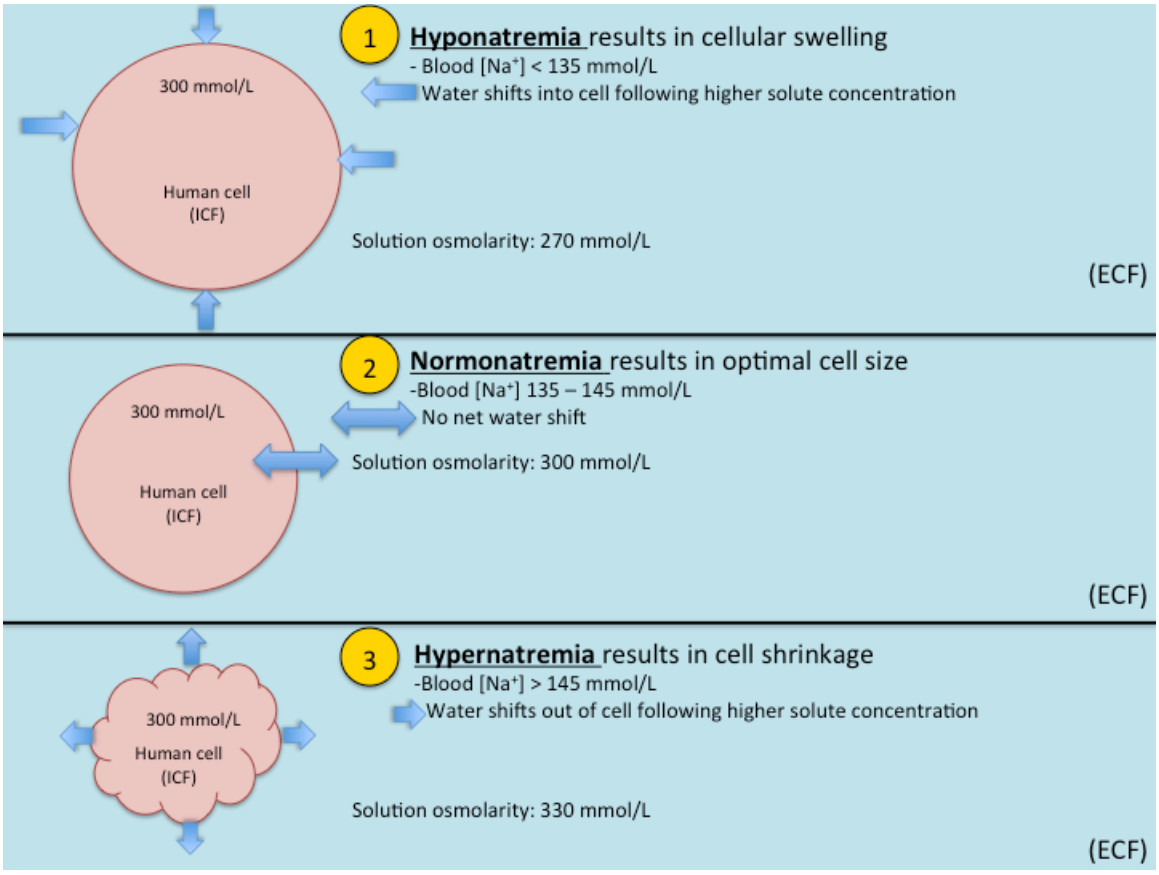

Figure 1. Schematic diagram of tonicity, water shift, and cellular volume. Arrows denote direction of water shift following higher solute concentrations. Extracellular fluid (ECF) and intracellular fluid (ICF) are abbreviated in the diagram. When calculating and converting measurements of [Na^+], mEq/L and mmol/L are interchangeable units. For consistency, all measurements will be reported in mmol/L.

Therefore the clinical significance of hyponatremia is cellular (and tissue) swelling, while the clinical consequence of hypernatremia is cellular crenation and tissue shrinkage. If the brain swells or shrinks excessively within the rigid confines of the skull, death likely occurs. For example, the brain can only swell an excess 8% of its volume before brain stem herniation begins to occur.[6,7]

Normonatremia (or more correctly, plasma osmolality) is continuously monitored within the brain via osmoreceptors that are located within highly vascularized brain structures called circumventricular organs (CVO).[3,8] The CVO's are both sensory and secretory and lack a blood brain barrier; thereby permitting the central nervous system to communicate directly with tonicity changes within peripheral blood.[3,8] When blood [Na^+] (or plasma tonicity) is too high, the CVO's respond by stimulating the secretion of anti-diuretic hormone (ADH/AVP) from the posterior pituitary gland into the circulation. The anti-diuretic hormone, AVP, prevents urinary water loss by facilitating water absorption at the kidney; thereby promoting fluid retention. If plasma tonicity continues to rise despite body water being maximally retained by ADH/AVP release, then the sensation of thirst is activated. Physiologically driven thirst stimulation motivates fluid intake behaviors designed to bring much needed water back into the system. Thus, the combination of water retention and fluid intake effectively serves to dilute elevated blood [Na^+] back into the normal physiological range (normonatremia). Conversely, if blood [Na^+] or plasma tonicity become too low, both ADH/AVP and thirst are suppressed so that water can exit the body. This urinary free water excretion, coupled with the absence of fluid intake, will essentially "concentrate" blood sodium levels back up into the normal physiological range by pouring off extra fluid.

Of lesser importance to tonicity (at least in this particular Focus section on natremia), is the regulation of circulating plasma water (plasma volume) by the amount of sodium circulating within the vascular space. Under-replaced sodium can decrease the amount of circulating plasma water, leaving tissues under-perfused and leading to cardiovascular instability. Decreases in plasma volume are detected by specialized volume/pressure receptors, called baroreceptors, which are located within the carotid bodies of the aortic arch. Baroreceptor activation, via an 8-10% decrease in blood pressure or plasma volume,[1] will stimulate sodium conservation by activating the renin-angiotensin-aldosterone system (RAAS). The RAAS system facilitates reabsorption of sodium at the kidney (i.e. not excreted in urine) and increases the palatability of sodium-rich foods.[1,9] Sodium conservation and subsequent ingestion of salt alone or in combination serves to increase circulating plasma volume back to baseline levels over time (19-24 hours),[10,11] while maintaining plasma tonicity through integrated coordination with the osmoregulatory system.[10]

Hyponatremia: water intoxication vs. sodium loss

When the sodium content (in millimoles) in relationship to a liter of plasma water is below 135 mmol/L (for most laboratories), a diagnosis of hyponatremia is biochemically confirmed, regardless of the presence or absence of clinical signs and symptoms. Hyponatremia can be caused by too much water in relationship to salt (water intoxication or overhydration), inappropriate fluid retention, or under-replaced sodium losses (impairing circulating plasma volume). Although the brain can adapt to chronic hyponatremia, by extruding organic osmolytes which normalize ECF tonicity and limits cerebral edema,[12] acute hyponatremia can be fatal if the magnitude or rate of blood [Na^+] decline is pronounced. Babies fed dilute formula,[13] children forced to drink excessive amounts of fluid as punishment,[14] athletes who drink excessively during exercise,[15] compulsive water drinkers (psychogenic polydipsia),[16] and hospitalized patients administered excessive amounts of dilute (hypotonic) intravenous (IV) fluids[17] are amongst otherwise healthy individuals who become severely ill or die from fluid overload hyponatremia. Of note, in most of these reported cases, fluids were either ingested or administered above the physiological dictates of thirst.

Hypernatremia: dehydration vs. salt poisoning

When the sodium content (in millimoles) in relationship to a liter of plasma water is above 145

mmol/L (for most laboratories), a diagnosis of hypernatremia is biochemically confirmed, regardless of the presence or absence of clinical signs and symptoms. Hypernatremia can be caused by too little water in relationship to salt (dehydration) or overzealous salt consumption. Dire complications associated with hypernatremia include subarachnoid bleeding and hemorrhage due to tissue shrinkage and/or ischemia due to dehydration.[18,19] Babies with difficulties breastfeeding[20] or accidental salt poisoning,[21] athletes who do not drink enough water during exercise[22] or report vomiting during long races,[23] depressed individuals who intentionally ingest large amounts of salt,[24] and nursing home or hospitalized patients who are not given adequate amounts of fluids[25] have all become severely ill or died tragically from hypernatremia. Of note, most of these reported cases were complicated by: significant gastrointestinal losses; the absence of available hypotonic fluids; human error (mistaking salt for sugar), or psychiatric disorders (i.e. dementia); all of which interfered with the ability to find (or ask) for water or to sense thirst.

In summary, behind every sodium value lays a unique, personal and sometimes tragic story. The following summary papers on hyponatremia and hypernatremia serve to highlight the evolutionary and physiological strength of the inherent mechanisms that protect normonatremia in humans. The rare and unusual deaths in otherwise healthy individuals from dysnatremia are characteristically those who: 1) willfully drink above the dictates of thirst (athletes); 2) unable to respond with appropriate drinking behaviors to normal internal cues (psychotics, unconscious patients); or 3) are responding to intensified signals from competing homeostats (hunger in infants, plasma volume losses in hospitalized patients). As such, every rare and untimely death from fluid dysregulation teaches us valuable lessons about the strength and limitations of the physiological mechanisms that govern fluid homeostasis. And although laboratory measurement of blood sodium levels appears routine, each numerical deviation beyond the normal range whispers secret stories and predictions that are relevant to both life and death.

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