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Thirst in Critically Ill Patients: From Physiology to Sensation

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Abstract

Critically ill patients often have distressful episodes of severe thirst, but the underlying complex biochemical, neurohormonal regulatory controls that regulate this primal sensation have rarely been addressed by clinicians. Subtle changes in plasma osmolality are the most potent stimulus for thirst. In response to increases in osmolality, osmoreceptors activate release of the neurohormone vasopressin (also known as antidiuretic hormone). The released vasopressin acts on the kidneys to conserve water to correct the hyperosmolar state. If this compensatory mechanism is unsuccessful, thirst arises to promote drinking. Thirst induced by marked volume loss, in contrast, is more closely related to the volemic and pressure changes regulated by the renin-angiotensin aldosterone system. Understanding the physiological mechanisms of thirst will help in understanding the pathophysiological consequences of underlying thirst-related disease and treatments in critically ill patients. Further clinical research is needed to elucidate the multiple inhibitory and excitatory neurohormonal stimuli that motivate patients' intense desire for water.

Keywords

thirst; thirst sensation; thirst physiology; osmolality; vasopressin; anti-diuretic hormone; hypovolemia; dehydration; angiotensin II

Thirst, the vital, often compelling, desire for water, is due to a complex system of neurohormonal and ionic signaling that regulates the body's water and sodium balance. Critically ill patients often experience intense thirst. In an assessment[1] of 10 symptoms, 70.8% of 171 intensive care unit (ICU) patients rated thirst as having the greatest intensity, and thirst was the second most prevalent symptom.

Moderate to severe thirst was similarly reported by 70% of 100 ICU patients[2] and was experienced by more than 80% of 36 chronically ill patients who had tracheotomies.[3] For a smaller percentage of patients, the sensation of thirst lingers at the end of life. Severe thirst with thirst scores of 7 or 8 (10-mm numeric rating scale) persisted in 18% of 88 terminally ill cancer patients,[4] and thirst was reported intermittently in 36% of 36 patients[5] until death occurred.

Like pain, thirst is a common sensation that until recently had not been recognized because many critically ill patients have communication difficulties and cannot self-report thirst to

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let clinicians know that the symptom is being experienced. In addition, like pain, thirst must be detected before it can be treated.

A review of the physiological mechanisms that influence thirst is useful for understanding this common and often distressful symptom. In this article, we provide information on the homeostatic mechanisms that may regulate the physiological sensation of thirst. The urge to drink water is driven by the central regulation of extracellular tonicity, termed osmotic thirst, and by the need to replace fluid deficits, termed hypovolemic thirst.[6,7] We present an overview of thirst regulation and the implications of osmotic thirst and hypovolemic thirst for ICU patients.

Essential Roles of Water and Thirst

Physiological thirst is a response to the need for the essential element of life: water. However, unique among vertebrates, humans respond to multiple nonphysiological or regulatory cues that may influence drinking, including social rituals,[8] customs,[9] certain pathological conditions,[10–12] habit,[13] a dry mouth (xerostomia),[14,15] and intake of food. These extrinsic prompts coexist with an intricate network of neuronal, humoral, and afferent signals that closely regulate and stabilize the body water within 0.22% (±165 mL) of a healthy person's body weight.[16] Whether nonhuman vertebrates respond to social cues to drink or have subjective feelings of thirst is not known.

Osmotic Thirst

Thirst has been hypothesized to have evolved as an essential primordial vegetative mechanism in the basal brain[17] that regulates the internal environment through multiple neuronal and hormonal controls and behavioral effectors to maintain homeostasis.[18] When this internal constancy is threatened, regulatory controls signal the kidneys and the sweat and salivary glands to mediate the rate of sodium and water loss. Osmotic thirst, or intracellular dehydration (water deficit), is activated in response to increases in tonicity when compensatory mechanisms are unsuccessful in conserving sufficient water to decrease serum osmolality and restore fluid balance.

The primary determinant of osmotic thirst in vertebrates is sodium, the major solute in extracellular fluid. Sodium exerts osmotic pressure to counterbalance the pressure exerted by intracellular solutes. Because of the dynamic equilibrium in the body's water to solute ratio, osmolality tends to change as water moves from regions of low concentrations of solute to regions of higher concentrations. When a water deficit or elevation in tonicity occurs, the concentration of circulating solute effectively reduces the intracellular volume as water moves from within the cell to the region of higher solute concentration in the extracellular space. This activity results in reduced cell volume and, eventually, intracellular dehydration.

Osmotic fluctuations are sensed by osmoreceptors in the circumventricular organs centrally located in the anterior wall of the third ventricle in the hypothalamus. Three circumventricular organs lack the blood-brain barrier, so rapid detection of osmotic signals in blood or interstitial fluid occurs.[20] In adjacent osmoreceptor sites, cells synthesize 2 neurohypophysial peptides: arginine vasopressin, also known as antidiuretic hormone, and the natriuretic hormone oxytocin.[21] The actual sensation of thirst appears to be activated deep within the cortex in response to changes in osmotic pressure in plasma or when major fluid loss occurs. Positron emission tomography has shown that the cortical circuitry pathways for thirst are anatomically within the cingulate cortex and cerebellum.[22,23]

Intrinsic encoded mechanisms keep plasma osmolality within a relatively narrow preset range, from about 275 to 295 mOsm/kg; the serum level of sodium is the principal determinant, at 135 to 145 mEq/L.[24] Serum sodium levels greater than 145 mEq/L are defined as hypernatremia and commonly are due to a water deficit, from inadequate intake of water or impaired thirst mechanisms. According to estimates, 7% of ICU patients experience hypernatremia. Hypernatremia is rarely listed as a primary cause of death, but it may be a contributing factor in the high 40% mortality rate in patients who have this solute and water disorder.[10]

Plasma osmolality is tightly regulated, and an increase as small as 1% to 2% greater than the normal range will stimulate increased excitatory output that triggers the release of vasopressin and the thirst sensation.[20] The secreted vasopressin peptides bind to specific receptors, vasopressin V_2 receptors, in the kidneys to increase the water permeability of the distal collecting tubules, thus decreasing water loss and increasing urine concentration. Leiper[24] has estimated that 70% of the stimulus to drink is determined by small increases in plasma osmolality.

Conversely, a decrease in osmolality of 1% to 2%, indicating osmotic dilution, inhibits vasopressin secretion, and the excess water is excreted as dilute urine.[20,24,25] Bourque[20](p519) described these rapid shifts in tonicity: “In a dehydrated individual, drinking the equivalent of two large glasses of water (~850 mL) lowers osmolality by approximately 6 mOsm/kg within 30 minutes” (see Sidebar 1).

Sidebar 1

The threshold stimulus point associated with the induction or inhibition of vasopressin release is set lower than the threshold associated with activation of the thirst sensation. The osmotic threshold for activation of thirst, and water-seeking cravings, is approximately 5 to 10 mOsm higher (serum osmolality, ~295 mOsm/kg H_2O) than the threshold for vasopressin release. The lower threshold set point for release of vasopressin allows humans to pursue their daily activities without continual disruptions by thirst sensations to seek water, or a hyperdipsogenic response.[6] One hypothesis is that differences in stimulus thresholds for vasopressin and thirst reflect the presence of an interactive neural circuit that closely regulates osmoregulatory control via the release of vasopressin and a parallel circuitry that osmotically activates thirst behavior.[26] Clinical evidence indicates that individuals vary widely in their osmotic set points for vasopressin and thirst activation. One person’s osmotic threshold for thirst activation may be set lower than another person’s threshold for vasopressin release.[27]

In addition to wide variations in threshold levels, aging may affect patients’ dipsogenic or thirst response to osmotic stimulus or pronounced volume loss. Older patients in clinical trials have reported significantly less thirst than younger participants have despite elevated plasma osmolality.[28–32] Even when allowed free access to water, the older, less thirsty participants did not drink sufficient fluid to restore their fluid deficits.[33–35] However, in 2 studies[36,37] on the response of healthy older adults to osmotic stimulus, older age was not a mediating factor. With these 2 exceptions, hypodipsia (reduced thirst) and a hyperosmotic state in older adults may represent a resetting in the threshold point for fluid regulation or an alteration in osmotic-vasopressin sensitivity in the brain to hypertonicity.[32] This resetting may represent a recalibration in the parameters that regulate an older adult’s homeostatic state.

Increasing evidence indicates the rapid complementary role played by peripheral or visceral osmoreceptors in fluid regulation. The widely distributed peripheral or visceral

osmoreceptors have been detected in the upper regions of the alimentary tract, oropharyngeal cavity, gastrointestinal tract and intestines, the splanchnic mesentery, the hepatic portal vein, and the liver. Visceral sensors located in the alimentary tract of rats preemptively signal when ingestion of dilute fluids occurs; this signal inhibits the release of vasopressin before any detectable reduction in the osmolality of extracellular fluid.[20,38,39] Stricker and Sved[40] have suggested that the osmotic fluid regulatory system operates as if a gating mechanism were present that inhibits peripheral signals when cerebral osmoreceptors detect euhydration; the gating mechanism is disinhibited when these osmoreceptors detect dehydration.

An example of the inhibitory role played by peripheral osmoreceptors in the oropharyngeal region was provided in a dehydration study.[41] Healthy adult control participants who ingested water by mouth experienced significant ($P < .05$) inhibition of both vasopressin release and lowering of thirst rates within 5 minutes after drinking, before any reduction in plasma osmolality occurred.[39] This effect occurred only in participants who ingested water by mouth, not in participants who received water via a nasogastric tube and not in participants in whom water ingested by mouth was simultaneously extracted from the stomach via a nasogastric tube. The investigators hypothesized that vasopressin is primarily sensitive to fluctuations in plasma osmolality, whereas peripherally located oropharyngeal signals may have a greater inhibitory effect on thirst mechanisms.

Hypovolemic Thirst

Under normal circumstances, intracellular volume and extracellular volume are carefully balanced. However, when this fluid equilibrium is disturbed, thirst is activated through a negative feedback system to restore homeostasis. The effect of dehydration on the close relationship between osmotic (intracellular volume) and hypovolemic (extracellular volume) loss that results in thirst activation is illustrated in the Figure. Earlier studies[6] suggested that increased extracellular plasma tonicity that resulted in cellular dehydration was the primary stimulus for thirst. Hypovolemia (ie, an extracellular deficit) was not recognized as a stimulus of thirst until the 1960s. Because osmotic and volemic dehydration usually occur after water and solute loss, recognizing these dual stimuli provided the opportunity to reexamine the intricate and often competing neuroendocrine osmotic interactions and fluid regulatory controls.

Hypovolemic thirst mechanisms associated with changes in intravascular volume and pressure are less sensitive than are those associated with osmotic changes. For example, a decrease of approximately 10% of the plasma volume[10,24] is required to initiate hypovolemic thirst, whereas only a minimal 1% to 2% increase in the plasma osmolality can stimulate thirst and drinking.[6] This reduced sensitivity to volume deficits is necessary to prevent excessive overadjustments to blood volume and blood pressure in response to normal postural changes that occur during physical activity.[24]

Marked reductions in plasma volume, as in hemorrhage, vomiting, diarrhea, sweating, and diuresis, activate an intricate neurohormonal circuitry of central osmotic sensors and peripheral volume and arterial oncotic pressure sensors.[18] In hemorrhage, this hypovolemic response includes the release of renin, arginine vasopressin, epinephrine, norepinephrine, corticotropin, and glucocorticoids. This neurohormonal cascade works in conjunction with the autonomic nervous system to reduce water and sodium loss through sympathetic stimulation by proximal tubular reabsorption in the kidneys and the reallocation of water in the intracellular and extracellular fluid compartments. Initially, little change occurs in the osmotic pressure of body water after the fluid deficit that accompanies sodium depletion due to sweating, urinating, vomiting, or diarrhea. As the sodium excretion or natriuresis

continues, water loss is reduced by gradual decreases in urination or sweating, causing a compensatory shift of fluid from the interstitial areas to the cells to increase cellular volume. In turn, increasing levels of angiotensin II and vasopressin prompted by these compensatory mechanisms activate thirst mechanisms, as well as the hormonal and neural circuitry that signals sodium appetite (see Sidebar 2).

Sidebar 2

Sodium appetite refers to the sodium deficiency that occurs with the loss of extracellular fluid. The sensation is sometimes interpreted as thirst or a "peculiar sensation in the mouth." The deficiency cannot be relieved solely by water intake without solute replacement.[18]

Thus, the mechanisms of osmotic and volemic thirst, at baseline, exert similar inhibitory control to maintain a balance between continuous inhibitory and excitatory neural activity. However, hypovolemia-induced thirst is distinguished from osmotic thirst by the increase in sodium appetite that accompanies fluid replacement. Correction of extracellular volume loss in hypovolemic hypotonic thirst requires replacement of both water and solute, mainly sodium.[18,42] This sodium deficit associated with hypo-osmolar and hypovolemic conditions may also occur in response to excessive fluid intake. This solute loss can occur in marathon runners who are hyper-hydrated and in patients with schizophrenia who drink compulsively.[20] Thus, hyponatremia, which occurs in 1% to 2% of hospitalized patients, can be associated with hypovolemic, euvolemic, or hypervolemic conditions, depending on the water or tonicity disturbance.[10] Vasopressin antagonists have recently been introduced for management of hypervolemic hyponatremia in patients who have congestive heart failure, nephrotic syndrome, or hepatic cirrhosis.

Central and Renal Angiotensinergic Influence on Fluid Regulation and Thirst

Angiotensin II is a second key neuropeptide involved in restoring the fluid and solute loss of hypovolemia. Synthesized in several regions of the brain, endogenous angiotensinogen, the precursor for angiotensins I, II, and III, responds to circulating peripheral angiotensin II that acts as a water-seeking or dipsogenic neurotransmitter to signal thirst, salt appetite, and release of vasopressin.[6,18] Actions of angiotensin II and all neurohormones associated with the fluid and thirst mechanisms are coordinated by the central nervous system in conjunction with the autonomic nervous system. In instances of progressively decreasing cardiac output (ie, hemorrhage or extracellular dehydration), the kidneys are stimulated to release renin. Renin transforms the plasma protein angiotensinogen into the relatively inactive angiotensin I, which subsequently is catalyzed by angiotensin-converting enzyme in the lungs into renal angiotensin II. The highly active angiotensin II causes vasoconstriction and acts directly on the sodium appetite centers. Released aldosterone, in turn, increases the reabsorption of sodium in the kidneys to mediate hypovolemic thirst by increasing body fluid retention and osmolality to restore plasma volume.[6,43]

The contribution of angiotensin II to thirst has been explored in studies on interdialytic weight gain after hemodialysis in patients with chronic kidney disease. However, the measurable outcomes (excessive weight gain and thirst intensity ratings) reported since the 1980s by patients with renal failure who had hemodialysis have been inconsistent. In a study published in 1986 by Yamamoto et al[44] the hyperdipsic thirst (excessive thirst) reported by a subgroup of patients receiving hemodialysis was reduced after 5 weeks of treatment with an angiotensin-converting enzyme inhibitor. Oldenburg et al[45] and Kuriyama et al[46] reported

similar findings of lower thirst scores and reductions in interdialytic weight gain after the suppression of angiotensin II levels. However, this association with a reduction in patients' thirst reports and moderation in interdialytic weight gain was not supported in subsequent clinical trials[47–49] of angiotensin-converting enzyme inhibitors.

Regulation of Volumetric Thirst

Hypervolemic states sensed by stretch-sensitive atrial baroreceptors activate the release of atrial natriuretic peptide. The released peptide has an immediate inhibitory effect on secretion of renin, vasopressin, and aldosterone, leading to a decrease in thirst, or the dipsogenic effect of angiotensin II.[50] Conversely, angiotensin II, which is influential in the maintenance of plasma volume and is a dipsogenic stimulus, is considered the endogenous antagonist of atrial natriuretic peptide.[6,51]

Identifying the Etiology of Thirst

Conditions that alter or disturb fluid homeostasis can be potential dipsogenic stimuli for physiological osmotic or hypovolemic thirst and can affect many ill patients. The list of potential causative conditions is extensive: nausea and/or vomiting,[52] hemorrhage,[53] chronic renal failure,[44,54,55] heart failure,[11] fluid and electrolyte imbalances,[56] endocrine disorders,[57] end-stage disease,[58] and commonly used medications[59,60] (see Table for medications that may affect thirst in ICU patients).

Although thirst has often been equated with dehydration and hyperosmolality, Morita et al[4] identified specific conditions, such as mouth breathing due to hypoxia or the stomatitis associated with malignant digestive tract obstructions[61] that may contribute to the intense thirst sensations experienced by terminally ill cancer patients. Dry mouth, or xerostomia, is another common thirst-related condition associated with systemic disorders such as Sjögren syndrome.[62] Dry mouth may also be experienced by patients who are orally intubated for treatment with mechanical ventilation. Additionally, the reports of thirst may reflect common fluid and electrolyte disturbances,[63] especially rapidly shifting hyponatremic and hypernatremic states,[10,64] experienced by ICU patients.

Dehydration and the Perception of Thirst

Dehydration often has been perceived as a major stimulus of thirst activation. However dehydration, broadly defined as inadequate fluid intake, hyperosmolar states, low levels of atrial natriuretic peptide, or increasing concentrations of angiotensin II, has not been consistently correlated with patients' thirst reports. In one study,[65] the thirst reports of 15 fluid-restricted non-ICU participants correlated with angiotensin II concentration ($r^2 = 0.30$) but not with serum osmolality ($r^2 = 0.10$), percentage of body water lost ($r^2 = 0.11$), or changes in plasma volume ($r^2 = 0.09$). In another experimental study,[66] 6 participants simply reduced their thirst ($P < .01$) by gargling with cold water for 2 minutes. However, the relief they obtained was transient, lasting only 30 minutes. Additionally, the participants' thirst ratings did not correlate with elevated serum osmolality and vasopressin levels or with changes in plasma renin activity.

Again, beyond the ICU, thirst scores of 88 cancer patients did not correlate with biomarkers for biochemical dehydration such as blood urea nitrogen, creatinine, sodium, and osmolality.[4] However, in a subgroup of 16 patients, a significant association was observed between severe thirst (numerical rating scale, scores >8) and hyperosmotic states (>300 mOsm/kg), and low levels of atrial natriuretic peptide (<15).

Clinical Implications

Thirst has been underevaluated, underappreciated, and understudied in the ICU and has been underreported in reports on symptom management. The intensity and pervasiveness of thirst clearly indicate that this sensation has yet to be fully explored by ICU clinicians. Perhaps clinicians feel more comfortable basing treatment on biochemical indices that can be quantitated rather than on subjective symptoms. For patients who experience severe thirst, the subjective sensation is both intense and personal. For clinicians, thirst can be viewed as an early-warning biochemical signal of osmotic and fluid imbalance. These clinical implications emphasize the need for clinicians to not only ask patients about the presence of thirst but also evaluate plasma sodium osmolality for the indications of intracellular volume loss and to assess extracellular volume loss by searching for the causes of absolute or relative states of hypovolemia.

Conclusion

Appreciating the physiological mechanisms of thirst will help in understanding the pathophysiological consequences of underlying thirst-related disease and therapies in critically ill patients. Physiological thirst can then be perceived as an osmoregulatory challenge for ICU nurses and as a call for effective interventions to relieve this distressing sensation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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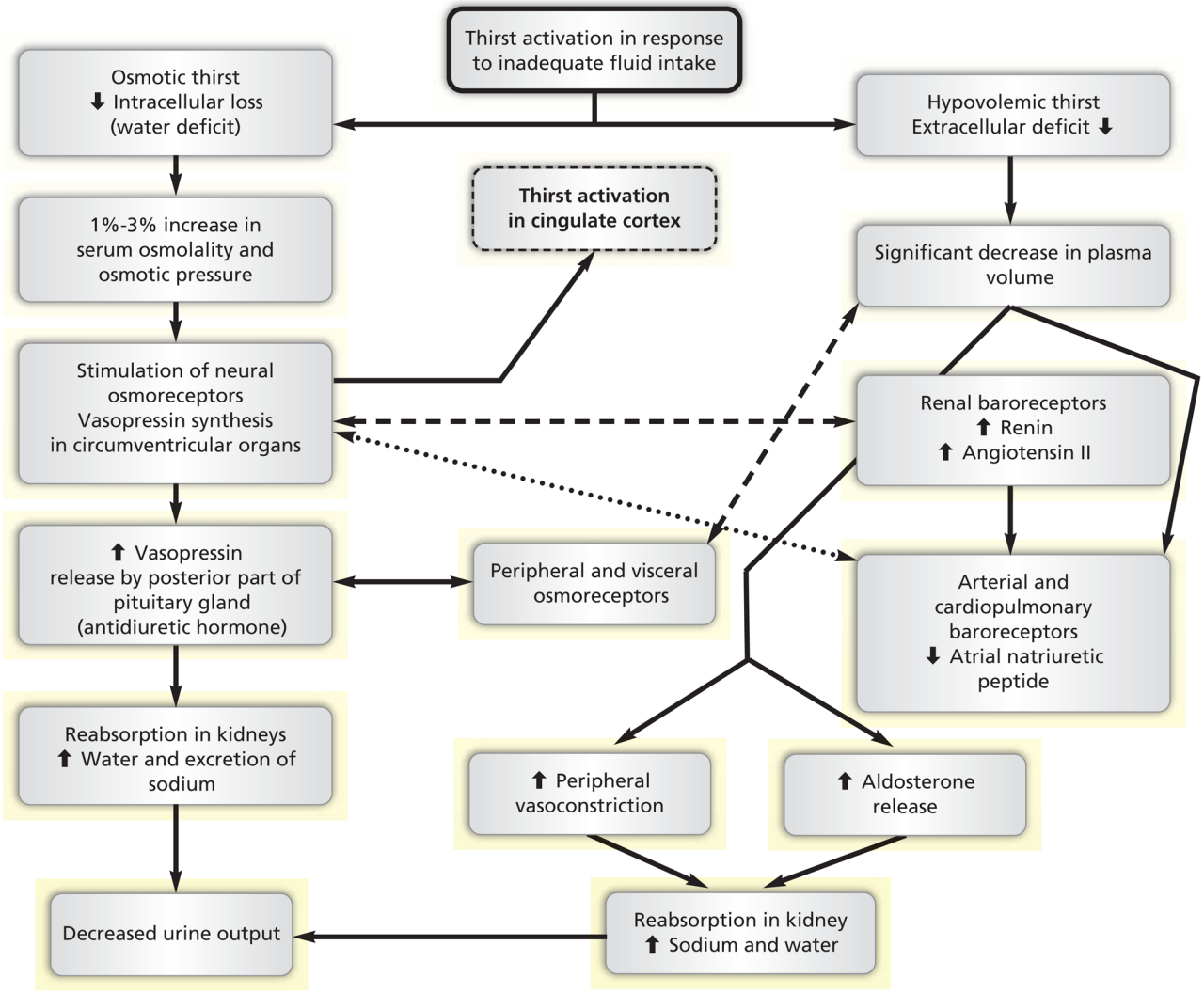

Figure.

Effect of dehydration on neurohormonal pathways that activate thirst. Dashed lines indicate potential relationship is under investigation. Dotted line indicates atrial natriuretic peptide decreases disinhibition in hypovolemia. ↑ indicates increase; ↓ indicates decrease.

Table 1

Table Common dipsogenic (thirst-producing) medications

Anticholinergics
Diuretics
Opioids
Tricyclic antidepressants
Nonsteroidal anti-inflammatory drugs
Corticosteroids
Proton pump inhibitors
Antihypertensives