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*Minireview*

# Thirst perception, drinking, arginine vasopressin activity and associated neurohumoral factors

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**ABSTRACT**
Thirst, drinking, and arginine vasopressin (AVP) secretion are essential correlated osmoregulatory mechanisms that are crucial for normal physiologic function and overall survival of humans. These homeostatic mechanisms require or are operated via complex central and peripheral neural connections with influence from other peptides and hormones including angiotensin II, atrial natriuretic peptide and relaxin. The effectiveness of these mechanisms declines with age, and the consequences manifest during hyperosmotic challenges as decreased thirst and urine concentrating ability. The neurohumoral cascades involved in the physiological response to alterations in fluid and electrolyte balance are examined.



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## INTRODUCTION

Thirst is a subjective sensation that triggers the conscious need for humans and animals to drink water. It is a major osmoregulatory mechanism involved in the maintenance of the body's hydromineral balance and therefore, extremely necessary for normal physiologic functions and survival. The desire to ingest fluids emerges from several factors including cultural, habitual and psychogenic triggers. Drinking may also arise as a regulatory response to reductions in body fluid content e.g. decreased extracellular fluid (ECF) volume (hypovolemia) or increased osmolality (hypertonicity). Drinking patterns are also influenced by plasma levels of certain hormones involved in hydromineral metabolism such as angiotensin II (A-II), arginine vasopressin (AVP), oxytocin, atrial natriuretic peptide (ANP), relaxin and aldosterone (Antunes-Rodrigues *et al*., 2004; Amabebe *et al.*, 2017; Begg, 2017). This review examines the neurohumoral mechanisms involved in the regulation of human's desire to drink water or fluid (thirst). Both the extracellular and intracellular compartments contribute to total body water loss but to varying degrees. Concurrent loss of NaCl (the major solute of the ECF) and water results in proportionately more ECF depletion than water loss alone. This is obvious in conditions of vomiting and diarrhoea where fluid is lost from the gastrointestinal tract. Loss of isotonic fluid usually occurs from the ECF compartment. However, an osmotic depletion of water from the intracellular fluid (ICF) compartment into the ECF leading to volume expansion occurs when hypertonic fluid is added to the extracellular compartment (McKinley and Johnson, 2004).

Several adaptive regulatory responses are employed during volume depletion of either the ICF or ECF. These responses which include activation of the renin-angiotensin system (RAS), AVP release, sympathetic activation, and increased renal sodium and water reabsorption, have the adaptive tendency of curtailing alterations in volume and composition of body fluid. Although of undoubted benefit to the animal, these mechanisms do not completely restore body fluids to the original state. Consequently, restoration of fluid deficit through drinking becomes inevitable. Therefore, thirst, which provides the conscious desire to acquire and ingest water, is a vital component of the closely regulated physiological mechanisms that maintain water and electrolyte homeostasis (Amabebe *et al.* 2017; Begg, 2017; McKinley and Johnson, 2004; Stachenfeld, 2014).

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*Osmoregulatory thirst and cellular dehydration*

As little as 1–2% increase in the effective plasma osmotic pressure stimulates thirst in mammals (Fitzsimons, 1998; McKinley and Johnson, 2004), and this relationship is directly proportional, i.e. thirst perception increase with increase in plasma osmolality (Ramsay and Thrasher, 1991). When the plasma osmolality (280–295 mOsmol/kg$H_2O$) is increased experimentally by increasing the concentration of solutes such as NaCl or sucrose that do not readily permeate cell membranes, thirst is stimulated. In contrast, systemic infusion of hypertonic solutions that more readily permeate nerve cell membranes (such as urea or D-glucose solutions) is relatively less effective in stimulating thirst (Fitzsimons, 1979; McKinley *et al.*, 1978; Zerbe and Robertson, 1983). In the former case, a transmembrane osmotic gradient is created resulting in cellular dehydration as water moves out of the cells by osmosis whereas cellular dehydration does not occur with the permeating solutes.

Specialized sensory brain cells respond to cellular osmolar changes to stimulate neural mechanisms that generate thirst and are termed osmoreceptors (Fitzsimons, 1979; Zerbe and Robertson, 1983). Although some osmoreceptors are located in the gastrointestinal tract, liver and kidneys, a significant amount of osmoreceptive neurons are found in the brain's preoptic/hypothalamic region. The likelihood of a more rostral tissue in the anterior wall of the third ventricle as the location of osmotic thirst-mediating sensors in relation to plasma and cerebrospinal fluid (CSF) $Na^+$ concentration was eventually proposed (Andersson, 1978).

*Neural control of osmotically-induced thirst*

Cerebral osmoreceptors capable of detecting body fluid osmolar changes and subsequently mediating thirst and AVP release are present in brain regions without the normal blood-brain barrier (BBB) (McKinley *et al.*, 1978). The neurons in the circumventricular organs (CVOs) i.e. the vascular organ of the lamina terminalis (OVLT) and subfornical organ (SFO) that lack BBB are confirmed locations of highly specialised and sensitive osmoreceptors (Fig. 1). The CVOs are located in the lamina terminalis, which forms the anterior wall of the third ventricle (Andersson, 1978; Antunes-Rodrigues *et al.*, 2004; Fitzsimons, 1998; Johnson *et al.*, 1996; McKinley *et al.*, 2003; McKinley *et al.*, 2004), and well positioned (especially the SFO) to mediate both blood-borne (e.g. A-II, $Na^+$) and central nervous system (CNS, e.g. renin, A-II) osmoregulatory signals (Coble *et al.*, 2015).

In addition, osmoreceptors have been identified in the median preoptic nucleus (MnPO), an integral part of the anteroventral third ventricle (AV3V) region, situated longitudinally between the two CVOs in the lamina terminalis but within the BBB. It is also activated by osmotic stimuli due to the presence of angiotensin type 1 receptor (AT1R) - a G-protein coupled receptor (Johnson *et al.*, 1996; McKinley and Johnson, 2004). The MnPO can initiate thirst in response to both osmotic and endocrine stimulations relayed to it by projections from the SFO and OVLT (Fitzsimons, 1976; Johnson *et al.*, 1996). A central angiotensinergic pathway is involved in osmoregulatory drinking as the MnPO receives descending angiotensinogernic signals (synapses) from the SFO (Johnson *et al.*, 1996).

The MnPO receives osmotically-induced afferent neural inputs from neurons in both CVOs and integrate these signals with volumetrically-induced visceral sensory afferents from the hindbrain structures (Fig. 1). In addition, the desire to drinking is reduced but not abolished even after combined ablation of both CVOs with a considerable part of the MnPO intact. This suggests that osmoreceptive neurons may also be found in the MnPO and/or osmotic signals from other parts of the brain, e.g., the nucleus tractus solitaries (NTS) and area postrema (AP), or within the body (e.g., hepatic portal system) may be integrated in this region (McKinley and Johnson, 2004).

The lamina terminalis is clearly the brain region where blood-borne stimuli including hypertonicity or hormones (e.g., A-II, ANP and relaxin), exert their dipsogenic action. Subsequent efferent neural pathways project from the lamina terminalis to other brain regions including the anterior cingulate and insular cortices to initiate and modify the thirst sensation and drinking (McKinley *et al*., 2003; McKinley *et al*., 2004; Stachenfeld, 2014). Drinking rapidly decreased the neural activities in these areas (McKinley *et al*., 2003). The lamina terminalis also sends neural inputs to the lateral hypothalamic area (LHA), paraventricular nucleus (PVN) and supraoptic nucleus (SON), which are believed to participate in generation of thirst (Fig. 1) (McKinley *et al*., 2003; McKinley *et al*., 2004; Stachenfeld, 2014).

*Hypovolemic thirst*

ECF can be depleted selectively without concomitant reduction in ICF. The ECF is depleted pathologically by excessive bleeding (haemorrhage), increased sodium and water excretion or accumulation of fluid in the interstitium or body cavities (oedema); and experimentally by fluid restriction, furosemide treatment and intraperitoneal polyethylene glycol injection (Coble *et al.*, 2015).

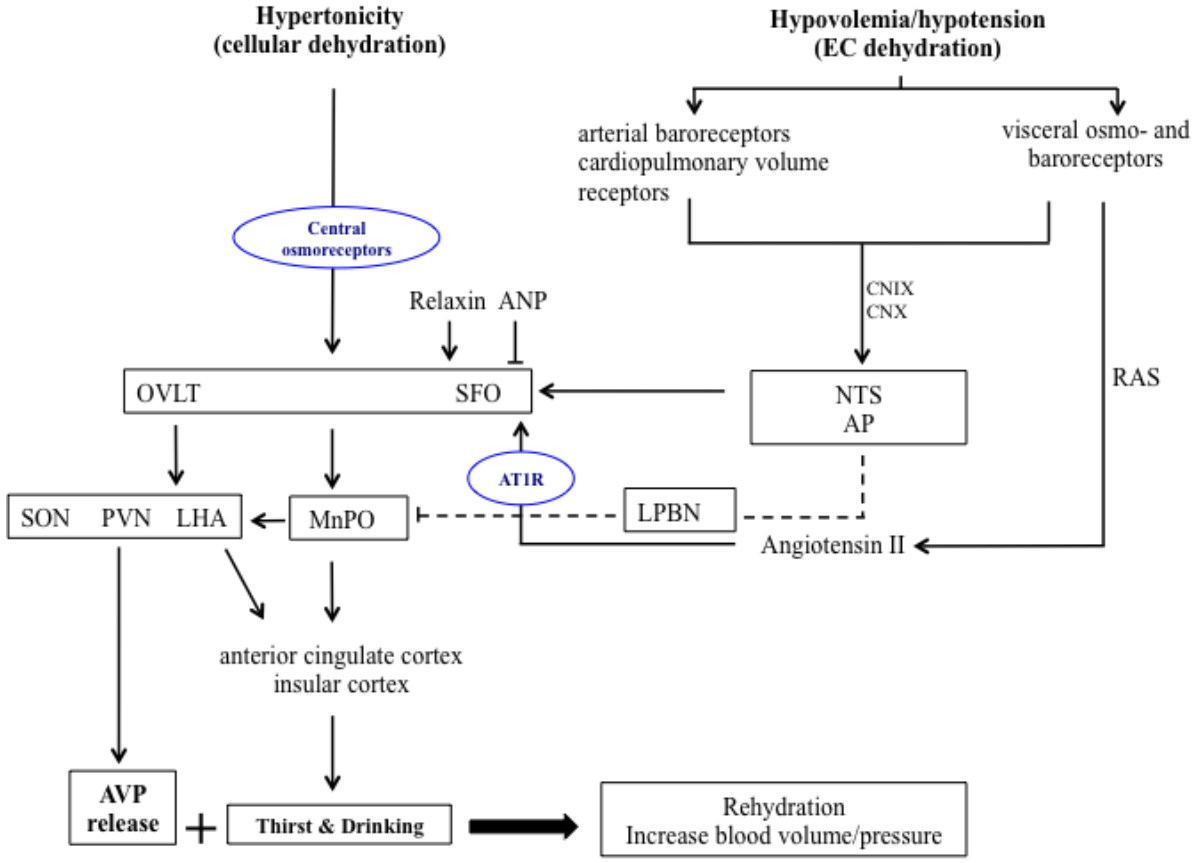


**Fig. 1.** Osmoregulatory neuroendocrine control of thirst and arginine vasopressin secretion. Osmoreceptors in the subfornical organ (SFO) and vascular organ of the lamina terminalis (OVLT) respond to cellular dehydration by stimulating thirst, drinking and arginine vasopressin (AVP) secretion via signals to the median preoptic nucleus (MnPO, angiotensinergic afferents), lateral hypothalamic area (LHA), and the supraoptic (SON) and paraventricular (PVN) nuclei. Similarly, extracellular (EC) dehydration is detected by peripheral baro- and visceral osmoreceptors and transmitted via the glossopharyngeal (CNIX) and vagus (CNX) nerves to the nucleus tractus solitarius (NTS) and area postrema (AP). These hindbrain nuclei stimulate drinking and water retention via connection with neurons of the lamina terminalis and hypothalamus. They can also send inhibitory signals through the lateral parabrachial nucleus (LPBN) to prevent excessive drinking and volume expansion after stimulation of specific thirst pathways. In addition, in response to decreased blood volume and pressure, the renin-angiotensin system (RAS) is activated and angiotensin II is produced which stimulates thirst by acting on angiotensin type 1 receptor (AT1R) on the circumventricular organs (CVOs). Relaxin has a similar dipsogenic effect on the CVOs; while atrial natriuretic peptide (ANP) is inhibitory. The eventual generation of thirst and drinking is also modified by inputs from higher centres including the anterior cingulate and insular cortices. *Adapted from: Amabebe et al., 2017 and McKinley and Johnson, 2004.*

The body responds to the resultant hypovolemia or extracellular dehydration by activating components of the neuroendocrine systems to mitigate the consequences of decreased cardiac output and declining blood pressure. These include activation of the sympathetic nervous system, which increases vascular tone, venous return, cardiac output, and reduces renal sodium and water excretion. Also, there is increase in plasma AVP, central and peripheral RAS components, catecholamines, adrenocorticotrophic hormone (ACTH), and glucocorticoids (cortisol) that stimulate various mechanisms to preserve sodium and water or redistribute blood and interstitial (ISF) to maintain adequate supply to vital organs such as the brain and heart. As these adaptive mechanisms do not completely replenish the body's hydromineral deficits, absolute correction involving the initiation of behaviours associated with obtaining and ingesting water (drinking) and sodium (salt appetite) becomes inevitable. The initiation of behaviours to correct ECF volume deficits is similar to the sympathetic and endocrine responses to extracellular dehydration. Both effector systems require information reflecting the status of blood and/or ISF volumes to be integrated in

the CNS through both endocrine and visceral afferent pathways (McKinley and Johnson, 2004; McKinley *et al*., 2006).

*Angiotensin-induced thirst*

Hypovolemia results in reduced renal perfusion and increased sympathetic stimulation of the juxtaglomerular cells of the kidney (Fitzsimons, 1998). This leads to the production of renin (angiotensinogenase) and the synthesis of its effector peptide, A-II from angiotensinogen and angiotensin I. Systemic administration of both the renin and A-II generate drinking in satiated animals. Similar to osmotically-induced drinking, A-II-induced thirst requires the nuclei of the lamina terminalis particularly the SFO that has high density of ATIR (Sakai *et al.,* 2007) for initial CNS processing and integration of this peripherally derived impulse (Johnson *et al*., 1996).

A more profound dipsogenic effect is observed by central (brain) injection of A-II into the lateral ventricle or SFO via interaction with ATIR (Coble *et al.,* 2014a; Coble *et al.,* 2014b). Components of the RAS such as renin, angiotensinogen, angiotensin I (A-I) and A-II are also produced by the SFO in response to increase in osmolar concentration of CSF, a protein-free derivative of plasma. SFO-generated A-II is sufficient to initiate drinking via protein kinase-Cα independently. However, the overall effect is determined by the expression levels of A-II receptors on the SFO and MnPO (Agassandian *et al.,* 2017; Coble *et al.,* 2014a; Coble *et al.,* 2014b; Sakai *et al.,* 2007). Circulating A-II acts on forebrain CVOs as an endocrine factor; and it activates angiotensinergic pathways projecting to central integrative regions in an autocrine or paracrine fashion (Johnson and Thunhorst, 1997; Lavoie and Sigmund, 2003) e.g. as the neurotransmitter for descending nerve impulses from the SFO to the MnPO (McKinley and Johnson, 2004).

The MnPO has high concentration of AT1R but unlike other structures of the lamina terminalis, it is not exposed to circulating A-II as it is inside the BBB (Fig. 1). Hence, its activities are influenced by angiotensinergic afferent neural inputs from the CVOs (McKinley *et al*., 2006). There are also ATIRs on postsynaptic neurons in the SON and PVN, which receive afferents from the SFO (Agassandian *et al.,* 2017; Gonzalez *et al.,* 2012). Osmotic stimulation also increases angiotensin-(1-7) A-(1-7) production. A-(1-7) is synthesised by type 2 angiotensin converting enzyme from A-II or A-I, and acts through MAS receptors found in forebrain structures (e.g. diencephalon and cerebral ventricles). It increases osmotically-induced water intake but not at basal conditions (dos-Santos *et al.,* 2017). Although the systemic and central RAS are distinct, their roles in the maintenance of body fluid balance are complementary. Further reading on the central RAS can be found in Antunes-Rodrigues *et al*. 2004.

*Thirst perception and estimated plasma AVP concentration*

Thirst is a "generalized deep-seated feeling of a desire for water" (Robertson, 1984). Thirst is distinct from drinking which is the actual fluid intake. Drinking is a behavioural mechanism influenced by several factors including age, personal, environmental and cultural factors. Oral ingestion of distilled water or hypertonic fluid and overnight 18-hour water deprivation to induce dehydration show a consistent thirst perception in man (Obika *et. al.,* 2009; Obika *et al.,* 2013; Obika and Ozoene, 2014). Thirst sensation is stimulated by increase in plasma osmolality (hypertonicity, dehydration), decrease in blood volume and pressure (hypovolemia and hypotension), stimulation of the RAS and increase in central and circulating A-II and dryness of mouth (Baylis and Ball, 2013). Hence, thirst perception is a subjective feeling of the need to drink water.

Attempts have been made to assess and relate thirst perception (TP) and plasma AVP concentration. Experimentally, acute changes in thirst are measured using a geometric rating scale called the Visual Analogue Scale (VAS) (Thompson and Campbell, 1997; Thompson *et. al.,* 1991; Takamata *et. al.,* 1994). This is obtained by asking study participants to indicate how thirsty they are by making a mark across an uncalibrated 10 cm line with it ends marked "very thirsty" and "not thirsty". It has been shown that TP ratings so obtained correlate with plasma AVP concentration and plasma osmolality in various physiological states in man (Amabebe *et al.,* 2012; Obika *et al.,* 2013; Obika and Ozoene, 2014).

*Hindbrain regulation of thirst*

To balance the neurohumoral signals that facilitate drinking, there are both stimulatory and inhibitory inputs acting on or through the hindbrain structures including the AP, medial NTS and lateral parabrachial nucleus (LPBN) to the MnPO (Fig. 1) (McKinley and Johnson, 2004; McKinley *et al*., 2006). Both arterial baroreceptors and volume cardiopulmonary receptors are capable of transmitting inhibitory thirst signals from the great veins and pulmonary arteries. Mechanical stretching of the arterial baroreceptors and

cardiopulmonary receptors attenuates experimentally induced drinking, while drinking is stimulated when reduced venous return to the heart is detected by both set of receptors (Fitzsimons and Moore-Gillion, 1980; Thrasher et al., 1982). Similarly, denervation of either the cardiopulmonary or sinoaortic baroreceptors significantly attenuates thirst while denervation of both sets of receptors completely abolishes drinking even with elevated circulating levels of A-II (Quillen et al., 1988).

Afferent signals from the cardiopulmonary and arterial baroreceptors are transmitted to the brain by the glossopharyngeal (IX) and vagus (X) cranial nerves, with most of these nerves terminating in the NTS (McKinley and Johnson, 2004) (Fig. 1). Lesions of the AP and NTS, result in exaggerated response to thirst-inducing hypovolemic stimulations (Edwards and Ritter, 1982; Wang and Edwards, 1997). These effects are plausibly due to loss of inhibitory input from the baroreceptors that are integrated in the NTS from where they are relayed to the forebrain structures via the LPBN (McKinley and Johnson, 2004; McKinley and Johnson, 2006). It is also possible that the AP exercise some form of inhibitory control over thirst induced by systemic blood volume expansion or acute increase in blood pressure (McKinley and Johnson, 2004) (Fig. 1). Also, atrial natriuretic peptide (ANP), a peptide hormone released from the cardiac atria inhibits thirst sensation and drinking in response to hypervolemia and hypertension by acting on the SFO (Antunes-Rodrigues *et al*., 1985; Antunes-Rodrigues *et al*., 2004). The action of ANP is discussed in more details below.

Because the AP-NTS region contains neuronal projections to the LPBN (McKinley and Johnson, 2004), lesions of the LPBN also produce excessive drinking to mediators of extracellular dehydration (Johnson and Thunhorst, 1997). A significant portion of the efferents from the AP-NTS to the LPBN contain serotonin (5-HT) (McKinley and Johnson, 2004), and bilateral injections of a non-selective 5-HT receptor antagonist, promote drinking and salt appetite in response to several thirst stimuli. In essence, the AP, NTS, and LPBN form a hindbrain inhibitory circuit that integrates osmoregulatory neuroendocrine signals derived from activation of peripheral visceral and baroreceptors and project same to the forebrain structures including the lamina terminalis and various hypothalamic nuclei that are associated with the thirst response (McKinley and Johnson, 2004). In turn, the LPBN and NTS receive reciprocal connections from many of the forebrain structures. Thirst and drinking behaviours are controlled within this visceral-neural network with projections from both excitatory and inhibitory endocrine and visceral afferent nerves.

Furthermore, thirst is stimulated by oral or intragastric sodium loading detected by oropharyngeal (Robertson, 1984; Obika *et al.*, 2014) and abdominal viscera receptors, such as gastric, hepatic portal and renal osmoreceptors, before any substantial increase in systemic plasma osmolality (Stricker *et. al.*, 2002). The response is promoted by simultaneous activation of the central osmoreceptors by dehydration and salt loading. Other integrative sites related to thirst and fluid intake includes the middle dorsal and median raphe nuclei (inhibitory), lateral preoptic region (osmoreception) and the septal region (both excitatory and inhibitory) (McKinley *et al.*, 2006).

*Other thirst regulating hormones*

Several other peptide and steroid hormones influence thirst. Some peptides e.g., relaxin (Baylis and Ball, 2013) and orexin (Hurley and Johnson, 2014) stimulate water intake, whereas others e.g., glucagon-like peptide-1 inhibit drinking (McKay *et al.*, 2014). Like the ANP, relaxin acts on the SFO of the lamina terminalis though in an antagonistic manner (Antunes-Rodrigues *et al*., 2004; McKinley and Johnson, 2004).

*Arginine vasopressin (AVP)*

**AVP** (antidiuretic hormone, ADH) is a nine amino acids peptide with a disulphide bridge linking the cysteine residues at positions 1 and 6 (Baylis and Ball, 2013). It is similar to oxytocin, differing only by two amino acids in position 3 – phe, and 8 – Arg. AVP is produced by the SON and PVN of the hypothalamus (Baylis and Ball, 2013; Amabebe *et al.*, 2017). Smaller amounts are also produced locally in many tissues outside the hypothalamus. As a result AVP also perform autocrine and paracrine functions in addition to its endocrine effect. The hypothalamic vasopressinergic magnocellular neurons containing AVP terminate in the posterior pituitary (neurohypophysis) where AVP is stored prior to secretion. Some vasopressinergic neurons also innervate other areas of brain and spinal cord enabling AVP to exert both systemic and local actions in the CNS (Mavani *et al*., 2015), e.g. AVP exerts is role in the regulation of ACTH release via the vasopressinergic parvocellular neurons that project to the hypophyseal-portal bed of the anterior pituitary (adenohypophysis) and secrete both AVP and corticotropin-releasing hormone (CRH) (Baylis and Ball, 2013).

The most sensitive stimulus for AVP secretion is an increase in plasma osmolality. Although AVP release is also stimulated by hypovolemia and hypotension, these stimuli require greater (5-10%) variations than changes in plasma osmolality (Robertson, 1975; Baylis and Ball, 2013). Increase in plasma osmolality produce a linear increase in AVP concentration (Baylis and Ball, 2013), while drinking abolishes the relationship between plasma osmolality and AVP release. AVP is central to the integrated neuroendocrine pathway involved in the physiological and pathophysiological adaptations to hypovolemia. A-II and relaxin stimulate AVP magnocellular neurons in the hypothalamus while ANP inhibits AVP neuron activity (Baylis and Ball, 2013).

The physiological concentration of plasma AVP is less than 2 pg/ml., making it quite difficult to measure. Being a small peptide, it is readily filtered through the glomeruli and excreted unchanged in the urine because it is not metabolised by the kidney. Copeptin, a more stable peptide with longer half-life and secreted along with AVP in equimolar amounts is used as a surrogate marker for estimating AVP secretion (Andersen *et al*., 1990). It is actually derived from the C-terminus of pre-pro-hormone of AVP, neurophysin II and copeptin and secreted by the hypothalamic PVN and SON (Acher *et al.* 2002). Copeptin levels correlate with AVP concentrations (Mavani *et al.*, 2015).

AVP acts mainly via its tissue-specific G protein-coupled receptors located in the CNS as well as peripheral organs (Holmes *et al*., 2003). These receptors subtypes include V1a, V1b (V3), and V2. V1a receptors are present in several tissues including the blood vessels, brain, adipose tissue, adrenal cortex, uterine smooth muscle cells, liver, cardiac myocytes, osteoblast and osteoclast. V1b receptors presently known as V3 receptors are mainly found in adenohypophysis, adrenal medulla, pancreatic islet cells of Langerhans, and white adipose tissue. V2 receptors that mediate the well-known AVP-stimulated water reabsorption from the kidneys (antidiuresis) (Holmes *et al*., 2003) are located in the basolateral membrane of the renal collecting duct, alveolar epithelium, vascular smooth muscle cell, osteoblast and osteoclast (Holmes *et al*., 2003; Koshimizu *et al*., 2012).

As a result of the widespread distribution of its receptor subtypes both centrally and peripherally, AVP mediates several other profound non-pressor and non-antidiuretic actions (Mavani *et al*., 2015). These actions include bone formation, glycolysis, lipid metabolism, diabetes, metabolic syndrome, infection, inflammation, cellular proliferation, cognition, social and emotional behaviour, pain, aging, hypothalamic-pituitary-adrenal axis and chronic kidney disease. These effects of AVP are reviewed in detail by (Mavani *et al*., 2015).

The effects of osmotic stimuli (hypertonic NaCl infusion) on thirst perception (TP) and plasma AVP concentration ($P_{AVP}$) at various times in healthy adults was examined and expressed mathematically in relation to plasma osmolality ($P_{osm}$) as:

$P_{AVP} = 1.48 (P_{osm} - 284.7)$ and,

$TP = 9.06 (P_{osm} - 293.5)$ (Robertson, 1984)

The osmotic threshold for the onset of thirst was 293.5 $mOsm/kgH_2O$, ~10 $mOsm/kgH_2O$ greater than the osmotic threshold for AVP release. This implies thirst sensation will not often be felt when plasma osmolality is within the physiological range of 280 - 295 $mOsm/Kg\ H_2O$ (Robertson, 1984), at least until after the antidiuretic effect of AVP is exhausted.

Thirst is primarily stimulated by an increase in plasma osmolality, which is regulated by changes in blood $Na^+$ concentration. Oral hypertonic fluid ingestion and fluid restriction consistently produce an increase in thirst perception (Obika *et. al.,* 2009; Obika *et al.,* 2013). However, voluntary ingestion of salt loads e.g. salted nuts containing 3.5 or 4.4 g NaCl for men and 1.9 or 3.7 g for women, did not increase thirst or drinking after 2 hours (Micah, 2014). This is contrary to the widely reported relationship between ingestion of hypertonic solution, dehydration and increase in thirst perception (Barney, 1997; Kenefick *et al*., 2006; Obika *et al*., 2009; Obika *et al*., 2013; Obika *et al*., 2014; Riebe *et al*., 1997). Using nuts as a means of experimental salt loading highlighted methodological concerns (Micah, 2014), and warrants further investigation.

Thirst perception ratings obtained by the VAS could be related to plasma AVP concentrations in normal subjects (Igbokwe and Obika, 2008). Plasma AVP concentration measured by enzyme-linked immunosorbent assay (ELISA) is also clearly related to thirst perception in humans (Amabebe *et al*., 2012). Furthermore, indirect estimation of AVP levels from thirst perception ratings and plasma osmolality values in euhydrate, dehydrated and rehydrated individuals have been reported (Obika and Ozoene, 2014). Therefore, thirst and AVP mechanisms operate in a complementary manner to regulate body fluid volume and osmolar concentration. Alterations of the normal secretion or function of AVP can result in profound disturbances in hydromineral homeostasis (Mckenna

and Thompson, 1998). Plasma AVP measurement is used clinically for diagnosis of conditions such as syndrome of inappropriate ADH secretion (SIADH), diabetes insipidus, ectopic AVP production and psychogenic water intoxication (Haynes, 1958).

*Atrial natriuretic peptide* (ANP)
ANP is synthesized and released by cardiac myocytes in the wall of the atria of the heart. It prevents over-expansion of ECF volume by increasing renal $Na^+$ excretion (natriuresis). Increase in ECF or blood volume cause mechanical stretching of the atria and eventual secretion of ANP. Endothelin stimulates, while nitric oxide inhibits ANP secretion (Dietz, 2005). ANP has a potent inhibitory action on thirst sensation, drinking (Burrell *et al.,* 1992), and AVP secretion (Baylis and Ball, 2013). Interestingly, this antidipsogenic action appears to be directed primarily against A-II-stimulated drinking, although it also inhibits osmotically-induced thirst e.g. injection of ANP into the SFO inhibits A-II-stimulated thirst and water intake (Ehlich and Fitts, 1990), via its receptors in the CVOs of the lamina terminalis.

*Relaxin*
Relaxin is synthesized and secreted in the female by the corpus luteum of the ovary, and during pregnancy by the gestational tissues including the placenta, chorion and decidua. It is also produced in the prostate and present in seminal fluid in males (MacLennan, 1991). Relaxin influences body fluid and electrolyte balance by stimulating AVP secretion and water intake by acting centrally or systemically. Significant amounts of relaxin receptors are found in both the SFO and OVLT, and were presumed to be the sites of its dipsogenic action (Osheroff and Phillips, 1991). However, subsequent ablation of the SFO, sparing the OVLT, abolished water intake in response to *i.v.* relaxin, indicating that the SFO is the preferred site of action of blood-borne relaxin (McKinley et al., 2006). A-II and relaxin may act synergistically to enhance thirst during pregnancy because circulating A-II potentiates the dipsogenic action of *i.v.* relaxin (Sinnayah et al., 1999; McKinley et al., 2006).

In pregnancy, plasma osmolality decreases by ~10 $mOsm/kgH_2O$ in some species, including humans (Lindheimer and Davison, 1995; Amabebe *et al.,* 2017). In such instance, thirst perception should diminish. However, water intake remains unchanged or may even increase in some instances despite the prevailing plasma hypotonicity. This is attributable to the dipsogenic effect of high level of relaxin during pregnancy. It is also suggested that there is a corresponding resetting of the central osmostat (osmotic thresholds) regulating thirst and AVP secretion plausibly due to central actions of relaxin and oestrogen (Stachenfeld, 2014). A new steady state is eventually established and the volume-determined AVP release mechanism is adapted to suit pregnancy needs (increased fluid retention), which is maintained until birth (Lindheimer and Davison, 1995). The resultant expanded blood volume is consequently acknowledged as normal (Barron, 1987). This transient hemodilution could be in response to rising oestrogen levels (Stachenfeld, 2014), however, this phenomenon requires further evaluation.

*Oestrogen*
The luteal phase of the menstrual cycle is characterised by high levels of oestrogen, progesterone and plasma RAS activity. The RAS components are also elevated in young women on oestrogen and progesterone contraceptive pills and a similar effect is seen in postmenopausal women receiving oral oestrogen replacement therapy. Oestrogen upregulates the gene expression of angiotensinogen in the liver and brain (Boschitsch, *et al.*, 2010; Greenland and Sernia, 2004; Kuroski de Bold, 1999; Stachenfeld, 2008, Stachenfeld, 2014).
Contrastingly, oestrogen also downregulates RAS activity by indirectly decreasing plasma renin concentration via a decrease in circulating adrenaline and noradrenaline (Amabebe and Robert, 2017; Schunkert *et al.*, 1997). It also attenuates RAS activity by inhibiting ATIR and angiotensin converting enzyme (ACE) expression in thirst-associated brain centres such as the SFO (Dean *et al.*, 2006; Gallagher *et al.*, 199; Kisley *et al.*, 1999a; Krause *et al.*, 2006). Oestrogen replacement decreases spontaneous and A-II-induced water intake and salt appetite (Kisley *et al.*, 1999b; Mecawi et al., 2007, Mecawi et al., 2008). Therefore, A-II, blood pressure and plausibly thirst sensation are usually maintained at normal levels during the luteal phase of the menstrual cycle and other high oestrogen states despite an increase in angiotensinogen levels (Amabebe and Robert, 2017; Boschitsch, *et al.*, 2010; Greenland and Sernia, 2004; Oelkers, 1996). Also, we have recently observed a non-significant increase in thirst during the follicular phase of the menstrual cycle until ovulation and a decrease thereafter (Nzoputam *et al.*, under review). Additionally, in rats, cerebral angiotensinogen concentrations are highest in the oestrus phase and lowest in the metoestrus phase corresponding with the cyclical fluctuations in oestrogen (Greenland and

Sernia, 2004). Whether oestrogen exerts its antidipsogenic effects during early follicular phase in humans remains unresolved.

Both ATIR and oestrogen receptors (ERα) are present in the SFO of the lamina terminalis (Fig. 2). Oestrogen inhibits the binding of A-II to AT1R and reduces the expression of AT1R in the SFO (Fujisawa *et al.*, 2001; Kisley *et al.*, 1999a; Rosas-Arellano *et al.*, 1999; Tanaka *et al.*, 2001). It reduces the sensitivity of the SFO and possibly other structures of the lamina terminalis to A-II stimulation, thereby attenuating the thirst and drinking responses (Fig. 2).

The anti-dipsogenic and anti-natriorexigenic effects of oestrogen are also possibly mediated via ERs on multiple hypothalamic nuclei including the SON, PVN, medial preoptic area (mPOA), LHA; and other regions of the lamina terminalis i.e. OVLT and MnPO. These brain areas including the SFO differentially express ERs (Table 1) (Amabebe and Robert, 2017; Santollo and Daniels, 2015).

In addition, oestrogen replacement in postmenopausal women increases circulating ANP. ANP inhibits the central action of A-II on the SFO and downregulates renin and ACE activities as well as AT1R expression and binding (Amabebe and Robert, 2017; Maffei *et al.*, 2001).

**Table 1:** Distribution of oestrogen receptors in specific hypothalamic nuclei and the lamina terminalis

| **Brain nuclei** | **Receptor subtype** |
|---|---|
| Subfornical organ | ERα |
| Vascular organ of the lamina terminalis | ERα, ERβ |
| Median preoptic nucleus | ERα, ERβ |
| Lateral hypothalamus | ERα, ERβ |
| Medial preoptic area | ERα, ERβ |
| Arcuate nucleus | ERα, ERβ |
| Supraoptic nucleus | ERα, GPER-1 |
| Paraventricular nucleus | ERα, GPER-1 |
| Nucleus tractus solitaries | ERα, ERβ, GPER-1 |
| Dorsal raphe | ERβ |

*ER*: oestrogen receptor; *GPER*: G protein-coupled oestrogen receptor 1.

*Adapted from: Amabebe and Robert, 2017.*

*Age-related osmoregulatory changes*

There is a characteristic reduction in homeostatic capacity with aging (Rolls and Philip, 1990). Though hydromineral balance is usually adequate in healthy independent older adults, in conditions of hypovolemia and hyperosmolality such as during fluid restriction, hypertonic saline infusion, exercise in warm climates or thermal dehydration, they exhibit decreased thirst and fluid intake (Beggs, 2017; Kenney and Chiu, 2001; Rolls and Philip, 1990) (Fig. 3).

The elderly are more susceptible to dysfunctional fluid and electrolyte balance, which manifest usually as dehydration (Fig. 3), and sometimes water overload and hyponatremia, due to several age-related osmoregulatory neuroendocrine changes associated with water intake and excretion (Begg, 2017; Rolls and Philip, 1990). Some of the age-related endocrine changes include decreased RAS activity and elevated circulating ANP and AVP levels (Begg, 2017) (Fig. 3). Complete restoration of fluid balance after osmotic stimulation is slower than in younger adults (Kenney and Chiu, 2001).

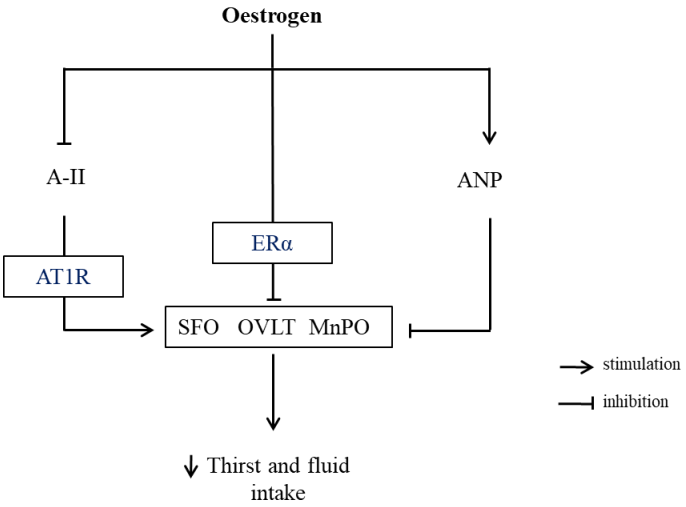


**Fig. 2.** Anti-dipsogenic action of oestrogen. Oestrogen decreases the expression of angiotensin II (A-II) and angiotensin type I receptors (AT1R) on the subfornical organ (SFO), vascular organ of the lamina terminalis (OVLT), and median preoptic nucleus (MnPO), and inhibits the binding of A-II to AT1R. It also increases the release of atrial natriuretic peptide (ANP) and directly inhibits oestrogen receptors (ERα) on the structures of the lamina terminalis. ANP antagonises the action of A-II on the SFO. Consequently, thirst sensation and fluid intake are reduced. These effects can also be seen in postmenopausal women receiving exogenous oestrogen. *Adapted from: Amabebe and Robert, 2017.*

The elderly show impaired response to dehydration/hypertonicity-induced reduction in ECF volume. This age-related deficient osmoregulatory adaptation is attributed to decreased sensitivity of the low and high-pressure baroreceptors (Philip *et al.*, 1993), and/or dysfunctional thirst integrating brain centres (Begg, 2017). Their kidneys also have inadequate water retention capacity secondary to relative resistance to AVP stimulation (Philip *et al.*, 1993). Ultimately, there is reduction in their ability to

concentrate urine (Begg, 2017) (Fig. 3). Although, these observations appear convincing, there are still studies with contrasting opinions i.e. greater thirst sensation in the elderly compared to younger study participants secondary to hyperosmotic stimulation.

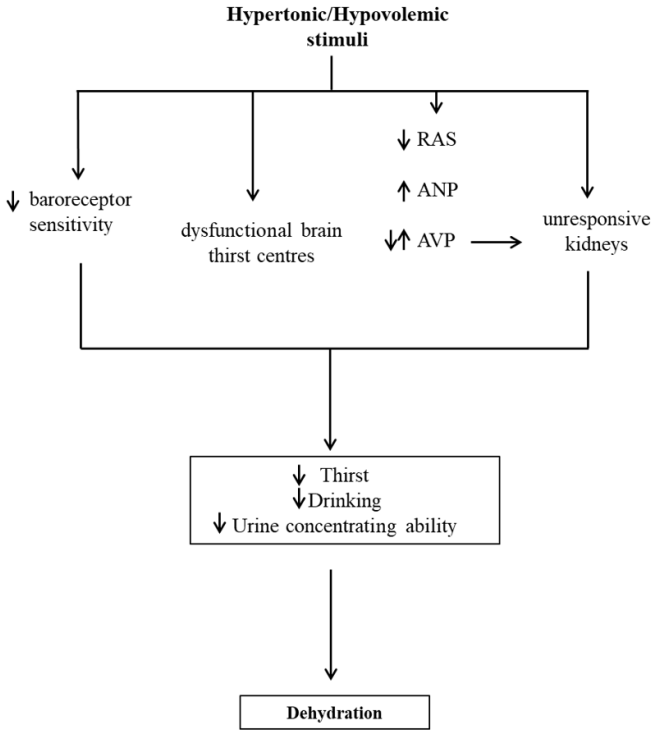


**Fig. 3.** Age-related impaired osmoregulatory mechanisms and increased susceptibility to dehydration. There is reduction in the functional capacity of the central neural connections that regulate thirst and drinking. This is accompanied by decreased arterial baroreceptor sensitivity and decreased renin-angiotensin system (RAS) activity. There is also increased levels of plasma atrial natriuretic peptide (ANP) that inhibits thirst perception. Though arginine vasopressin (AVP) levels could either be increased or decreased, the kidneys are usually unresponsive to AVP activities. This altered osmoregulation, which becomes obvious when the elderly are exposed to hypertonic or hypovolemic stimulation culminates in reduced thirst, fluid intake and ability to produce concentrated urine thereby predisposing them to dehydration.

These opposing views have been attributed to variations in the method of hyperosmotic stimulation employed such as overnight fasting (dehydration) or infusion/injection of hypertonic solution (Begg, 2017). Future investigation involving the application of both methods in the same individuals (elderly vs. younger population) and environment at different times could resolve these discrepancies.

In summary, thirst, drinking and vasopressin secretion are essential processes for osmoregulation, which is critical to the overall survival of humans. These homeostatic mechanisms require or are operated via complex but complementary central and peripheral neural connections with influence from other peptides and hormones and could be affected by several factors including aging.

*Abbrevations*

ACE, angiotensin converting enzyme; ADH, antidiuretic hormone; A-I, angiotensin I; A-II, angiotensin II; A-(1-7), angiotensin-(1-7); ANP, atrial natriuretic peptide; AP, area postrema; AT1R, angiotensin type 1 receptor; AVP, arginine vasopressin; BBB, blood brain barrier; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; CVO, circumventricular organ; ECF, extracellular fluid; ER, oestrogen receptor; ICF, intracellular fluid; i.v., intravenous; LHA, lateral hypothalamic area; LPBN, lateral parabrachial nucleus; MnPO, median preoptic nucleus; NTS, nucleus tractus solitarius; OVLT, vascular organ of the lamina terminalis; PVN, paraventricular nucleus; RAS, renin-angiotensin system; SFO, subfornical organ; SON, supraoptic nucleus; VAS, Visual Analogue Scale.

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