

Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia

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Ayus JC, Achinger SG, Arieff A. Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. *Am J Physiol Renal Physiol* 295: F619–F624, 2008. First published May 7, 2008; doi:10.1152/ajprenal.00502.2007.—Hyponatremia is the most common electrolyte abnormality in hospitalized patients. When symptomatic (hyponatremic encephalopathy), the overall morbidity is 34%. Individuals most susceptible to death or permanent brain damage are prepubescent children and menstruant women. Failure of the brain to adapt to the hyponatremia leads to brain damage. Major factors that can impair brain adaptation include hypoxia and peptide hormones. In children, physical factors—discrepancy between skull size and brain size—are important in the genesis of brain damage. In adults, certain hormones—estrogen and vasopressin (usually elevated in cases of hyponatremia)—have been shown to impair brain adaptation, decreasing both cerebral blood flow and oxygen utilization. Initially, hyponatremia leads to an influx of water into the brain, primarily through glial cells and largely via the water channel aquaporin (AQP)4. Water is thus shunted into astrocytes, which swell, largely preserving neuronal cell volume. The initial brain response to swelling is adaptation, utilizing the Na⁺-K⁺-ATPase system to extrude cellular Na⁺. In menstruant women, estrogen + vasopressin inhibits the Na⁺-K⁺-ATPase system and decreases cerebral oxygen utilization, impairing brain adaptation. Cerebral edema compresses the respiratory centers and also forces blood out of the brain, both lowering arterial PO₂ and decreasing oxygen utilization. The hypoxemia further impairs brain adaptation. Hyponatremic encephalopathy leads to brain damage when brain adaptation is impaired and is a consequence of both cerebral hypoxia and peptide hormones.

cerebral edema; aquaporin; astrocytes

HYPONATREMIC ENCEPHALOPATHY is defined as central nervous system dysfunction secondary to hyponatremia. In a review of the literature from 1975 to 2006, among all patients with hyponatremic encephalopathy where the outcome was known ($n = 344$) the overall morbidity and mortality is 42%, clearly establishing the disorder as a life-threatening medical emergency (29). Failure to recognize and promptly treat this disorder frequently leads to death or permanent brain damage (8, 11, 15, 22, 25). A key factor leading to an adverse outcome in patients with hyponatremic encephalopathy is a failure of the brain to regulate its volume in an integrative manner. Unrestrained brain swelling will often lead to death or permanent brain damage.

A number of important risk factors for hyponatremic brain damage have been described in the past decade, including sex (menstruant women), age (prepubescent children), physical factors (discrepancy between skull size and brain size), the actions of multiple hormones (particularly vasopressin and estrogen), and the presence of hypoxia (Fig. 1). The outcome for patients with hyponatremic encephalopathy depends upon the ability of the brain to regulate its volume to prevent

swelling and thus adapt to the hyponatremia. All of the aforementioned risk factors tend to impair the ability of the brain to adapt to hyponatremia.

Blood-Brain Barrier: Structure and Function

Brain adaptation to osmotic stress involves interaction between the blood-brain barrier (BBB) and the various pathways that the brain employs to alter its intracellular solute concentration. It is first necessary to examine the structure and function of the BBB (28, 52, 84, 93).

The brain is separated from the systemic circulation by the BBB, which impedes the entry of various substances that are not lipid soluble. Although water movement across the BBB is largely by osmotic gradients, the brain has multiple mechanisms for handling water fluxes (4, 6, 64). The BBB is a complex entity that starts with tight junctions between vascular endothelial cells that interface with glial cells (astrocytes) (6, 81). Astrocytes, and the astrocyte foot processes that abut the endothelial cells of the brain capillaries, form the bulk of the BBB (1, 80) (Fig. 2). This structure performs many functions that maintain the fluid and electrolyte concentration of the brain extracellular space (72, 80). Among these functions is shunting of potassium from the cerebrospinal fluid (CSF) through mechanisms that take up and release potassium in the perivascular space around neurons (49, 92). Much of this

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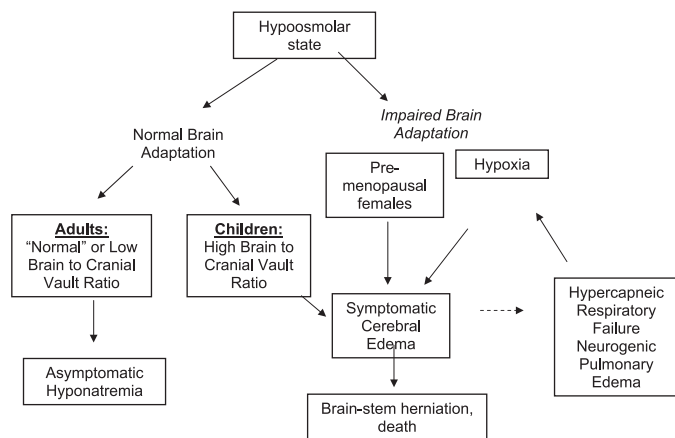


Fig. 1. Diagrammatic depiction of the factors that may contribute to brain adaptation and its failure in patients with hyponatremia. Factors on *left* depict normal adaptation, while those on *right* show progressive factors that can lead to impaired brain adaptation, cerebral edema, and death or permanent brain damage.

function is accomplished through a concentration of aquaporin (AQP) water channels, particularly AQP4 and, to a lesser extent, AQP1 water channels (55, 69, 82). There are also potassium channels located at the endfeet around the perivascular space (27, 92). The glial cells also have an important role in brain water handling. Glial cells selectively swell after hypotonic stress and neurons do not, suggesting the existence of glia-specific water pores, which appear to consist of both AQP4 and AQP1 (55, 69, 82). Recent evidence has suggested that the presence of AQP4 in the brain is important in the development of cerebral edema in response to hyponatremia, suggesting that these channels may have an important role not only in normal water regulation in the brain but also in the pathogenesis of hyponatremia-induced cerebral edema (69). In effect, during states of cytotoxic brain edema, water is shunted through the astrocytes, which swell, thus protecting the neurons from this influx of water (Fig. 3). Therefore, the astrocytes are the principal regulator of the brain water content because they comprise the bulk of the intracellular space (67) and they specifically swell, with sparing of neurons, after hyposmolar episodes (56, 80). Therefore the response of these cells follow-

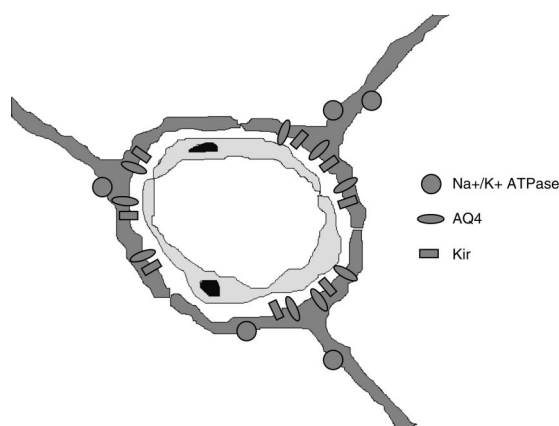


Fig. 2. Blood-brain barrier and cerebral capillary. Highlighted is the interaction of glial cell endfeet with the vascular endothelial cell and the positioning of aquaporin 4 (AQP4) water channels, Na⁺-K⁺-ATPase, and Kir₄ potassium channels.

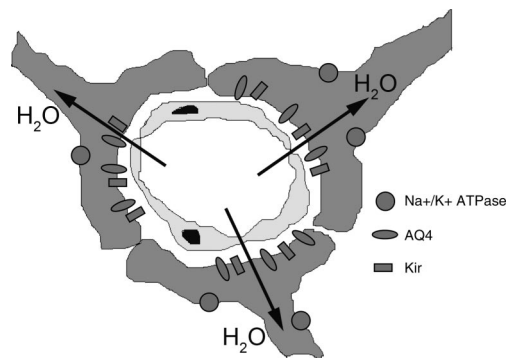


Fig. 3. Cytotoxic cerebral edema. Shown is the movement of water through aquaporin 4 channels into the glial cell. Glial cells selectively swell during cytotoxic edema, and neurons (not shown) are relatively spared.

ing osmolar stress is an important determinant of the changes in brain volume during hyponatremic insults (42).

Brain Adaptation Against Cerebral Edema

Glial cells do not act as perfect osmometers. Therefore, when the brain is exposed to a hypotonic environment there is initial swelling. The glial cell then rapidly expels solutes and water in order to restore cell volume. This response is an energy-dependent phenomenon and requires the Na⁺-K⁺-ATPase system (Fig. 3). The enzyme Na⁺-K⁺-ATPase is ubiquitous and plays an essential role in cellular ion homeostasis. In the brain this enzyme is very important in the response of the cell to volume stress in response to hypotonic insult (87).

Most brain cell volume regulation occurs at the expense of the astrocytes, thereby preserving the nerve cell volume. There are general adaptive mechanisms that are utilized by cells to adapt to an increase in cell volume. However, the astrocyte responds to cellular swelling differently from many other cells as to the basic mechanisms of the response (67). The glial cell utilizes ATP-dependent mechanisms (90) at this level of decreased osmolality, and this requires the Na⁺-K⁺-ATPase system, which is of primary importance for the extrusion of ions from the glial cell. Water obligatorily follows the extruded ions, reducing brain volume and protecting it from cerebral edema. This response can rapidly restore cell volume both *in vitro* (67, 75) and *in vivo* (12, 63, 87).

Brain cells may be reacting not only to changes in cell volume caused by swelling but also to changes in cellular concentration of cytosolic macromolecules (59). Cellular swelling activates potassium and anion channels, allowing passage of Cl⁻ and bicarbonate, but also amino acids. Cell swelling activates the Na⁺/Ca²⁺ exchanger along with Ca²⁺-ATPase, all of which lead to loss of cellular Na⁺. Activation of the Na⁺-K⁺-ATPase system leads to replacement of intracellular Na⁺ with K⁺. Cell swelling inhibits glycolysis and stimulates flux through the pentose phosphate pathway. This tends to enhance the availability of NADPH, which tends to protect the cell against oxidative stress (70).

In addition to inorganic osmolytes, organic osmolytes play an important role in brain cell volume regulation (71, 86). Animal studies have shown that osmolytes, including glycine, taurine, creatine, and myoinositol, have been shown to efflux from cells during hyposmolar states and accumulate during hyperosmolar states (18, 33, 60). Furthermore, human studies

using MRI have shown that in hyponatremia osmolyte efflux from the brain parallels changes in sodium concentration (89). In summary, during times of systemic hyposmolality water enters the brain through AQP4 channels located in the glial cell endfeet surrounding brain capillaries. Immediate shunting of CSF does occur, which will accommodate some of the brain swelling, but this is a limited mechanism (37, 55). The glial cell then acts to reduce its intracellular volume, and it immediately begins to do so by energy-dependent extrusion of solutes via the $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump (Fig. 3) (88).

Role of Sex and Age

Observations in hyponatremic subjects initially appear inconsistent at first but can be resolved by awareness of the many risk factors associated with age and sex. For instance, an elderly man may acutely develop a serum sodium below 110 mmol/l after transurethral resection of the prostate, and a mentally ill male patient may ingest large volumes of water and develop hyponatremia of a similar magnitude. However, encephalopathy does not necessarily develop in either (16, 39, 90). At the other end of the spectrum, young women after elective surgery have been shown to develop acute hyponatremic encephalopathy and fatal respiratory arrest due to brain stem herniation with serum sodium as high as 128 mmol/l (8, 25, 39). There appear to be various factors that lead to a higher incidence of brain damage associated with hyponatremic encephalopathy in menstruant women (11, 14).

Estrogens have a core steroidal structure similar to ouabain and cardiac glycosides (such as digoxin), which are inhibitors of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ system (30). Ouabain (and related compounds) inhibits the catalytic activity of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ enzyme, and estrogen likely acts in a similar mechanism to reduce the activity of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ system (30, 35, 77). Female sex hormones have been shown to inhibit the activity of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump (44, 76). The uptake of sodium by isolated synaptosomes from hyponatremic animals is increased in female rats compared with male rats, suggesting an impairment in sodium extrusion (40, 42). Female sex hormones can impair energy-dependent astrocyte cell volume regulation that actively extrudes ions from the intracellular space of the edematous astrocyte. Estrogens tend to impair brain adaptation to hyponatremia, while androgens may enhance it (5, 35, 41, 47, 53). In addition, estrogen appears to regulate water movement and neurotransmission by affecting AQP4 expression (81) and perhaps AQP1 expression as well (45).

Additionally, prepubescent children are another high-risk group for a poor outcome associated with hyponatremic encephalopathy (11, 13). Although many factors probably contribute to this association, the presence of a high size ratio of brain to cranial vault appears to be an important factor, because brain development is complete around age 6 but the skull does not attain full size until adulthood (34). Adaptation of the brain to hyponatremia can be impeded by these physical factors (38, 57). In addition, the pediatric brain has much less $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity than the adult brain (12, 48, 91). These factors lead to increased risk that has been observed in children, although it is notable that in young babies fontanelles are still open, increasing cranial vault compliance, and good outcomes have been reported among babies with hyponatremia (54).

Role of Vasopressin

Hyponatremia, except in cases of pure water intoxication, virtually always occurs in the presence of increased plasma levels of vasopressin. Vasopressin leads to decreased cerebral oxygen utilization in female rat brain but not in male rats (57). Vasopressin probably does not actually cross the BBB, but instead binds to astrocytes, which make up much of the BBB and are in close contact with small cerebral blood vessels (7, 84, 93). The net result is vasoconstriction in the female brain (57). This vasoconstriction leads to decreased cerebral oxygen utilization in the female brain (57). As seen below, the resulting cerebral hypoxia secondarily impairs brain adaptation even further (87).

Additionally, vasopressin facilitates direct movement of water into brain cells independent of the effects of hyponatremia (74). Vasopressin and estrogen appear to work in tandem. At a more cellular level, the movement of water into brain is controlled largely by the water channel protein AQP4, which is largely found in astrocyte foot processes (69).

Arginine vasopressin (AVP) and/or estrogen have several detrimental effects on the brain that impair brain adaptation. These include a direct effect on cerebral blood vessels to decrease cerebral perfusion (57), decreased synthesis of ATP and phosphocreatine, lower intracellular pH and cellular buffering (3, 40), and additionally decreased Ca^{2+} influx (53). Estrogen also appears to increase secretion of vasopressin, further impairing cerebral blood flow (26, 61). All of these processes impair outward transport (from brain cells to extracellular fluid) of Na^+ and K^+ (41, 66). Thus the brain's ability to adapt is impaired, leading to increasing edema (58). Interestingly, AQP4 also appears to regulate the effects of estrogen on water movement (81). In summary, vasopressin, estrogen, and AQP4 all exert influences on the degree of cerebral adaptation to hyposmolar stress, although in cases of hyponatremia where vasopressin levels are suppressed these vasoactive activities of vasopressin will likely not apply.

Role of Hypoxia

Clinical studies over the last two decades have pointed to hypoxia as an important risk factor for a poor outcome in patients with hyponatremic encephalopathy (Fig. 4). This was suggested in 1986 (8) and confirmed by several large epidemiologic studies that have demonstrated that in patients with hyponatremia hypoxia is a major risk factor for death or permanent brain damage (14, 15, 25). This was true even after adjustment for other comorbid conditions in patients with hyponatremic encephalopathy (25, 65), which included coronary artery disease, chronic renal failure, obstructive uropathy, and chronic obstructive pulmonary disease.

Hypoxemia develops among individuals with hyponatremic encephalopathy through either of two mechanisms: hypercapnic respiratory failure and neurogenic pulmonary edema (17). Hypercapnic respiratory failure most likely develops as a consequence of central respiratory depression and is often a first sign of impending brain herniation. The hypoxemia that develops because of the central respiratory depression is a maladaptive response and further worsens astrocyte cell volume regulatory mechanisms and worsens brain edema. Neurogenic pulmonary edema, on the other hand, is a well-described complication of cerebral edema from other situations that may

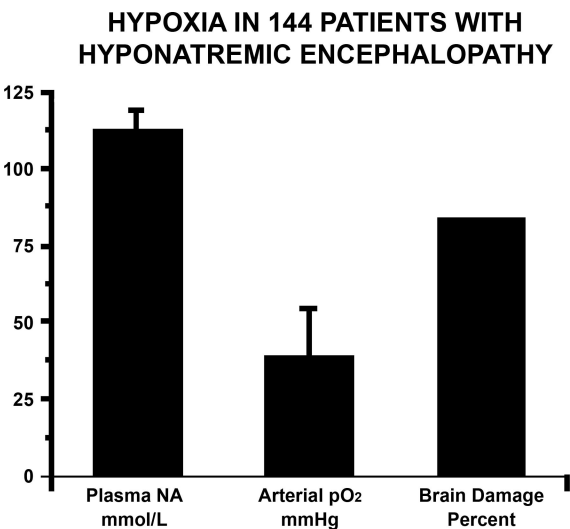


Fig. 4. Hypoxia in 144 patients with hyponatremic encephalopathy, showing associated brain damage. All patients had hypoxemia, with mean $PO_2 = 38$ mmHg when plasma Na was 112 mmol/l. Eighty-three percent of patients either died or suffered permanent brain damage. The data are extracted from Refs. 8, 10, 11, 13, 15, 17, 24, 25, 51, 64, and 82.

lead to increased intracranial pressure. It occurs in the setting of hyponatremic encephalopathy as well and can even be a presenting manifestation (17). Neurogenic pulmonary edema is a complex disorder during which there is increased vascular permeability and increased catecholamine release that often occurs secondary to elevated intracranial pressure (36, 62). However, the common denominator in patients with neurogenic pulmonary edema appears to be increased intracranial pressure. It is most likely that the pathogenesis of neurogenic pulmonary edema is multifactorial and includes the latter two mechanisms. Thus hyponatremic encephalopathy with cerebral edema is the most likely cause of the pulmonary edema observed in patients with hyponatremic encephalopathy (17, 24).

Hypoxemia worsens clinical outcomes in hyponatremic encephalopathy by impairing brain adaptation to hyposmolar states (Fig. 5). Brain adaptation to hyponatremia requires active transport of sodium, which is an oxygen-requiring pro-

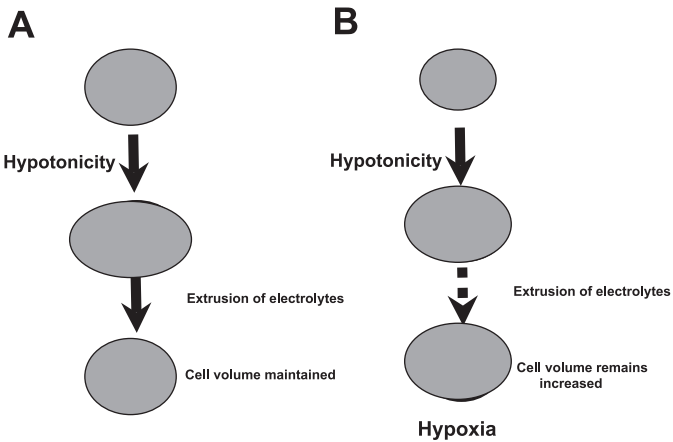


Fig. 5. Adaptation of the brain (glial cells) to hyponatremia in normoxic (A) and hypoxic (B) states. Hypoxia impairs the $Na^+-K^+-ATPase$ system, and loss of cellular water and solutes is diminished, leading to impairment in brain adaptation to hyponatremia.

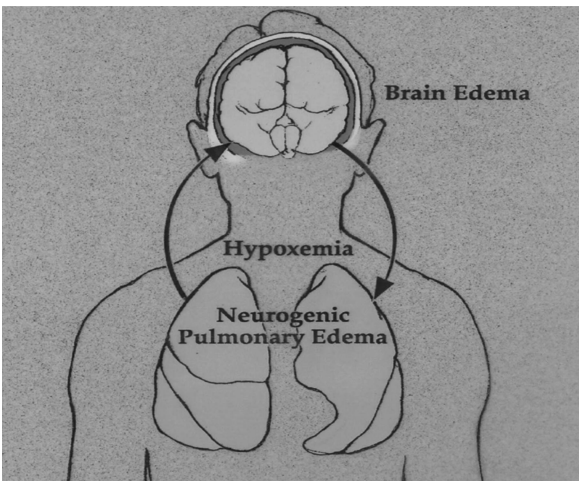


Fig. 6. Depiction of the intimate relationship of brain edema, hypoxia, and neurogenic pulmonary edema. Cerebral edema leads to neurogenic pulmonary edema, which worsens hypoxia, and this in turn worsens the underlying brain edema.

cess. It has been shown that hypoxia will impair energy-dependent mechanisms such as astrocyte cell volume regulation (75) (Fig. 5), and, in fact, impairment of energy utilization in the brain alone can lead to diffuse cerebral edema (“cytotoxic” cerebral edema) (78) related to the impairment of cell volume regulatory mechanisms (19). This impairment in volume regulatory mechanisms through hypoxia can worsen underlying cerebral edema, and thus hypoxia can lead to a vicious cycle, resulting in a worsening of patient outcome (9) (Fig. 6). Under ordinary circumstances, hypoxia leads to a compensatory increase of cerebral blood flow as an attempt to increase cerebral oxygen delivery (79); however, in the presence of hyponatremia, hypoxia actually leads to a decrease of cerebral blood flow (19), thus further impairing brain adaptation. Hypoxia further prevents brain generation of high-energy phosphates (ATP, phosphocreatine) (19, 40, 73), leads to increased cerebral lactate and *N*-acetyl aspartate (NAA) generation, and further lowers brain intracellular pH and neuronal energy status (32). These additional factors can further worsen brain adaptation to hyponatremia.

In addition, hypoxia in normonatremic animals is associated with brain histological changes that have the same distribution of lesions seen in animals in which hyponatremia has been

Table 1. Factors that impair brain adaptation in hyponatremic encephalopathy

Risk Factor	Pathophysiological Mechanism
Children	Increased brain-to-intracranial volume ratio
Females	Sex steroids (estrogens) inhibit brain adaptation through inhibition of $Na^+-K^+-ATPase$
Increased vasopressin levels	Decreased cerebral perfusion Decreased oxygen delivery to astrocytes Decreased intracellular pH Decreased cellular buffering Decreased synthesis of ATP and phosphocreatine
Hypoxemia	Impaired brain adaptation

Adapted from Ref. 63a.

overcorrected (19–21, 23). Thus the aforementioned studies suggest that hypoxia is a major contributor to the brain damage associated with hyponatremic encephalopathy, not only by impairing brain adaptation but also by contributing to the development of histological brain damage.

In summary, physical characteristics of the cranial vault and impairments of brain cell adaptive responses to hyponatremia play an important role in shaping the poor outcomes observed in certain high-risk groups for hyponatremic encephalopathy (Table 1). These risk groups are premenopausal females, children, and patients with hypoxia. The main defense against cerebral edema, the active extrusion of electrolytes from the brain via the $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump, can be significantly impaired by the presence of estrogens and by hypoxia. Furthermore, the effects of vasopressin on the brain can have additional adverse consequences by further worsening brain ischemia. These findings underscore the importance of identification of patients at risk for a poor outcome and of the paramount role that brain adaptive responses play in determining patient outcomes in hyponatremic encephalopathy.

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