Age-Associated Osmoregulatory Alterations in Thirst, Drinking Pattern and Arginine Vasopressin Secretion in Man

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Abstract:*We examined the renal, hormonal and central thirst and arginine vasopressin (AVP) osmoregulatory systems that accompany the aging process and how these influence the risk of altered water and electrolyte balance in the elderly. When deprived of fluid or confronted with a hyperosmotic or hypovolemic stimulus, elderly people exhibit a decreased perception of thirst and reduced fluid intake. Altered hydromineralbalance is a common feature in elderly people due to impaired capacity to restore and maintain fluid balance. The consequent hypovolemia appears to be induced by decreased thirst sensation and baroreceptor sensitivity. More so, there is reduced oropharyngeal-induced inhibition of AVP release after drinking and the kidneys gradually become unresponsive to even higher levels of circulating AVP, thereby either leading to volume overload or reducing the body's water retention capacity. These defects combine to increase the susceptibility of elderly people to disturbances in water and electrolyte balance, which manifest as dehydration/hypovolemia and hypernatremia, or overhydration and hyponatremia.*

Keywords:*aging, thirst, drinking, arginine vasopressin, dehydration, overhydration*

I. Introduction

Several health benefits are associated with adequate hydration both during regular unchallenged daily hydration and in response to dehydration. Rehydration i.e. restoration of body fluid balance, primarily includes thirst, which stimulates voluntary fluid intake (drinking). Thirst sensations including dry mouth and throat increase with dehydration and decrease with rehydration[1]. Thirst emanatesthrough a complex interplay between physiological control systems and behavioral influences. The difference between physiologically determined thirst (homeostatic) and drinking behavior triggered by non-homeostatic stimuli is shown in figure 1[2].

Dehydration stimulates physiological thirst via two main homeostatic mechanisms: i) increased cellular tonicity (cellular dehydration) detected by osmoreceptors in the central nervous system (CNS), and ii) decreased extracellular fluid volume (ECF, extracellular dehydration) sensed by baroreceptors in the large blood vessels[2]. In humans, cellular dehydration is a more potent thirst stimulus, compared to extracellular dehydration. Increase in effective plasma osmotic pressure stimulates drinking. Central and peripheral osmoreceptorsdetect the degree of dehydration/hypertonicity and signal the hypothalamus to generate several thirst-associated homeostatic mechanisms. Similarly, animal models have shown thirst is dependent on a tonicity sensor that is found in the circumventricular organs of the brain lackingthe blood-brain barrier[2,3]. Thirst thresholds are set based on the sensitivity of the osmoreceptors, and thirst is triggered due to a deviation of the sensed plasma osmolality from the "normal" operating point. This osmotic thirst control system can be defined as a single feedback loop[4](Fig. 2).
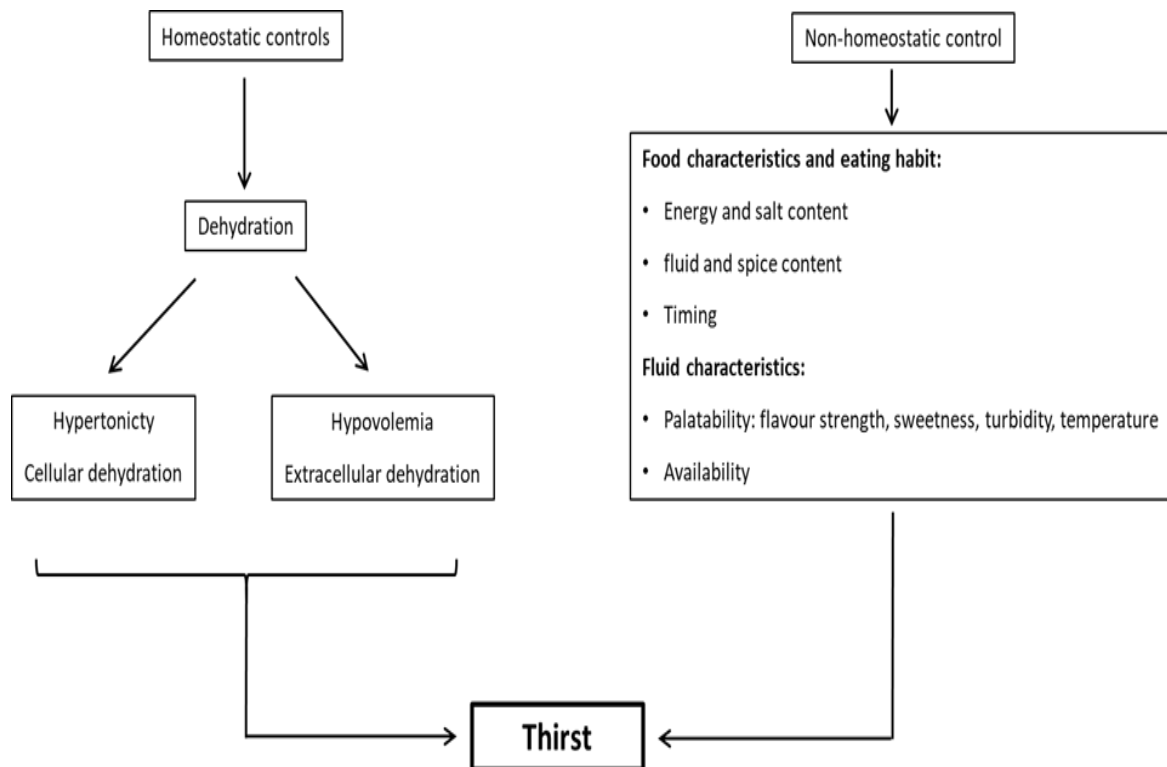
Figure 1. Physiological and behavioural (non-homeostatic) thirst control in humans.Dehydration (stress) increases cellular tonicity and decreases extracellular volume thereby stimulating thirst sensations.
Adapted from:Kenney and Chiu[2].

Hypovolemic thirst involves a more complex mechanism (double feedback loop) (Fig. 2). It involves both volume detectors (baroreceptors) in the vascular compartment, which are activated with decreased blood volume; and renal mechanisms that stimulate the renin-angiotensin aldosterone system (RAAS) in response to decreased renal perfusion and NaCl concentration at the macula densa. Hormonal activation of saltintakefurthercomplicates both volumetric and osmotic thirst (Fig. 2). However, volumetrically inducedthirst appears to be less predominant in young adults, and hypovolemia only develops into a crucial thirst stimulus during severe dehydration[5-7].

A third mechanism termed "oropharyngeal metering" also helps regulate thirst. This regulates the volume of fluid ingested through an integrated signal that correlateswith the cumulative volume of fluid ingested[8]. Oropharyngeal inhibition of thirst after drinking is unaffected in healthy elderly men althoughsuppressionof AVP release is reduced[9].

In the elderly, evidences of relative impact of cellular and extracellular dehydration are beginning to emerge[2]. Although regulation of the physiological thirst mechanism in young adults has been studied extensively, there is still limited data in relation to difference in thirst sensation and fluid intake in the elderly. This review examined the characteristic alterations in renal, hormonal and central thirst and AVP osmoregulatory systems that accompany the aging process and how these influence the risk of altered water and electrolyte balance in the elderly.
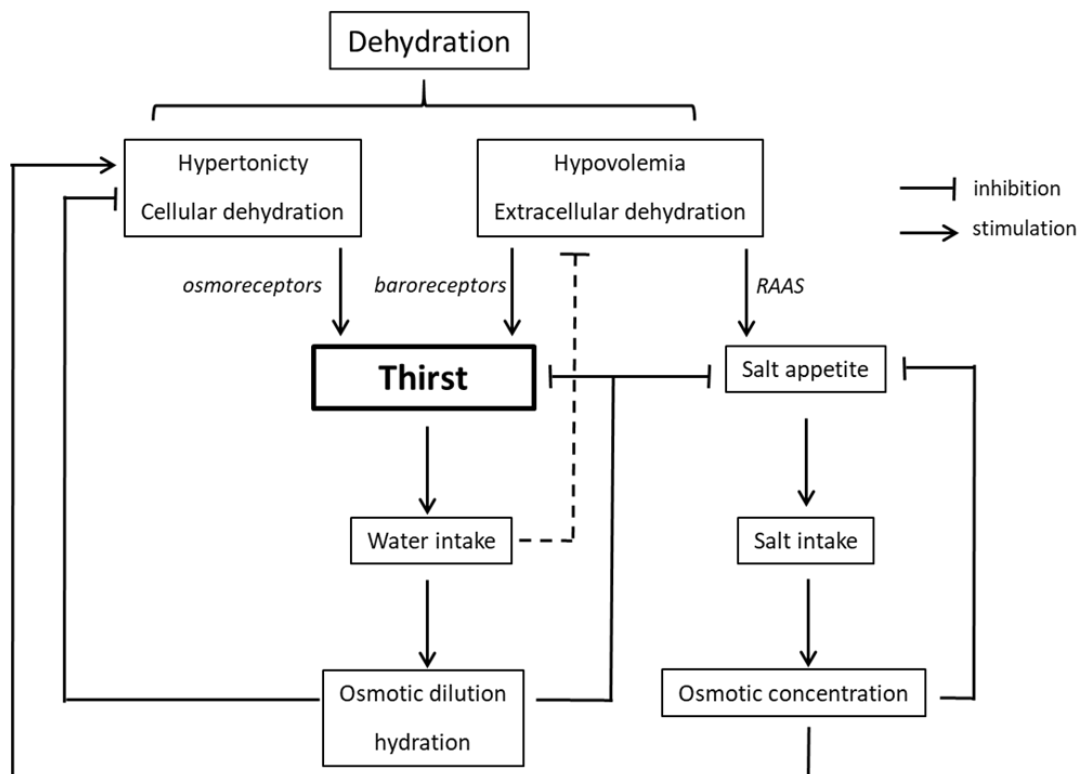
Figure 2. Homeostatic control of thirst.Osmotic thirst is a single feedback loop with water intake restoring hydration. Hypovolemic thirst is controlled in a double negative feedback fashion involving both water and salt intake to correct the plasma volume deficit and prevent excess osmotic dilution. *RAAS*, Renin-angiotensin-aldosterone system. Adapted from: Stricker and Verbalis[4];Kenney and Chiu[2].

Thirst and drinking patterns in the elderly
　　　　Most dataon altered hydration status in the elderly are obtainedfrom anecdotalevidence and datadeduced from clinical and institutionalizedcohorts. In one study,dehydration was observed in about 25% of non-ambulatorygeriatric hospital patients[10]. Another report showed majority of patients over 65 years from six clinical settings had increasedplasmaosmolalities (296mOsm/kgH$_2$O), and a randomly selected sub-group (n = 58)showed mean plasma osmolality of 304-308 mOsm/kgH$_2$O attime of admission[11]. Usually, many older patients do not spontaneously ask for fluids when hospitalized[12].Relating thesedata to non-hospitalized, healthyolder population leads to less reliableconclusionthat many older adultsare usually in astate ofhyperosmolar hypohydration. Despite the data from geriatric clinical settings cited above,only about 1% of elderlypatientsadmitted to local hospitals are dehydrated.This is a more reliable indicator of thehydration status of independently living elderlypopulation[13].Even in hyperosmolar institutionalized patients (mean age 81 years), a correlation betweenage and osmolality may be absent[11].

Baselineplasma volume, osmolality and euhydration in the elderly
　　　　Elderly subjects reporting for laboratory studies designed to test fluid homeostasisareoften in a normal state of hydration[14,15]. However, an elevated plasma osmolality (~3-6 mOsm/kgH$_2$O)is often observed in the elderly at "baseline" compared to youngadults[14,16-18]. "Healthy, active older individuals are believed to be hyperosmotic and hypovolemic" due to these slight differences in blood tonicity[17]. However, because an overnight fast without pre-experimental fluid intake is usually required in such studies, the reported "baseline" plasma osmotic status may indeedindicate a dehydrated state[2]. An overnight fast could in effect be mild dehydration that selectively leaveselderly subjects slightly hyperosmotic and hypovolemic if renal function is defective. Differences in plasma osmolality between these two age groups arealsoobserved in studies where pre-exercise fluid intake is standardized[17]. Furthermore, baseline differences in both plasma volume and osmolality are minimizedwhen both the old and young are matched for body composition and maximal aerobic capacity[15]. Because the elevated osmolality of the elderly is not related toincreased plasma Na$^+$ concentration, it may more strongly reflect increases in other osmotically active analytesincludingglucose and blood urea nitrogen[15].

Non-thirst factors related to dehydration in the elderly

Non-osmoregulatorythirst factors such as the availability and palatabilityof fluids influence voluntary fluid intake after dehydration. Although thirst and volume of fluid ingested are separate phenomena, they appear tobe affected in parallel by age.Older subjects do not significantly increase fluid intake after fluid restriction despite increase in the availability and palatability of the fluids[19,20]. Healthy older men offered a variety of fluid including water, mineral water, cola and orange juice after 24-hourfluid restriction and consumption of dry diet showed preference for orange juice[20,21]. This suggested preference for higher palatability, yet no significant differences in the total amount of fluidsconsumedover a 2-hour periodwas observed. Although this implies that palatability alone is inadequate to mask the age-associated reduced thirst, the tonicity of the fluid consumed may be crucialas drinking continues[22], and in the effectiveness of rehydration[5]. For example, isotonic fluid appears more effective than water (hypotonic) for rehydration after exercise in heat in healthy young subjects[23].

Disturbances of body fluid homeostasis in the elderly

As shown in table 1, changes in the regulation of fluidbalance in the elderly result from multiple effects of aging: alterations in body composition, changes in renal function, and impaired hypothalamic-pituitary control of thirst and arginine vasopressin(AVP) secretion[24]. Together these changes result indecreased homeostatic reserve, andimpairedadaptive responses to environmental and metabolic stressors[7,25].

Body composition

Total body fat increase by 5-10% in the elderly with a corresponding decrease in total body water. In a 70 kg elderly male, thechange in body composition can lead to a 7-8 l decreasein total body water compared toa young male of the same weight[25].Plasma volume canalsodecrease by about 1/5 relative to body weight and surface area in older men compared totheiryounger counterparts[26]. Consequently, acorresponding acute reduction or increasein body water leads to greater extent of altered osmolality in elderly compared to younger individuals. Therefore, significant alterations in concentration of electrolytes such as sodium are more likely to occur in states of relatively mild dehydration or volume overload in the elderly[7]. Despite similar weight loss and changes in plasma volume, the elderly retainedsignificantly increased plasma osmolalitycomparedto younger controls. Increased plasma osmolality secondary to retention of relatively smaller volumes of fluid plausiblyexplains the much higher incidence of hypernatremia in the elderly[7].

Renal function

Several aspects of renal function associated with water homeostasis are controlled through the release of AVP from the posterior pituitary. There are also intrinsic renal mechanisms that are crucial in the maintenance of fluid balance in the elderly. Age-relatedchanges in the kidney functional architecture include reduced parenchymal mass, interstitial fibrosis, progressive glomerulosclerosis, tubulopathy, and development of afferent-efferent arteriolar shunts[27]. Over the age of 80, the normal kidney mass reduces by 25% with a histopathological appearance similar to that observed in chronic tubulo-interstitial disease[28]. There is also a 40% reduction in renal volume[29]. These functional shifts from the normal were termed "inelasticity" in fluid homeostasis[25]. Such alterationsare not usually of immediate consequences during healthy conditions.However, under conditions of stress, disease, dehydration, or hypervolemia, thesemild impairments in normal kidneyfunction may cause considerable water and electrolyteimbalance[25], manifesting clinically as depletional or dilutional states such as hyper- and hypoosmolality or hyper- and hypovolemia[24,28].

Glomerular filtration rate

About 30% of healthy elderly individuals maintain a normal glomerular filtration rate (GFR). However, after age 40, GFR decreased by approximately $1ml/min/1.73m^2$/year in the remaining 70% with only few exceptions. The decline is further accelerated after age 65[16,28,30]. Whether these alterations are inevitable consequences of aging, or are due tosubclinical pathologic conditions remains unresolved. Reduced GFR leads to a decreased delivery of free water to the distal diluting segments of the nephron secondary to increased proximal renal tubular fluid absorption[31]. The result is a decreased dilutional capacity of the kidney, seen asareduced ability to excrete a free water load[7,32]. Following a water load of 20 ml/kg body weight, acomparison of free water excretion between elderly (mean age = 68 years) and young subjectsshoweda significant decline in maximal free water clearance in the older group,although they were able to achieve normal excretion eventually[16]. This may be due to decreased distal renal tubular delivery of water and increased osmotic gradient for water reabsorption due to reduced prostaglandin synthesisand increased antidiuretic action of AVP in the elderly[33]. Prostaglandins antagonize AVP's antidiuretic action and decrease the osmotic gradient for water reabsorption by increasing medullary and papillary blood flow[33]. Impaired excretion of excess body water predisposes the elderly to dilutional states that lead to overhydration, hypoosmolality and hyponatremia.

Table 1: Age-associated alterations in hydromineral balance

Mechanism	Manifestation
Brain thirst centers	Decreased response to osmotic stimuli
Volume detectors (Baroreceptors)	Decreased response to hypovolemia
Renal function	Decreased renal mass and volume
	Reduced renal perfusion
	Decreased GFR
	Impaired free water clearance
	Impaired urine concentrating ability
	Impaired RAAS and Na^+ retention
	Decreased sensitivity to AVP
AVP secretion	Normal or elevated circulating levels
	Increased response to osmotic stimuli
	Reduced oropharyngeal inhibition
	Low nocturnal secretion
ANP secretion	Elevated circulating levels
	Increased sensitivity to stimulation
Renin	Decreased circulating levels
Aldosterone	Decreased plasma levels
	Increased mineralocorticoid receptors
	Reduced sodium appetite
Fluid intake	Reduced thirst sensation

ANP, atrial natriuretic peptide; *AVP*, arginine vasopressin; *GFR*, glomerular filtration rate; *RAAS*, renin-angiotensin-aldosterone system. Adapted from: Miller[24].

Impairedrenalconcentrating ability

In addition toreduced diluting capacity, the aging kidney can also develop impaired ability to optimallyconserve body water during dehydration[34]. In such volume-depleted state, maximal urine concentration is crucial to prevent further water loss especially in the absence of fluid ingestion.Urine concentration ability drops from a youthful peak of ~1200 mOsm/kgH$_2$O to≤ 500 mOsm/kgH$_2$O from 80 years of age[35]. Phillips *et al.*had initially reported older subjects showed significantly less urine concentrating ability in comparisonto younger controls despite having higher plasma osmolality and AVP levels after 24 hours fluid restriction[36]. This is suggestive of concentrating defect(s)mostlylimited to intrinsic renal factors e.g. increased relative resistance to AVP stimulation[9]. Decreased urine concentrating ability aggravatesseveral conditions observed in the elderly such as decreased thirst, diarrhea, vomiting, and poor oral fluid intake, hence, exacerbating the subsequent dehydration, hyperosmolality and hypovolemia.

Alteredneuroendocrine control of water balance

Central neurohumoral control of thirst and AVP secretion are key regulators of normal fluid balance in individuals with relatively normal renal function. Plasma osmolality is maintained within tight limits via AVP secretion, renal response to AVP, and appropriately controlled thirst and drinking. Each of these mechanismsis considerably affected by aging[37].

AVP secretion in the elderly

AVP plays a central role in regulating renal water excretion by controllingtranscription and apical membrane insertion of aquaporin-2 (AQP2) water channels in the distal collecting tubules and ducts of the nephron[38]. These effects are dependent on the interaction of AVP with type 2 vasopressin receptor (V2R) expressed in the renal collecting ducts. Increased membrane bound AQP2 enhances water permeability of the collecting duct;therebyinducingantidiuresis i.e. decreased renal free water excretion.

AVP is a nonapeptideproduced by the cell bodies of the supraoptic and paraventricular nuclei and packaged in granules withneurophysin (its carrier protein). It isconveyed down axons to the posterior pituitary where it is stored and eventuallyreleasedin response to specific stimuli[39]. The secretion of AVP is primarily determined bymomentarycontrol of osmoreceptors located in the circumventricular organs and median preoptic nucleus. Thenormalosmotic threshold for AVP release is within a relatively narrow range i.e. a1-2%increase in plasma osmolality above the normal range is adequate to trigger an increase in plasma AVP concentration of 1 pg/ml with corresponding rapid and significantlydecreasedfree water excretion and urine flow[39]. Any increase in plasma osmolality above the threshold will induce a proportional increase in AVP secretion[31], with maximum antidiuresisisachieved whenplasma AVP levels rise above 5pg/ml[39]. This extraordinarily sensitive mechanism maintains plasma osmolality around275 -295 mOsm/kgH$_2$O.

There is also a secondary hemodynamic and volume dependent AVP regulatorymechanismcontrolled by baroreceptors located in the cardiac atria and large arteries. In contrast to the very sensitive osmotic regulation of AVP secretion, the AVP response to a volume or hemodynamic stimulus requires approximately

8-10% decrease in effective arterial volume to be activated[31,39]. The interaction between osmoreceptor- and baroreceptor-mediated AVPregulationsensures an integrated AVP secretory pattern that is linear, however, with a variable slope that is influenced by alterations in volume and hemodynamic status[31].

Aging also affects secretion and end organ effects of AVP. Basal AVP levels in healthy elderly individuals are greater than or at least equivalent to those of young people. However, in some instances,the basal AVP levels between the two groupsare similar[40], and rarely lower basal AVP levels in older subjects have been reported[41]. Notwithstandingthe basal AVP levels, the elderlyare more sensitive to hyperosmolalityexhibitedbyincrease in AVP secretion per unit change in plasma osmolality than theyoung. This corresponds with an increase in osmoreceptor sensitivity in the elderly and may compensate for the diminished salt and water retention capacity of the kidney. This observation was made in studies of dehydrated elderly participants subjected to hypertonic saline infusion[34], and havebeenvalidated[41]. Though the elderly may experience a 3-fold increase in AVP secretion per unit change in osmolality[36],osmoticAVP secretionis maintained rather than augmented[21]. The elderly has also shown no correlation between AVP secretion and osmolality[42].

Rowe et al.,[43]observed92% (11/12) of young study participants augmented AVP secretion in response to a change in position compared to 53% (8/15) of the elderly participantsthat had a similar response. There was also an increased sympathetic norepinephrine production in response to positional changes regardless of AVP secretory status. Therefore, aging may not affect AVP secretion via impairment of the baroreceptor afferent-efferent loop. Rather, itmay result in inadequate transmission of postural signals from vasomotor centers (VMCs) of the brainstem where these stimuli are integrated to the hypothalamus where AVP secretion is regulated. Thisdefect would consequently impair normal AVP release in response to positional changes. In essence, the amplifiedosmotic AVP secretion in the elderly mightindicate a compensatory responseto an impaired normal baroreceptor-mediated control of AVP release[43].

While a diminished baroreceptor influence on AVP release may arise from a defective neurologic connection between the VMC and hypothalamus, the action of atrial natriuretic peptide (ANP),a key mediator of AVP secretion may also be involved. In addition to diminished normal baroreceptor response to increases in central pressure, the elderly also show more profuse secretion of ANP[44].

Elevated ANP may directly inhibit AVP secretion during head out water immersion (HOI)[44]. This hypothesis corresponds with earlier reports ofsuppressionofosmotically induced AVP secretion in both young and elderly subjects by exogenous ANP infusion. ANP inhibits AVP neuron activity[32] and elevated levels have been found in the aged[37], although not without opposing views[45]. Therefore, whether ANP exercisesconsiderable physiologic control over AVP release in the elderly warrants further investigation.

Regulation of AVP activity

Activation of V2R by AVP stimulates production of cyclic-AMP (cAMP) through activation of adenylyl cyclase. Subsequently, newly synthesizedand existing AQP2 water channels are transferred from intracellular storage vesicles to the apical plasma membrane of the renal collecting duct epithelial cells[46]. AQP2s form channels once they are inserted into the apical membrane. Water molecules are absorbed from the lumen of the collecting duct through these channels into the renal medullary interstitium driven by the medullary osmotic gradient. The resulting antidiuresisconcentrates urine to an osmolality corresponding to that at the tip of inner renal medulla[39].

BecauseAVP levels are typicallyhigh in the elderly, a pituitary secretory defect is unlikely the reason forreducedurine concentrating abilityobserved in this age group. Ratherit could be the result of a diminished normal renal responsivity to AVP. As demonstrated in murine models of aging[38], reducedV2R expression and/or decreased second messenger response to AVP-V2Rinteraction would both result in reduced maximal urine concentration. Lower basal AQP2 water channel expression includinga reduced capacityto upregulate AQP2 synthesis and mobilization despite adequate AVP releasewas observed in aging rats. Other animal models have indicatedreduced AVP-V2R signaling in the thick ascending limb and collecting ducts may also have adverse effects on creating the medullary concentrating gradient necessary for optimal urine concentration[47,48].

Presently, human studies on this subject are meager; hence, the existence of such age-related alterations in human kidneys remains unproven.In addition to age-related alterations in V2R expression and function, the clinical importance of sex-related changes have been elucidated.Again, animal models have shown a 2.6-, 1.7-fold greater mRNA, and V2R protein expression respectively in female rodents compared to theirmale counterparts[49]. This is because the V2R is located on the X-chromosome, in a position that is suggestive of partial inactivation of the V2R gene based on X-inactivation tests in heterozygous human fibroblasts[50]. The clinical utility of the V2R agonist desmopressin has also been documented[51,52], consistent with the studies in animal models. Elevated AVP levels in females may also be attributed to higher estrogen levels, which act on central estrogen receptors in the hypothalamus and structures of the lamina termnialis to stimulate AVP release. In addition, postmenopausal women on estrogen therapy show elevated basal plasma AVP, a lower osmotic

threshold for AVP secretion (280 vs 285 mOsmol/kgH$_2$O) and plasma volume expansion with associated water and sodium retention[53]. Taken together, theseobservationssuggest that increased V2R expression and estrogen-induced AVP release in females may cause greater responsiveness to the renal effects of exogenously administered AVP or desmopressin. This indicates the likelihood of similar increased sensitivity to endogenous AVP,more frequently resulting in hyponatremia from syndrome of inappropriate antidiuretic hormone secretion(SIADH)especially in elderly females who exhibit other factors that decrease water excretion.

Regulation of thirst

Stimulation of centralosmoreceptors produces impulses that are transmitted to the cerebral cortex resulting in thirst and water-seeking behavior[54]. The osmotic threshold for thirst is ~10 mOsm/kgH$_2$O (293.5 vs. 284.7) above that for AVP release[55]. Theproximity of the thresholds regulating thirst sensation and AVP release has important physiologic implications. Thus, slightosmolaralterations relative to an individual's osmotic set point induce changes first in AVP release and AVP-mediated alterations in renal water excretion. Agreater shift in plasmaosmolarconcentration triggers the more potent thirst response that either increases or decreases thirst and fluid intake in order to reestablish normal plasma osmolality. The result of this osmoregulatorymechanism is the initial unconscious increase in AVP-mediated urine concentration inresponse to increased plasma osmolality.Subsequently, the more potent behavioral response of water seeking is initiated if the increase in plasma osmolality becomes more profound.

Intrinsic thirstdefectsoccur with aging.Thirst or mouth dryness is increased in elderly males restricted from fluid intake for 24 hours. Despite significantlyhigher serum [Na$^+$] and plasma osmolality compared to their younger counterparts, such older men drank lesser amount of water[19]. Furthermore, when allowed to drink water ad libitum, elderly subjects drank less and could not adequately restore serum [Na$^+$] to pre-deprivation levels in contrast to young adults. These suggest a weakened response to osmotically induced thirst in the elderly[19,20]. Although a reduced thirst response may be present in the elderly,for equivalent degrees of thirst, rate of fluid intake in healthy elderly and young controls is similar. Therefore, the observed decrease in the degree of thirst for any given level of plasma osmolality in elderly subjects is perhaps due to a higher osmolar set point for thirst. This ultimatelyresults in a net decrease in the volume of fluid ingested[17]. In contrast, when hypertonic saline infusions and HOI are employed as the osmotic stimulants, the response to osmotic thirstwithout change in plasma volume is not substantiallyimpacted by normal aging[41,44,56]. Instead, plasma volume dependent baroreceptor-mediated thirst regulation is attenuated[56]. Volume dependent thirst control may indeed take precedence and maskcontrasting osmotic stimuli, at least in young people[57]. In a discreetly selected dehydrated cohort, HOI inducedgreatly inhibited thirst and fluid intake in young compared to elderly subjects[44]. Although net thirst was similar between the groups, a relatively higher baroreceptor-mediated inhibition of thirst in the young was suggested. These data further supports the hypothesis of intrinsic thirst defects that occur with normal aging.Although, the neural pathways involved are not well defined, dysfunctional brain thirst centers have been implicated in the age-associatedalterations in thirst[21,37].

Rather than aging per se, subclinical and cumulative brain defectsfrom age-associated illness may be actively involved in processes leading to decreased thirst perception. Elderly patients who experiencedseveral mildchronicillnesses may have been erroneouslyincluded in study populations previously described as "healthy". It is quite difficult to determine how the possible inclusion of such patients affectedinitial studies of aging and thirst perception[40,41]. However, more rigorous studies on carefully selected healthy non-institutionalizedelderly subjects appear to validate the earlierobservations of the existence of intrinsic neuroendocrine defects in thirst sensation with normal aging[37]. Despite reportsof attendant decrease in thirst with aging,the relationships betweenosmolar changes, volume status, and other related stimuli, and their interaction to mediate thirst in the elderlyisstillinadequately understood.

Integration of age-related alterations in thirst, AVP release andrenal function

The manifestations of the range of physiological alterations that occur with aging are appropriately described by the concept of "homeostatic inelasticity"[28]. Aging causes specificmodifications that affectnormal water and electrolyte balance at many discreet locations along the neuroendocrine-renal axis associated with themaintenance of normal fluidhomeostasis. The result of these alterations is diminished homeostatic reserve to accommodate both increases and decreases in fluid volume and osmolality in the elderly. The overall effect is increased susceptibility to iatrogenic and pathologic causes of alteredfluid homeostasis due to bothdecreased ability to preserve and acquire fluids. This leads to dehydration and hyperosmolality, while a decreased ability to excrete excess fluid leads tooverhydration and hypoosmolality/hyponatremia[7,37].

In the elderly, the primary threat to dehydration and hyperosmolality appears to be a reduced thirst sensation and consequently an altered drinking response to thirst. Thiscould be partly via loss of normal neural connections that transmit sensory impulse to higher cortical thirst centersfrom which the thirst response emanates. There is an age-associateddecreased sensitivity to osmolar stimulation resulting in a deficient thirst

response[21,37]. Thisisdue to an age-related resetting of the osmotic set point for thirst perception leading to a diminishedthirst response[17,21]. Most importantly, in the absence of an appropriate thirst response, the critical homeostaticmechanisms responsible for the conscious desire to replace lost body fluid, which is the only sufficient physiological means of correcting a hyperosmolar state is compromised.

Impaired GFR and subsequentreduction in maximal urine concentrating ability also contribute to the danger of age-related susceptibility to dehydration and hyperosmolality. Decreased renal function is a common and almost unavoidable feature of aging[30,58]. While the development of such deficit is somewhat not certain,distinguishing those at high risk of such defect is usually challenging.Because majority of otherwise "normal" elderly patients experience a decrease in renal function, whether such a change is unavoidable or not is still subject to debate. However, whenever there isa progressive thirst defectthe consequencesare obvious: decreased GFR causes decreased excretion of free water and encouragesaltered body water composition (hypoosmolality).

Additionally, corresponding age-acquired end organ insensitivity to the actions of AVP[59], which worsens renal water losses,has been demonstrated in animal models. Together, these effects plausiblytrigger the pathophysiological pathway leading to mild hyperosmolalityaggravated by disturbed thirst and drinking in response to the hyperosmolar stimulation.The ultimate result isheightened pathological degrees of hypernatremia and hyperosmolality.

The elderly are also prone to overhydration and hypoosmolalitydue to a paradoxical reduction in maximal water excretion[16,33]. The clinical consequences of this defect are profound in situations of unwitting or deliberateoverhydration. The elderly are at a greater risk of developing diseases that are related to volume overload such as congestive heart failure. Inadvertent iatrogenic overhydration from intravenous and enteral hydration therapy is also common in this age group due to reduced capacity to excrete excess fluid load.

In the elderly, the release and end organ effects of AVP are two interesting yet poorly understood aspects of water regulation. There is a growing consensus that basal AVP secretion is at least retained[39], andosmotically induced AVP secretion is increased during normal aging[41]. Therefore, AVP secretion isone endocrine responsethatincreasesinsteadof decrease with age. Although there may be reduced renal sensitivity to AVP, it is not completely eliminated. This may account for theincreasedrisk of idiopathic SIADH in the elderly[60].We hypothesize that the increased risk of SIADH in the elderly population is due to enhanced AVP release, inability to adequatelyinhibit AVP release during fluid intake[9], and an intrinsic reduced capacity to maximally excrete excess water[16,33]. Empirical proof of this hypothesis is still required, despite the prevalence of experimental data.

Excessive fluid intake may also contribute to the observed age-related increased risk of overhydration and hypoosmolality, though it is not the major cause of hypoosmolality in most elderly patients. Increase in plasma volume in the elderly does not stimulate the normal inhibition of thirst observed in young people[44]. Therefore, increased thirst response would exacerbate the effects of excessive renal water retention leading to more adverse consequences of hyponatremia and hypoosmolality.

II. Conclusion

When deprived offluidor confronted with a hyperosmotic or hypovolemic stimulus, elderly peopleexperience a reduced perception of thirst and fluid intake. Disturbed water balance is a common feature in elderly people. They exhibit an impaired capacity to restore and maintain fluid balance e.g., expansion of plasma volume in response to dehydration.The consequent hypovolemia appears to be inducedby decreased thirst sensation and baroreceptor sensitivity. This defective osmoregulatory capacity could be attributed to dysfunctional thirst brain centers and resetting of the osmotic operating set point for thirst sensation, which requires a higher and possibly deleterious degree of hyperosmolality to stimulate thirst and drinking. Additionally, there is reduced oropharyngeal-induced inhibition of AVP release after drinking and the kidneys gradually become unresponsive to even higher levels of plasma AVP, thereby either leading to volume overload or reducing the body's water retention capacity. These defects combine to increase the susceptibility of elderly people to disturbances in water and electrolyte balance, which manifest as dehydration/hypovolemia and hypernatremia, or overhydration and hyponatremia.

Competing interest
None declared.

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