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Hyponatremia and the Brain

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Hyponatremia is defined by low serum sodium concentration and is the most common electrolyte disorder encountered in clinical practice. Serum sodium is the main determinant of plasma osmolality, which, in turn, affects cell volume. In the presence of low extracellular osmolality, cells will swell if the adaptation mechanisms involved in the cell volume maintenance are inadequate. The most dramatic effects of hyponatremia on the brain are seen when serum sodium concentration decreases in a short period, allowing little or no adaptation. The brain is constrained inside a nonextensible envelope; thus, brain swelling carries a significant morbidity because of the compression of brain parenchyma over the rigid skull. Serum sodium concentration is an important determinant of several biological pathways in the nervous system, and recent studies have suggested that hyponatremia carries a significant risk of neurological impairment even in the absence of brain edema. The brain can also be affected by the treatment of hyponatremia, which, if not undertaken cautiously, could lead to osmotic demyelination syndrome, a rare demyelinating brain disorder that occurs after rapid correction of severe hyponatremia. This review summarizes the pathophysiology of brain complications of hyponatremia and its treatment.

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Plasma osmolality refers to the quantity of solute dissolved into 1 kg of plasma.[1,2] The serum is separated from the inside of the cell by the cell membrane. The cell membrane is highly permeable to water but not to some ions (e.g., potassium and sodium), and is called semipermeable. The ability of water to move across the cell membrane is related to the tonicity of the plasma that determines the direction and the magnitude of water movement.[3]

The serum sodium (SNa) concentration is the main extracellular osmolyte, and therefore, the most important determinant of serum osmolality.[4] The permeability of the cell membrane to water is due to the presence of water channels called aquaporins (AQPs) that mediate bidirectional water transport.[5] In the central nervous system (CNS), the blood−brain barrier (BBB) separates the brain parenchyma from the plasmatic space. The BBB is composed of several layers; the outermost layer is astrocyte end-feet, which is responsible for water exchange between the brain parenchyma and the vascular space.[6] Astrocyte end-feet express a high number of AQP 4, but other forms of AQP have been identified in astrocytes and other CNS cell types.[5]

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At equilibrium, extracellular osmolality equals intracellular osmolality, and the net movement of water across the cell membrane is null. When the SNa concentration is reduced, hypo-osmolality and hypotonicity will ensue, and the water will flow from the extracellular space into the intracellular compartment. This movement of water into the cell will cause cell swelling, and conversely, in the presence of hypertonicity, cells will shrink because of water movement from inside to outside the cell. In the mammalian CNS, even minimal changes in the intracellular volume and the associated brain swelling or shrinking might lead to dramatic symptoms. Macromolecular crowding refers to the behavior of protein inside the cell with respect to the salt and water content of the cytoplasm.[7] It has been shown that many cellular functions (e.g., enzymatic activity) depend of the ionic strength of the cytoplasm, the cell volume, and the macromolecular crowding.[8] Therefore, the maintenance of a normal cell volume and normal intracellular ionic strength is essential. The ability to respond to brisk changes in extracellular osmolality has been evolutionarily conserved across species throughout the evolution process.

The present review details the mechanisms of brain adaptation to hyponatremia, the consequences of hyponatremia on the brain, and discusses the treatment of hyponatremia and the risk associated with excessive correction of SNa from a neurological perspective.

MECHANISMS OF BRAIN CELLS ADAPTATION TO HYPO-OSMOTIC CHALLENGE

Cells have developed several mechanisms to counteract the deleterious effect of extracellular hypotonicity on cell volume. These mechanisms are collectively called regulatory volume decrease (RVD) because their aim is to restore the initial volume after swelling induced by hypotonicity.[9] They essentially involve the extrusion of intracellular osmotically active solutes that will induce obligated intracellular loss of water and prevent or reduce cell swelling. RVD has been well studied in isolated brain cells, mostly in astrocytes and neurons.[10–13] Neuronal cell lines exposed to hypotonicity quickly experience an increase in their volume up to 2-fold in the first minutes, and after a slow decrease in the volume, this reaches a plateau at approximately 60% to 80% of volume recovery in the first 15 minutes.[11] The same is true for glial cell lines.[10] However, these observations should be interpreted along with some caveats. First, not all neuronal cells react alike during hypo-osmolality; some differences have been noted across different neuronal cells.[14] Second, most studies done on RVD in brain cells used either cultured or immortalized cell lines that displayed notable differences with *in vivo* cells. Lastly, regional variability and interspecies variability in glial phenotype have been described, which might have an impact on some biological functions.[15–17] Therefore, it is possible that not only do *in vivo* astrocytes not exhibit the exact same behavior as *in vitro* astrocytes when confronted with hypotonic stress, but also that not all astrocytes in the brain exhibit the same pattern of changes during hyponatremia.

Cellular Mechanisms of RVD, Osmotic Sensing, Signal Transduction, and Efflux Pathways

An osmolyte is a noncell membrane permeable substance that can exert a net movement of water across a semipermeable membrane. Osmolytes are categorized as electrolytes and nonelectrolyte or organic osmolytes. The most common electrolyte osmolytes present in the mammalian brain are sodium, potassium, and chloride ions, and the most common organic osmolytes are myoinositol, betaine, glutamine, taurine, and γ-aminobutyric acid.

The occurrence of RVD implies a sensor for extracellular osmolality, a signal transducer that will translate the information on extracellular osmolality to the channels responsible for intracellular osmolyte depletion. The word osmosensor refers to a sensory element that can detect changes in plasma osmolality.[18] In the mammalian brain, the true nature of the osmosensor is still elusive. The transient receptor potential vanilloid 4 (TRPV4) channel is a member of the broader class of the TRPV channel family that has been shown to be essential for tonicity sensing and transduction trough modulation of calcium influx in several cell lines.[19] In cortical astrocytes and muller glia (retinal glial cells), TRPV4 forms a molecular complex with AQP 4, the main water channel present in astrocyte end-feet. The integrity of that molecular complex is necessary for calcium influx, which has been linked to RVD with an hypo-osmotic challenge.[20,21] Other researchers have suggested that calcium influx is not essential for RVD, and also that inhibition of the TRPV channel does not significantly affect RVD in astrocytes.[22] Because of the complexity and the importance of the process, it is likely that osmosensing operates through at least a few redundant pathways that might not be identical for all brain cells.

Upon sensing, the hypo-osmotic signal must be transduced inside the cell, and protein kinases and calcium are believed to be involved in the transduction of the signal of RVD in astrocytes and neurons. For example, inhibition of protein kinase C can significantly reduce the efflux of potassium and taurine in hypo-osmotically challenged glial cells, which suggests that G-coupled protein receptor with protein kinase C activity is a likely transducer for hypo-osmotic stimuli.[23] After signal transduction, the osmolyte must flow inside or outside the cell trough special channels. The responsible channels for intracellular electrolytes depletion are collectively called volume sensitive channels (for review, see Strange *et al.*[24]). They have been identified in nearly all CNS cells.[25–27] Although these channels can be blocked pharmacologically, their precise identities remain elusive. As for organic osmolytes, several organic osmolyte transporters have been identified in the mammalian brain. For example, these include the γ-aminobutyric acid−betaine transporter and the sodium myoinositol transporter.[28] The channels are bidirectional, and the movement of organic osmolytes through them is dependent on the net concentration gradient. Some interconnections between the volume sensitive channel and the organic osmolyte channels have been described.[29]

Brain Adaptation to Hyponatremia

After onset of systemic hypotonicity from hyponatremia, the brain water content will increase to commensurate the extent of the hyponatremia if the brain behaves like a perfect osmometer. However, studies have shown that after either chronic or acute hyponatremia, the brain water content does not increase as predicted. For instance, after 6 hours of hyponatremia, the brain only increases by 40% of what is predicted, and after 4 days of hyponatremia,