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Review:

Osmoregulatory Adaptations During Lactation: Thirst, Arginine Vasopressin and Plasma Osmolality Responses

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Summary: Pregnancy and lactation are accompanied by an increase in circulating blood volume secondary to a 10 mOsmol/kgH_20 decrease in plasma osmolality, decrease in the osmotic threshold for thirst and arginine vasopressin (AVP) release, prolactin-induced AVP, oxytocin and aldosterone release, as well as increased water intake and retention. The increased blood volume as a result of increased thirst; drinking and fluid retention could be beneficial for milk production and secretion during lactation. Furthermore, AVP can directly initiate milk ejection similar to oxytocin by interacting with both vasopressin and oxytocin receptors located in myoepithelial cells of the mammary gland. This review explores how osmotic equilibrium is maintained during lactation through changes in thirst, AVP release and plasma osmolality; and highlights the potential role of AVP in milk secretion.

Keywords*:* Lactation, Prolactin, Thirst, Arginine Vasopressin, Plasma osmolality

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INTRODUCTION

During pregnancy, the plasma osmolality decreases by about 10 mOsmol/kgH_20 compared with non-pregnant levels (284 - 295 mOsmol/kgH_20). There is a parallel resetting of the osmotic thresholds for thirst perception and arginine vasopressin (AVP) secretion (Lindheimer and Davison, 1995). This results in increased desire to drink (water intake), increased water retention and dilution of the body fluid as AVP concentration is not regulated at the habitual plasma osmolality level. Thus, a new steady state is established and the volume-determined AVP release mechanism is adjusted as pregnancy progresses and maintained until delivery. This is accompanied by an increase in intravascular volume characteristic of pregnancy (Lindheimer and Davison, 1995), and the expanded blood volume is then recognized as normal (Barron, 1987).

Regulation of body fluid

Approximately 65% of the total body weight of young healthy humans is comprised of water. As a result, water is the largest constituent of the human body. The percentage of total body water (TBW) is lower in females due to a relatively higher adiposity (fat content). In a 60 kg healthy, non-pregnant premenopausal woman with a low lean mass, the TBW is about 55%, i.e. 33 - 34 L of her body is composed of water (Stachenfeld, 2014).

Two-third (65%) of the TBW is contained in the cells (intracellular fluid, ICF), while the remaining is contained in the extracellular compartment (extracellular fluid, ECF). The ECF compartment is further separated in to plasma volume (1/4), interstitial (3/4) and transcellular fluid compartments. The volume of water contained in the bloodstream or plasma (about 3 L) is required for the maintenance of fluid balance and blood pressure by the body's osmoregulatory and cardiovascular systems (Stachenfeld, 2014).

In order to maintain accurate hydromineral homeostasis, a network of neuroendocrine mechanisms has been established. This neurohormonal system (hypothalamic-neurohypophyseal system) consists of osmoreceptors and nuclei that detect changes in volume and osmolality of body fluids. They are sensitive to osmotic and nonosmotic changes in the ICF and ECF compartments (Antunes-Rodrigues et al., 2004). The SON and PVN of the hypothalamus consist of vasopressinergic and oxytotic magnocellular neurosecretory neurons that project to the posterior pituitary (neurohypophysis). These neurons synthesize AVP and oxytocin, which are transported via the

hypothalamo-hypohyseal tract to and stored in the posterior pituitary (Antunes-Rodrigues et al., 2004). AVP is released in response to stimulation of the central (brain) osmoreceptors and is the key hormone in the regulation of fluid and electrolyte balance (Baylis and Ball, 2013; Stachenfeld, 2014). The major determinant for both thirst and AVP secretion is plasma osmolality. Plasma osmolality is maintained within the normal limits of 284 – 295 mOsmol/kgH_2O by the osmoregulatory systems for thirst, AVP secretion; and renal water clearance action of AVP. There is a linear relationship between plasma osmolality, thirst perception and AVP secretion (Igbokwe and Obika, 2008). Thirst and AVP secretion increase in a linear fashion in response to plasma osmolality. The mean osmotic threshold for thirst is 281 mOsmol/kgH_2O, while that of AVP release is 284 mOsmol/kgH_2O. When plasma osmolality increases beyond these thresholds, thirst is stimulated and AVP is released (Baylis and Ball, 2013). As a result of these relationships, plasma AVP concentrations have been successfully estimated from thirst perception and plasma osmolality values (Amabebe et al., 2012; Obika et al., 2013; Obika and Ozoene, 2014).

Osmoregulatory and endocrine signals are integrated in the lamina terminalis located in the anteroventral wall of the third ventricle. The lamina terminalis harbours the circumventricular organs - subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT) devoid of the normal blood brain barrier (BBB). Osmoreceptor-Na^+ receptor neurons located in these structures are sensitive to variations in plasma osmolality or plasma and cerebrospinal fluid (CSF) sodium concentration (Antunes-Rodrigues et al., 2004; McKinley et al., 2004a; Stachenfeld, 2014). Increase in water intake as a result of hypertonic stimulation of the anteroventral portion of the third ventricle, which is the central (brain) area majorly responsible for the regulation of body fluid balance as well as cardiovascular and renal function was first reported in goats and later confirmed in rats (Antunes-Rodrigues et al., 2004). Another structure located in the lamina terminalis involved in the osmotic and volumetric control of thirst and drinking is the median preoptic nucleus (MPN). Lesions to this area impair the drinking and AVP responses to hypertonic saline including other osmotic and volume regulatory mechanisms (Antunes-Rodrigues et al., 2004; McKinley et al. 2004a; Stachenfeld, 2014). The role of the lamina terminalis in osmoregulatory water intake has also been demonstrated in humans (McKinley et al., 2004a).

The absence of the normal BBB around the circumventricular organs allows direct contact between the neurons of these organs and the blood. Osmotic signals from these organs are transmitted to the hypothalamic SON and PVN via glutaminergic afferent pathways (Baylis and Ball, 2013; Stachenfeld, 2014). Furthermore, due to their contact with plasma ionic concentrations and hormones, these organs integrate osmoregulatory- and hormonally-induced drinking through the action of atrial natriuretic peptide (ANP), angiotensin II and relaxin (Fig. 1). Angiotensin II and relaxin stimulate the cells of the SFO and OVLT, which in turn stimulate the SON, PVN, lateral hypothalamic area (LHA) and MPN, thereby increasing thirst and AVP release. In contrast, ANP antagonizes the action of angiotensin II on the SFO, thereby inhibiting dehydration-induced thirst and AVP secretion (Antunes-Rodrigues et al., 2004; Baylis and Ball, 2013; McKinley et al., 2004a).

In addition to changes in plasma osmolality, low plasma/blood volume and pressure stimulate thirst and AVP release (Fig. 1). Peripheral Stretch (baro-) receptors in the cardiac atria, ventricles, as well as the superior and inferior vena cava detect variations in blood volume, and the receptors in the aortic arch and carotid sinuses detect changes in arterial blood pressure. These changes can also be sensed by peripheral hepatic, gastric and renal osmo- and volume receptors (McKinley et al., 2004a), e.g. the macula densa of the kidney's juxtaglomerular apparatus that contains both osmotic and volume receptors. An approximately 10% reduction in blood volume (Stachenfeld, 2014), or a 5 - 10% decrease in arterial blood pressure (Baylis and Ball, 2013), triggers an increase in plasma AVP concentration. These stretch signals are transmitted via the glossopharyngeal and vagus nerves to the nucleus tractus solitarius (NTS) in the brain stem, from which postsynaptic connections are made with the SON and PVN via the cirumventricular organs (Antunes-Rodrigues et al., 2004; Baylis and Ball, 2013; Stachenfeld, 2014). Therefore, an acute alteration in plasma osmolality and circulating volume can induce an extensive response including thirst perception (drinking), sodium intake, renin-angiotensin-aldosterone system activity, sympathetic nervous system activity, and ANP secretion (Stachenfeld, 2014). Further reading on the homeostatic regulation of hydromineral balance can be found in Geerling and Loewy, 2008; McKinley et al., 2004b, 2004c; McKinley et al., 2006; Stricker and Hoffmann, 2007; and Thornton et al., 2010.

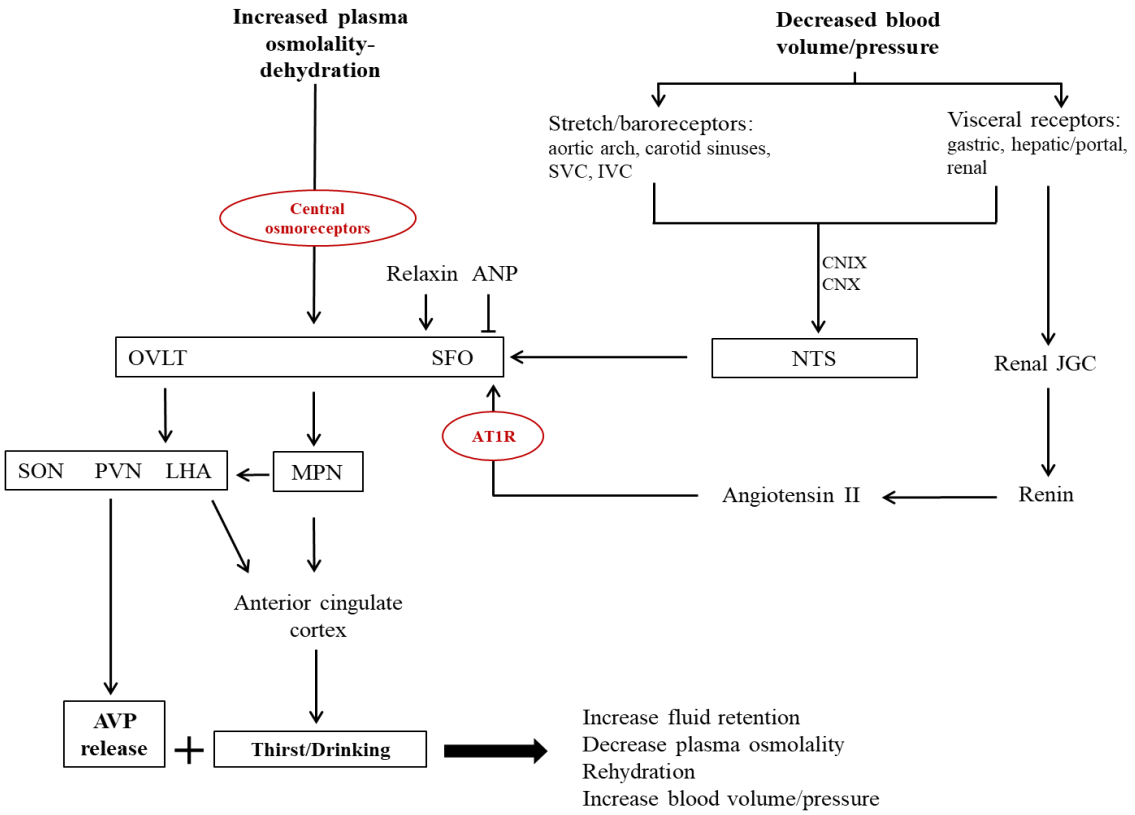

Figure 1. Neurohormonal regulation of osmotic and volumetric thirst sensation and AVP release. Osmoreceptors in the subfornical organ (SFO) and Organum vasculosum of the lamina terminalis (OVLT) respond to increased plasma osmolality. These circumventricular organs stimulate thirst, drinking and arginine vasopressin (AVP) secretion via their connections with the median preoptic nucleus (MPN), lateral hypothalamic area (LHA), and the supraoptic (SON) and paraventricular (PVN) nuclei. Similarly, hypovolemic signals from peripheral baro- and visceral osmoreceptors are transmitted by the glossopharyngeal (CNIX) and vagus (CNX) nerves to the nucleus tractus solitarius (NTS), which triggers drinking and water retention via its connection with neurons of the lamina terminalis and hypothalamus. Also, in response to hypovolemia, angiotensin II is produced and stimulates thirst by interacting with angiotensin type 1 receptor (AT1R) on the SFO and OVLT. Relaxin has a similar dipsogenic effect on the circumventricular organs; whereas atrial natriuretic peptide (ANP) inhibits the SFO and hence, antidipsogenic. The genesis of thirst and drinking is also modified by inputs from the anterior cingulate cortex. *IVC*, Inferior vena cava; *JGC*, Juxtaglomerular cells; *SVC*, Superior vena cava. Adapted from: Amabebe and Robert, 2017.

Lactation-induced osmoregulatory neuroendocrine adaptation

During peripartum, i.e. the last month before and the first few months after delivery characterized by physiological hyperprolactinaemia (Torner et al., 2002; Donner et al., 2007; Slattery et al., 2008; Donner and Neumann, 2009), there is an increase in AVP synthesis and release into the blood and within the central nervous system (Walker et al., 2001; Yue et al., 2006). This has been attributed to the regulatory role of prolactin (PRL) on neuroendocrine adaptation and stimulation of the AVP system (Donner and Neumann, 2009). Hyperprolactinaemia influences the hyperosmolality- and hypovolemia-induced AVP response (Coiro et al., 2011). This is perhaps due to the localization of PRL receptors on oxytocin and AVP neurons of the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus (Mejia et al., 2003; Kokay et al., 2006; Torner et al., 2008). It could also be by transmission of messages from the osmo- and baroreceptors to AVP-secreting cells. This is supported by evidence of PRL neurons and synapses in the SON and PVN (Mejia et al., 2003; Kokay et al., 2006), as well as the nucleus solitarius i.e. the integration center for baroreceptor stimulation (Coiro et al., 2011). PRL influences the regulation of AVP and oxytocin release by enhancing the activity of neuronal nitric oxide synthase in the SON and PVN with resultant osmoregulatory responses (Donner and Neumann, 2009; Vega et al., 2010; Otukonyong et al., 2000). PRL stimulates AVP and oxytocin release in ovariectomized animals treated with estrogen (Donner and Neumann, 2009).

Like gestation, the period of lactation is characterized by decreased plasma osmotic pressure or osmolality and elevated AVP concentration as a result of the resetting of the regulatory mechanisms of the AVP system. The adjusted relationship between plasma osmolality and AVP release is similar to that seen in pregnancy i.e. a decrease in the osmolar

threshold for AVP release. Like oxytocin, the suckling stimulus can release AVP leading to blood dilution and increased circulating blood volume (Suzuki et al., 2000). By extension, this osmoregulatory adaption could include decreased threshold for thirst and increased desire to drink water.

Furthermore, suckling has been reported as a potent stimulus of thirst in lactating women independent of AVP secretion or any change in osmoregulation. Nerve impulses to the hypothalamic SON and PVN during suckling could trigger parallel thirst and oxytocin release. Both thirst and oxytocin release were correlated and an afferent from an oxytotic neuron or a dipsogenic effect of oxytocin was implicated (James et al., 1995). Whether it was the suckling stimulus or oxytocin secretion that initiates the desire to drink was unclear. Another explanation for this observation was that thirst might be stimulated in anticipation of fluid loss from lactation – "anticipatory thirst" (James et al., 1995). In addition, anecdotal reports from breastfeeding mothers indicate suckling stimulates thirst sensation (Mulford, 1990). The mechanisms underpinning these adaptations are still unresolved. Hence, this review focuses on the physiological osmoregulation of thirst, AVP and plasma osmolality during lactation.

Prolactin stimulates thirst and water retention

PRL is crucial for the maintenance of osmotic equilibrium in amphibians, fishes, birds and mammals (Bliss and Lote, 1982; Ensor et al., 1972; Horrobin et al., 1971; Marshall et al., 1975). In humans, PRL stimulates thirst and salt intake (Burstyn et al., 1972; Ensor et al., 1972; Horrobin et al., 1971). It increases plasma osmolality and has also been shown to have antidiuretic and antinatriuretic properties (Ensor et al., 1972; Horrobin et al., 1971), possibly through altered renal haemodynamics (Bliss and Lote, 1982), and participation of PRL receptors in the kidney and adrenals (Marshall et al., 1975). PRL reduces urine flow by reducing renal plasma flow and glomerular filtration rate (GFR) (Bliss and Lote, 1982). It also stimulates renal water reabsorption by direct action on collecting tubule permeability via a cyclic adenosine monophosphate (cAMP)-dependent mechanism similar to AVP (Miller and van Gemert, 1976; Wallin and Lee, 1976). Also, PRL can initiate antidiuresis by increasing renal water reabsorption independent of AVP concentration and changes in GFR (Jones et al., 2002; Morrissey et al., 2001; Wallin and Lee, 1976). This direct/independent antidiuretic effect of PRL was confirmed in AVP-deficient Brattleboro rats with hereditary hypothalamic diabetes insipidus (HHDI) (Miller and van Gemert, 1976; Morrissey et al., 2001; Wallin and Lee, 1976). PRL can also stimulate AVP-independent water reabsorption by stimulating the release of aldosterone from the zona glomerulosa of the adrenal cortex (Fig. 2) (Glasow et al., 1996; Kau et al., 1999). Therefore, a synergistic and/or permissive effect between PRL and AVP may be involved, as supraphysiologic levels of PRL did not exhibit antidiuretic effect in a vasopressin-deficient state in man (Berl et al., 1976). Plasma PRL levels parallels plasma osmolality (Buckman and Peake, 1973; Relkin, 1974), after intravenous injection of hypertonic sodium chloride and gastric or intravenous water loading. The role of PRL in maintaining fluid and electrolyte balance in mammals may just be modulatory and not the major controlling factor (Horrobin, 1980).

Extracellular dehydration and volume depletion as may occur during lactation (secretion of isotonic milk) stimulates PRL secretion (Fig. 2). PRL in turn increases thirst sensation, drinking and fluid retention conceivably by acting synergistically with angiotensin II (Kaufman, 1981a, b; Kaufman et al., 1981; Kaufman and Mackay, 1983). It is important to note that this effect is particularly connected with pathways of extracellularly induced thirst, and hence the involvement of extracellular-mediated angiotensin II stimulus (Kaufman 1981a; Kaufman and Mackay, 1983). The relationship between PRL secretion/plasma levels, plasma osmolality and amount of fluid ingested is absent in intracellular dehydration (Kaufman and Mackay, 1983).

A plausible explanation for the dipsogenic action of PRL is by its interaction with receptors in the SFO (Fig. 2). Prolactin receptor mRNA is located in the SFO (Hindmarch et al., 2008), and depolarization has been observed when neurons in this region were treated with PRL. The report concluded that the SFO is a potential target for the central autonomic integration actions of PRL (Black et al., 2014). The SFO is a well-known brain area for the integration of osmotic and volumetric thirst sensations and AVP release (Fig. 1), and via its neuronal connections with the OVLT, MPN, SON, PVN, other hypothalamic regions and NTS (Figs. 1 and 2), it stimulates thirst and controls fluid and electrolyte balance (McKinley et al., 2004a; McKinley et al., 2006). The SFO and other circumventricular organs are also directly exposed to vascular contents including PRL because they lack BBB. Therefore, the hormonal influence on thirst, AVP release and osmoregulation may not be limited to angiotensin II, relaxin and ANP alone as postulated by Antunes-Rodrigues et al., 2004; McKinley et al., 2004a, b, c, and 2006. The dipsogenic and hypervolemic actions of PRL could be adaptive or homeostatic mechanisms to maintain adequate fluid supply necessary for isotonic milk production (galactopoiesis) and secretion. This phenomenon has been underestimated as evident in the paucity of data, necessitating more investigation to elucidate the homeostatic significance of PRL levels and the physiological and biochemical pathways involved.

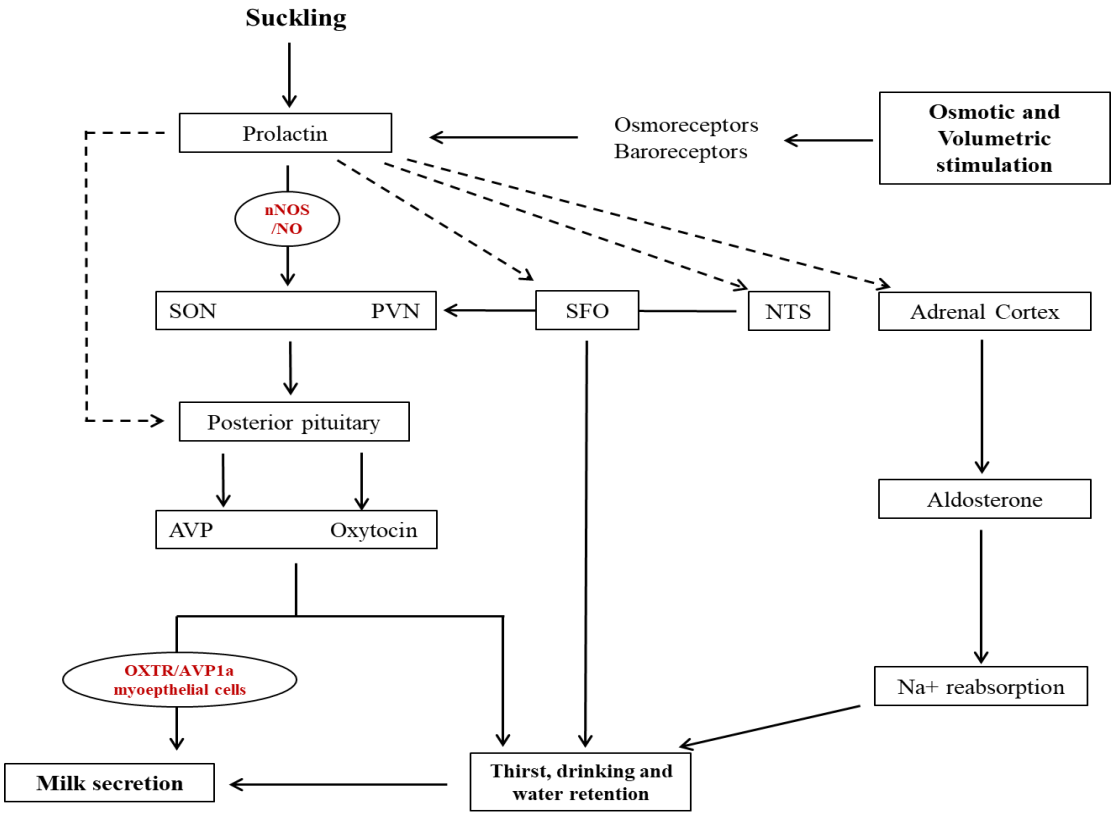

Figure 2. Interaction between milk ejection and osmoregulatory reflexes. Suckling stimulates arginine vasopressin (AVP) and oxytocin release from the vasopressinergic and oxytotic magnocellular neurons of the neurohypophysis (posterior pituitary) through the release of prolactin from the anterior pituitary. Prolactin influences the activity of the neurons in the neurohypophysis via a neuronal nitric oxide synthase (nNOS)/nitric oxide (NO)-mediated mechanism on the hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei. Prolactin release is also stimulated by hyperosmotic and hypovolemic changes that characterize lactation. The resultant physiologic hyperprolactinemia can induce thirst, drinking and decrease water excretion by the stimulatory action of prolactin on the neurohypophysis, subfornical organ (SFO), nucleus tractus solitarius (NTS), and adrenal cortex. This is necessary for isotonic milk production and secretion. Both AVP and oxytocin initiate milk ejection by acting on both oxytocin (OTXR) and AVP1a receptors on the myoepithelial cells of the mammary gland. The process of galactopoiesis requires enough water, which is drawn from the blood thereby increasing osmolality, which stimulates the thirst mechanism and trigger AVP release.

Arginine Vasopressin and Milk ejection

Suckling induces the release of both oxytocin and AVP (Fig. 2) and intravenous infusions of AVP increase milk ejection in rats and goats similar to oxytocin (Högberg et al., 2014; Olsson et al., 2003; Olsson and Högberg, 2009; Suzuki et al., 2000). The role of AVP was said to increase water retention necessary for milk production (Olsson and Högberg, 2009; Suzuki et al., 2000). Because milk is composed mainly of water, it could be advantageous to increase water retention through the kidneys during milk production (Högberg et al., 2014). An AVP-stimulated milk ejection reflex, similar to the oxytocin response, could occur through action on the myoepthelial cells surrounding the alveoli either by interaction with oxytocin receptor or vasopressin receptors (AVP1a) on these cells (Fig. 2) (Högberg et al., 2014).

However, in lactating mothers, though suckling induces thirst, it may not be associated with AVP release (James et al., 1995). Instead, increase in thirst sensation during suckling was associated with an increase in plasma oxytocin (i.e. the hormone wildly known to stimulate contraction of the myoepithelial cells surrounding the alveoli). The exact mechanism underlying these observations is unclear, but a stimulation of thirst via an oxytotic neuron or a dipsogenic action of oxytocin was suggested (James et al., 1995). These observations somewhat differ from the lactation-induced reduction in the threshold for AVP release, increased plasma AVP concentration observed after suckling and the low plasma osmolality-high AVP status established during lactation (similar to pregnancy) in rats (Suzuki et al., 2000). However, increase in thirst (and plausibly drinking), and AVP induced by different mechanisms could cause haemodilution and increase circulating plasma volume required for adequate lactation. The action of AVP during lactation in humans may just be maintenance of osmotic homeostasis to facilitate milk production but not milk ejection.

Since oxytocin and AVP differ by only two amino acid in their peptide structure, it has been hypothesized that both hormones can respond to the same stimuli and bind to the same receptors (Zingg, 1996). Elevated amount and activity of AVP was detected in the secretory apparatus of the mammary glands of lactating goats after dehydration and AVP infusion. The possibility of the secretory and myoepithelial cells being targets of this heightened AVP activity was suggested (Dahlborn et al., 1990). Subsequently, both oxytocin and AVP type 1a (AVP1a) receptors were found on the myoepithelial cells surrounding the alveoli of the mammary gland and AVP induce contraction of these cells in rabbits and goats (Högberg et al., 2014; Lollivier et al., 2006; Soloff et al., 1989; Zingg, 1996). Furthermore, the oxytocin receptor (OXTR) has been described as a non-selective AVP receptor with an equal affinity for both oxytocin and AVP (Peter et al., 1995); and the amino acid sequences of AVP type 3 (AVP3) and OXTR are 45% homologous (Holmes et al., 2003; Sugimoto et al., 1994). Also, intravenous infusions of AVP increased milk secretion similar to oxytocin in goats (Högberg et al., 2014; Olsson et al., 2001; Olsson et al., 2003). Though the physiological role of AVP in relation to milk ejection is still unresolved (especially in humans), these reports indicate that like oxytocin, AVP can stimulate milk ejection by acting on the myoepithelial cells (Högberg et al., 2014; Olsson et al., 2003; Olsson and Högberg, 2009). This is also supported by the ability of AVP to bind to both AVP1a and OXTR on myoepithelial cells, and warrants further investigation in humans.

In summary, there is an obvious dearth of recent investigations on the osmoregulatory adaptations observed during lactation in humans. This has limited our understanding of the neuroendocrine mechanisms that trigger and/or accompany the process or period of galactopoiesis and milk secretion. In this review, we have explored the dipsogenic and antidiuretic properties of PRL, whose only distinctly defined function in humans is milk production in postpartum females. We have also highlighted a possible AVP-mediated milk ejection reflex similar to the established oxytocin-dependent response. Taken together with the reduced osmotic threshold for thirst and AVP release observed in lactation (like in pregnancy), these osmoregulatory responses increase drinking and fluid retention with a consequent expansion of blood volume. Plausibly, this is crucial for effective production and secretion of isotonic milk and maintenance of osmotic equilibrium for the overall health of both the mother and infant.

This heralds the need for more studies to further explicate and validate (especially in humans) the molecular mechanisms by which PRL performs its osmoregulatory actions and the action of AVP on the myoepithelial cells of the mammary glands in relation to milk secretion or milk let down.

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