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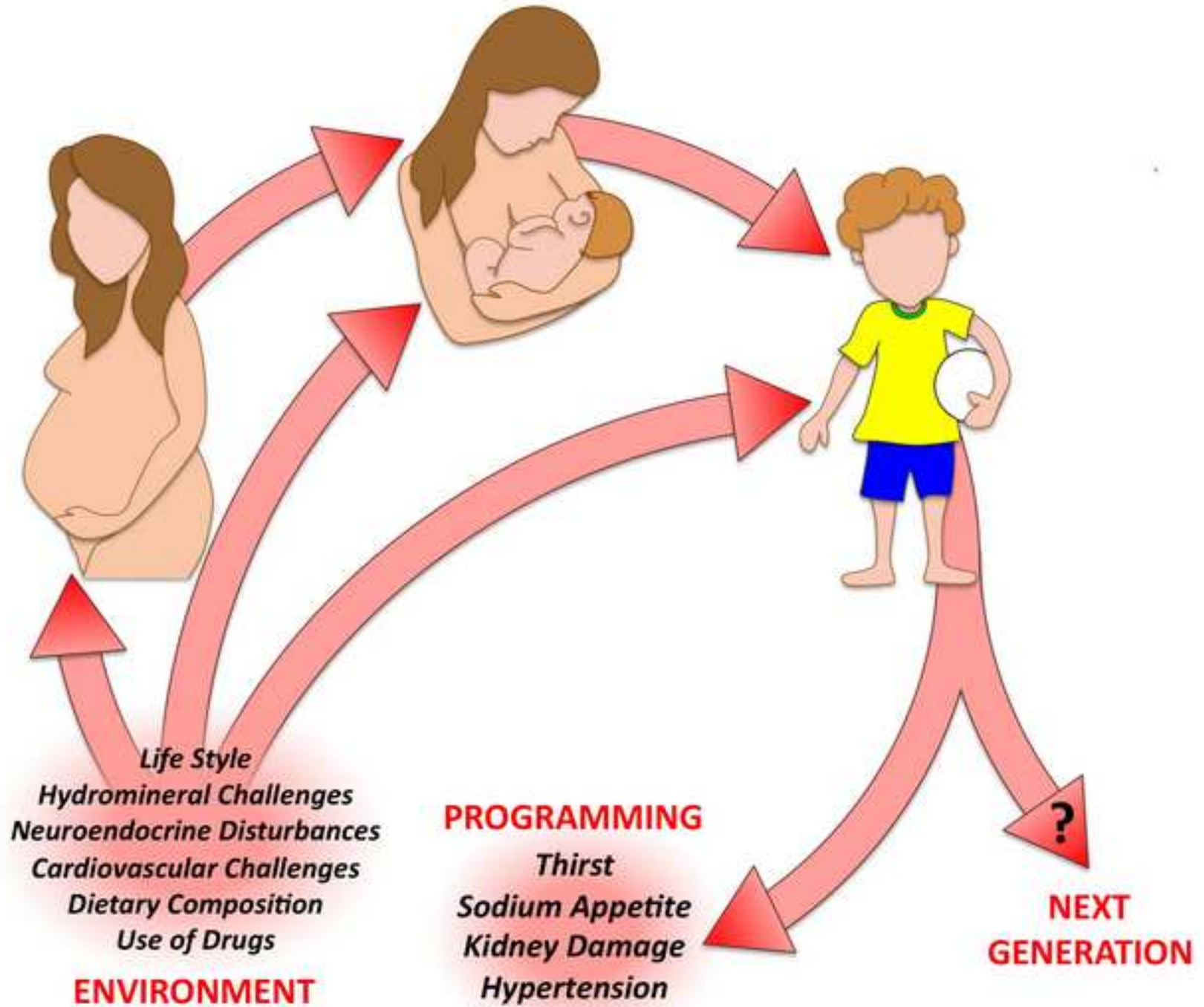Carmen Perillan Luis C. Reis Laura Vivas Juan Arguelles

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Life Style
Hydromineral Challenges
Neuroendocrine Disturbances
Cardiovascular Challenges
Dietary Composition
Use of Drugs

ENVIRONMENT

PROGRAMMING
Thirst
Sodium Appetite
Kidney Damage
Hypertension

?

**NEXT
GENERATION**

Highlights

- We review here the ontogeny of thirst and sodium appetite

- Thirst and sodium appetite are programmed by the developmental environment

- Hydromineral/neuroendocrine disorders and lifestyle are the main programming factors

- Several neuroendocrine systems are epigenetically regulated and potentially involved

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DEVELOPMENTAL PROGRAMMING OF THIRST AND SODIUM APPETITE

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Contents

Abbreviation list

ACE – Angiotensin converting enzyme
ALD – Aldosterone
ANG II – Angiotensin II
ANP – Atrial natriuretic peptide
AP – Area postrema
AT_1 – Angiotensin receptor type 1
AT_2 – Angiotensin receptor type 2
AVP – Vasopressin
CVO – Circumventricular organ
DRN – Dorsal raphe nucleus
HSD2 – 11 beta-hydroxysteroid dehydrogenase type 2 enzyme
ICV – Intracerebroventricular
LPBN – Lateral parabrachial nucleus
LT – *lamina terminalis*
MnPO – Median preoptic nucleus
NTS – Nucleus of the solitary tract
OVLT – *organum vasculosum* of the *lamina terminalis*
PEG – Polyethylene glycol
PVN – Paraventricular nucleus
RAAS – Renin-angiotensin-aldosterone system
SFO – Subfornical organ
SHR – Spontaneously hypertensive rats
SON – Supraoptic nucleus

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Abstract

Thirst and sodium appetite are the sensations responsible for the motivated behaviors of water and salt intake, respectively, and both are essential responses for the maintenance of hydromineral homeostasis in animals. These sensations and their related behaviors develop very early in the postnatal period in animals. Many studies have demonstrated several pre- and postnatal stimuli that are responsible for the developmental programming of thirst and sodium appetite and, consequently, the pattern of water and salt intake in adulthood in need-free or need-induced conditions. The literature systematically reports the involvement of dietary changes, hydromineral and cardiovascular challenges, renin-angiotensin system and steroid hormone disturbances, and lifestyle in these developmental factors. Therefore, this review will address how pre- and postnatal challenges can program lifelong thirst and sodium appetite in animals and humans, as well as which neuroendocrine substrates are involved. In addition, the possible epigenetic molecular mechanisms responsible for the developmental programming of drinking behavior, the clinical implications of hydromineral disturbances during pre- and postnatal periods, and the developmental origins of adult hydromineral behavior will be discussed.

Key Words: Thirst, sodium appetite, developmental programming, renin-angiotensin system, lifestyle, epigenetic, neuroendocrine

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1. Introduction

The loss or gain of body water and sodium, which occurs during different states of fluid disturbance, elicits reflexive and behavioral responses that equilibrate the rate of fluid depletion or expansion, ultimately restoring body fluid levels. To activate the appropriate homeostatic responses, the central nervous system must receive and integrate multiple types of sensory input from specialized receptors that monitor the body fluid status. These signals are detected by taste receptors, peripheral osmo/Na^{+}-receptors, volume receptors and arterial/cardiopulmonary baroreceptors, which activate the nucleus of the solitary tract (NTS; Vivas *et al.*, 2013), the *lamina terminalis* (LT), and one of the sensory circumventricular organs (CVOs), the area postrema (AP). The LT comprises the median preoptic nucleus (MnPO) and two other sensory CVOs: the subfornical organ (SFO) and the *organum vasculosum* of the *lamina terminalis* (OVLT; Antunes-Rodrigues *et al.*, 2004). The SFO and OVLT are devoid of the blood–brain barrier, and both contain cells that are sensitive to humoral signals, plasma and cerebrospinal fluid (CSF) sodium concentrations (Vivas *et al.*, 1990; Noda, 2006), osmolality (Sladek & Johnson, 1983) and angiotensin II (ANG II) levels (Simpson *et al.*, 1978). The LT, AP and NTS modulate neural circuitry, which includes integrative areas such as the paraventricular (PVN), supraoptic (SON), lateral parabrachial (LPBN) and dorsal raphe (DRN) nuclei. In this context, the modulation of water and sodium intake involves interactions between the CVO receptive areas (LT, AP, and NTS), the serotonergic pathways from the DRN, the gustatory information from the LPBN and the OTergic/AVPergic pathways within the SON and PVN (Fig. 1). Once these signals act on the above-mentioned neurochemical networks, they trigger the appropriate sympathetic, endocrine and behavioral responses to restore the hydromineral balance (Vivas *et al.*, 2013).

-----PLEASE INSERT FIGURE 1 ABOUT HERE-----

In pregnancy, several adaptations in maternal hemodynamic, hormonal and biochemical variables occur that allow for normal fetal growth and development. Studies conducted in recent decades have produced evidence to support the importance of the environment during sensitive periods of gestation and early postnatal life. The

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consequences of the developmental environment might persist until adulthood, affecting tissue structure and function. In fact, research has shown that this process, known as "developmental programming," might result in adult diseases; this hypothesis is often called "developmental origins of adult disease" (Barker *et al.*, 2002). Barker and colleagues formulated this hypothesis based on observations collected from economically poor regions of England with i) the highest rates of infant mortality due to malnutrition, mainly in the early 20th century, and ii) the highest rates of mortality from coronary heart disease some decades later (Barker and Osmond, 1986). More recently, a large amount of research has been carried out to evaluate how the adult phenotype is a consequence of environmental signals operating on genes during development.

It is possible that the so-called "programming phenomenon" is a type of "phenotypic plasticity" for the expression of different phenotypes from the same genotype. Thus, this phenomenon is due to pre-existing genetic variations and is the result of the interaction of a variety of environmental events such as adaptation, developmental programming and epigenetic alterations. The ultimate goal of this type of process is to provide a strategy to adapt to a constantly fluctuating environment, minimizing the genotypic disadvantage that each individual might have in relation to its surroundings (Brakefield *et al.*, 2005).

The hydroelectrolyte homeostatic systems that regulate thirst and sodium appetite are not exempt from developmental programming effects. Many studies indicate that during sensitive periods of ontogeny, different pre- and/or postnatal challenges modify fluid intake patterns of offspring during development and in adulthood in need-free and/or need-induced conditions (Arguelles *et al.,* 2000; Perillan *et al.*, 2007; Mecawi *et al.,* 2009; Leshem, 2009a; 2009b; Macchione *et al,*. 2012).

In view of these findings, the literature regarding the ontogeny of the mechanisms related to ingestive behavior, i.e., thirst and sodium appetite, and how developmental challenges can alter the lifelong patterns of water and salt intake will be reviewed. The potential neuroendocrine and molecular mechanisms responsible for the programming of drinking behavior, as well as the possible clinical implications, will also be addressed.

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2. Ontogeny of thirst and sodium appetite

Early development is considered a crucial period for the establishment of behavior. In the rat, the mechanisms responsible for drinking make their first appearance abruptly and sequentially at critical ages. Wirth and Epstein (1976) showed that newborn rats could not be made to drink water in response to any known stimulus of thirst but that drinking could be induced by cellular dehydration at postnatal day 2, by hypovolemia at postnatal day 4, and by isoproterenol at postnatal day 6. ANG II-induced intake undergoes a similar ontogenetic progression. Drinking in response to intracranial ANG II occurs at postnatal day 2, but at this stage, the pups cannot distinguish between milk and water (Ellis *et al*., 1984). However, by postnatal day 8, the adult response has appeared, and the pups drink more water than milk in response to intracranial ANG II administration (Ellis *et al*., 1984). Thirst elicited by activation of the brain renin-angiotensin system (RAAS) in the suckling rat becomes more specific to water after 16 days (Leshem *et al.*, 1988), and the mechanisms of thirst aroused by renin or intracellular dehydration are fully developed before weaning (Leshem and Epstein, 1988).

Accordingly, rat pups develop the thirst mechanism during a period when they are still completely dependent on their mother's milk and before they need these mechanisms because maternal milk ensures the pup's hydration and nutrition. When rat pups exhibit thirst during their life, they lap and swallow, repeatedly opening their mouths in a different motor pattern from that of suckling. Thus, it is clear that the neural mechanisms for thirst and the act of drinking are innate (Fitzsimons, 1998).

At present, there are no experimental data investigating the postnatal ontogeny of thirst in humans, so it is currently unknown to what extent thirst is "hard-wired" at birth. One unexplored possibility is that there is little differentiation between hunger and thirst in newborn animals, at least in mammals, given that in this case, the developmental system of food/fluid intake involves both needs being met simultaneously via the ingestion of breast milk. If this is the case, then because the food/fluid intake seems to be developed in newborns (Ellis *et al*., 1984), mammals might have to learn to differentiate hunger and thirst later in development, either during or post weaning, when both supplies are differentiated (Hall *et al*., 2000).

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A key difference between breast milk (provided directly from the breast) and substitutes is that breast milk changes its nutritional composition during feeding (Hall, 1975). The foremilk is thin and watery and has relatively little nutritional content compared with the hindmilk, available later in the feed (if the infant continues to feed from the same breast), which contains far greater quantities of fats and other nutrients (Bishara *et al.*, 2008). Therefore, it is possible that the nutritional differences between foremilk and hindmilk allow for the differential satisfaction of thirst and hunger in breast-fed infants, something that is not possible for bottle-fed infants, who consume a relatively homogenous mixture. For slightly different reasons, Hall (1975) argued that the foremilk/hindmilk nutritional difference might be important for the development of appetite regulation, providing a potential connection between bottle-feeding and the development of obesity. However, as there is little empirical data investigating the postnatal development of thirst in humans, this has yet to be substantiated (Harshaw, 2008).

Sodium preference is a hedonic response directly dependent on the sodium concentration in the solution being offered (Bare, 1949). It also plays an important role in the amount of sodium consumed by mammals, including humans, in need-free conditions in which physiological requirements are absent. Between postnatal days 10 and 15, the preference for highly hypertonic NaCl solutions (2% or greater) prevails, whereas after weaning and during adulthood, the preference values approach isotonic concentrations (near 0.9% NaCl) in rats (Midkiff and Bernstein, 1983; Moe, 1986). Thus, the sodium preference-aversion curve is age-dependent, which might be due to maturational changes in the development of the taste system (Farbman, 1965) and the chorda tympani nerve responses (Hill and Almli, 1980). Previous research on the ontogeny of sodium appetite has shown that a sodium deficit caused by adrenalectomy or furosemide administration induces sodium intake at 12 days of age (Moe, 1986). However, direct stimulation of the brain RAAS by intracranial injection of renin increases the intake of a NaCl solution, rather than milk, as early as 3 days postnatally in rats (Leshem *et al.*, 1994). During this critical developmental window, the renin-induced sodium appetite is dissociated from thirst because i) hypertonic NaCl is preferred to water, ii) the appetite develops faster than thirst and iii) 3-day-old renin-stimulated pups avidly lick dry NaCl. These results show that the activation of brain ANG II in 3-day-old rat pups evokes a precocious and specific sodium appetite.

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Humans do not start life with an obvious salt preference. There has been sufficient research to suggest that human neonates do not differentially ingest salt and water solutions (Beauchamp *et al*., 1986; Harris *et al*., 1990; Zinner *et al*., 2002), and earlier studies have concluded that babies are indifferent to salt or reject it (Nowlis, 1973; Crook, 1978; Desor *et al*., 1975). In fact, human infants of less than 4 months of age ingest water and moderate concentrations of sodium chloride solution in equal amounts, and the differentiation between them begins at 4-24 months of age, at which point, the infants exhibit a heightened acceptance of saline solution relative to water. However, at 31-60 months of age, children tend to reject saline solution in favor of water (Beauchamp *et al*., 1986). Thus, those changes in salt preference might also reflect, at least in part, the effects of previous experiences (Harris *et al*., 1990; Stein *et al*., 2012). As reviewed by Leshem (2009a), humans do not seem to have a robust sodium appetite compared with thirst, unlike all other mammals that have been studied. However, like other animals, humans also love to eat salt, a behavior that has important cultural and hedonic components and probably varies with genes, gender, hormones, health status and, as we will review here, several perinatal factors.

3. Thirst and sodium appetite programming

During pregnancy and early lactation, the developing animal is completely dependent on its mother for all nutritional requirements. Therefore, it is not surprising that maternal nutrition and hydromineral variations can influence fetal health and wellbeing. Additionally, those influences can persist into adulthood and might result in an increased risk for hydromineral disorders and cardiovascular disease (Barker and Osmond, 1986; Barker, 2002; McArdle *et al*., 2006).

Both animal models and human studies have provided valuable information for clarifying the developmental programming of thirst and salt appetite. This review will highlight investigations that have studied the relationship between altered prenatal and postnatal environments and the programming of fluid intake using a variety of nutritional, hydromineral and endocrine manipulations.

3.1. *Dietary manipulation and the programming of fluid intake*

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Maternal malnutrition models have been developed with several experimental protocols. When rat dams are fed a hypocaloric diet, their offspring display restricted growth and hyperphagia, as well as the development of hypertension, hyperleptinemia and obesity in adult life (Vickers *et al*., 2000). Specifically, changes in kidney morphophysiology (and more specifically, nephron number) might play an important role in hypertension originating from fetal undernutrition. Rats exposed to intrauterine food restriction exhibit a reduced nephron number, decreased glomerular filtration rate and increased blood pressure in adulthood (Regina *et al*., 2001; Chou *et al*., 2008; Hoppe *et al*., 2007; Langley-Evans *et al*., 1999; Moritz *et al*., 2003). Thus, fetal undernutrition leads to lifelong morphofunctional-renal abnormalities and hypertension programming (Langey-Evans *et al*., 1999). In this context, important issues that need to be evaluated in kidney deficiency and hypertension programming by maternal undernutrition are the roles and consequences of these changes on fluid intake by those offspring in adulthood.

Smart and Dobbing (1977) demonstrated that maternal food restriction induces a neonatal growth reduction in offspring, which, when placed in a Skinner box test, drank more frequently during ingestive behavior tests in response to water deprivation and tended to run more quickly down an alleyway for water compared with control rats. Additionally, Hoppe *et al*. (2007) showed that protein restriction during pregnancy and lactation did not influence need-free water intake in adult offspring; however, Alwasel et al. (2012) observed an intense increase in need-free water ingestion among the offspring of mothers fed a low-protein diet when water was the only fluid offered. Interestingly, when both water and isotonic saline solutions were offered, the low-protein-programmed offspring demonstrated an elevated preference for sodium, which could have been related to their increased sodium excretion (Alwasel et al., 2009). These data are consistent with those observed by Langley-Evans and Jackson (1996), who demonstrated that rats from mothers fed a low-protein diet were resistant to hypertension caused by salt overload over 7 days, probably due to a renal sodium wasting phenotype. Additionally, whereas the control animals avoided the mandatory intake of hypertonic saline during the first day of salt overload, the animals from mothers fed a low-protein diet showed an increased intake of this solution compared with their previous intake of water.

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Several studies have found that an increased salt sensitivity is associated with compromised intrauterine fetal growth leading to low birth weight in human babies (Simonetti *et al*., 2008). In accordance with this finding, salt taste preference was inversely correlated to birth weight over the first 4 years (Stein *et al*., 2006) and was absent at 10–15 years of age (Shirazki *et al*., 2007). These data indicate that developmental undernutrition (from protein or food restriction) and a low birth weight could lead to changes in renal function and sodium excretion, which, in turn, might be responsible for the expression of a natriophilic phenotype. Thus, some reports have described the greater risk of developing hypertension in low-protein diet-programmed offspring (Sahajpal and Ashton, 2003; Eriksson et al., 2007) as being closely related to intense sodium retention due to the increased Na^+-K^+-$2Cl^-$ transporters on the ascending limb of the loop of Henle (Manning et al., 2002) or the increased sensitivity to components from the RAAS (Manning & Vehaskari, 2005). Recently, De Lima et al. (2013) demonstrated that maternal protein restriction led to reduced AT_1 receptor and AVP expression in the hypothalamus of adult offspring that was associated with an attenuation of the thirst response to ICV ANG II administration. Additionally, these animals showed reduced fractional sodium excretion related to increased systolic blood pressure. Therefore, there are clearly conflicting views regarding the influence of a low-protein diet during fetal and neonatal life on fluid intake. However, in general, perinatal protein restriction is related to changes in sodium excretion and sensitivity and results in the predisposition to develop hypertension.

3.2. *Hydromineral challenges and the programming of fluid intake*

Because dietary food alterations during the fetal and neonatal periods can alter the pattern of fluid intake in adulthood, it seems plausible to suggest that hydromineral challenges during sensitive periods of ontogeny might also modify the offspring's pattern of fluid intake in need-free and need-induced conditions (Mouw *et al*., 1978; Contreras and Kosten, 1983; Crystal and Bernstein, 1995; 1998; Galaverna *et al*., 1995; Contreras and Ryan, 1990; Curtis *et al*., 2004).

In this context, it has been shown that episodes of extracellular dehydration due to the administration of polyethylene glycol (PEG) in pregnant rats (which mimics human vomiting episodes during pregnancy) leads to an increased salt appetite among

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adult offspring (Nicolaidis *et al*., 1990). In fact, salt preference studies performed in humans reveal that offspring from women who experienced moderate to severe vomiting during pregnancy were more likely to prefer and to consume foods high in salt than those whose mothers experienced little or no such symptoms (Crystal and Bernstein, 1995; Leshem 1998). Other studies have also demonstrated that 16-week-old infants whose mothers vomited excessively during early pregnancy drank more concentrated salt solutions than their control counterparts and showed less aversive facial reactions to salty solutions (Crystal and Bernstein, 1998), indicating that maternal dehydration can lead to an enhanced salt preference in offspring (Malaga *et al*., 2005).

Galaverna *et al*., (1995) also observed an enhanced salt appetite in rat offspring from dams submitted to acute and repeated mineralofluid losses during pregnancy after diuretic-natriuretic treatment. In this context, a reported history of mineralofluid loss such as that from hemorrhage, exercise-induced dehydration, or neonatal diuretic therapy might increase the avidity for salt and the attendant health risks (Leshem, 1998). These findings are relevant considering that nearly two-thirds of all pregnant women experience nausea and/or vomiting during this period (Whitehead *et al*., 1992).

In rats, Mansano *et al*. (2007) observed that maternal water restriction over an 11-day period increased natremia and osmolality and was associated with an increase in aldosterone plasma concentrations in offspring at 21 days old. These responses could facilitate offspring survival under expected drought conditions and predispose these animals to suffer from diseases such as hypertension in adulthood (Mansano et al., 2007). In fact, maternal water deprivation during the last 3 days of pregnancy resulted in a significant increase in ANG II type 1 (AT_1), ANG II type 2 (AT_2) and angiotensinogen expression in the forebrain and in intracerebroventricular (ICV) angiotensin II-induced thirst in male offspring (Zhang *et al*., 2011).

Mouw *et al*. (1978) found that although prenatal and early postnatal dietary sodium deprivation had no effect on salt preference, it did induce a persistent increase in water intake, whereas pre- and postnatal dietary sodium overload reduced water intake and increased sodium preference both in need-free conditions and after 10 days of dietary sodium deprivation (Contreras and Kosten, 1983; Curtis *et al*., 2004). A very similar response was observed in the offspring of ewes fed with a high-salt diet and of ewes that grazed on saltbush during pregnancy and lactation; these offspring displayed reduced food and water intake in adulthood (Chadwick *et al*., 2009). Dietary sodium

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restriction in postnatal life in rats also inhibited the normal remodeling of the chorda tympani nerve structure by increasing its terminal fields in the NTS in adulthood (Sollars *et al.,* 2006). The absence of remodeling chorda tympani nerve terminals in sodium-restricted rats might be responsible for the changes in sodium taste, leading to changes in sodium appetite/satiety in adult animals. Recently, Hara et al. (2014) showed that offspring from salt-sensitive Dahl rat dams fed a high-salt diet during pregnancy had a significant reduction in salt intake in their young life. On the other hand, offspring from Dahl dams fed a high-salt diet during lactation had an increased salt appetite, demonstrating that the effect of a perinatal high-salt diet on sodium appetite programming is dependent on the stage of development. A high-salt environment *in utero* was also responsible for a hypertensive phenotype in adult rats, increasing pressor responsiveness to ANG II and beta-adrenergic stimulation (Arguelles *et al*., 1996, 2000; Contreras, 1989; 1993; Contreras *et al*., 2000; Vidonho et al., 2004). Furthermore, a maternal high-salt diet in ewes in mid-to-late pregnancy programs the offspring to overexpress the key elements of renal RAAS, including angiotensinogen, angiotensin converting enzyme (ACE), and AT_1 and AT_2 receptors, at 90 days old, thus indicating changes in renal development and physiology (Mao *et al*., 2013). These findings suggest that high salt intake during pregnancy programs the RAAS to be overactive in adulthood, perhaps leading to exaggerated water and salt intake and the possible risk of developing renal and cardiovascular diseases (Mao *et al*., 2013). However, it is not only long-term manipulation of dietary sodium that can lead to alterations in sodium preference. Leshem *et al.* (1996) demonstrated that in 12-day-old suckling rats subjected to acute sodium depletion, the subsequent adults' avidity for hypertonic saline was substantially enhanced. Additionally, in humans, a large body of evidence suggests that both congenital and experimental factors influence the salt preference (Kochli *et al.*, 2005; Leshem, 2009b). Accordingly, Stein et al. (1996, 2012) propose a persistent effect of early experience on human salt preferences. Perhaps some underlying mechanisms could be coincident with the one proposed by Roitman et al. (2002), who described neuronal alterations common to salt and drug sensitization.

Accumulating evidence indicates that the ability to taste salt is inborn, although responses to salty foods are strongly influenced by environmental factors in humans (Mattes, 1997). Very recently, Goldstein and Leshem (2014) suggested that the attraction to salt is conditioned by the postingestive benefits. They found some evidence

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of beneficial effects of dietary sodium that might contribute to the predilection for salt or salt-flavor-enhanced foods by conditioning for the increased requirement during growth. In this context, dietary experiences during development and increased physical activity during childhood (7-12 years of age) might be responsible for greater salt preference and intake (Verma *et al*., 2007). Additionally, the relationship between parental and offspring food preferences seems generally weak (Rozin, 1991). Measures of salt consumption and salt usage obtained from mothers were unrelated to individual differences in the acceptability of salty foods (Beauchamp and Moran, 1984). However, healthy diets depend on environmental factors, including food availability and the child-feeding practices of the adults (Birch and Davison 2001; Kral and Rauh, 2010).

The evidence presented here suggests that exposure to an altered osmotic environment during ontogeny can program the adult systems that govern thirst and sodium appetite, and if persistent through adulthood, these alterations might have adverse clinical effects such as that on the incidence of hypertension. In addition, these data indicate a direct alteration of intake patterns and, therefore, adjustments in the means of balancing the fluid and hydroelectrolyte states. However, there is little information regarding how these stimuli might provoke the behavioral and endocrine alterations found throughout development and what modifications occur at the neuronal and/or brain circuit levels. Assuming that in mammals, the periods of pregnancy and lactation are characterized by hydroelectrolyte and osmoregulatory remodeling, resulting in an increase in sodium appetite (Barelare and Richter, 1938; Leshem *et al*., 2002; Deloof *et al*., 2000; Macchione *et al*. 2012), Vivas's group used a rat model of voluntary access to hypertonic sodium chloride solution during the pregnancy and lactation periods as a programming model (Macchione *et al*., 2012). At the behavioral level, the results showed that the offspring that developed in a sodium-rich environment (PM-Na group) drank reduced amounts of water not only during Furosemide–sodium depletion but also during need-free conditions as adults compared with the manipulated control animals (PM-Ctrol group). This study showed how the availability of a rich source of sodium could modify the brain pattern of cell activity, inducing a comparatively higher brain cell activity after sodium depletion in key areas involved with osmoreception and osmoregulation such as the SFO and AVP neurons from the hypothalamic magnocellular SON and PVN nuclei, accompanied by an inverse effect in the NTS (Macchione *et al.*, 2012, Fig. 2),. The fact that sodium-exposed animals have

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increased activity in these areas might reflect a sensitization of the osmosensitive circuits in these animals as a result of plasticity changes induced by perinatal manipulation. Moreover, in the case of the SONs of PM-Na animals, we found a greater number of vasopressinergic cells activated by both furosemide doses (20% and 35% increases in the response to low and high doses of furosemide, respectively) compared with PM-Ctrol animals, suggesting a comparatively major activation of the vasopressinergic system. Because this system is mainly involved in renal water recapture, minimizing the drop in blood pressure as a result of hypovolemia caused by sodium depletion, our results show increased vasopressinergic activity and decreased thirst during the test. These observations might be explained by an SFO-SON pathway sensitization induced by perinatal sodium availability that allows PM-Na animals to have a larger anticipatory response, thereby reabsorbing more water after furosemide treatment and drinking less water, resulting in a more hypertonic cocktail during the intake test. Another explanation of our results involves plasticity changes in the osmosensitive mechanisms that might alter the osmotic threshold for AVP release and subsequent water drinking. Previous studies from the Ross laboratory demonstrated that the plasma osmolality threshold for AVP release was increased in offspring exposed *in utero* to an 8-10 mEq/l increase in maternal hypernatremia in response to maternal water restriction. In the same model, the authors demonstrated alterations in the pituitary AVP content and in hypothalamic AVP synthesis (Ramirez *et al.*, 2002; Desai *et al.*, 2003).

-----PLEASE INSERT FIGURE 2 ABOUT HERE-----

3.3. *The renin-angiotensin system and the programming of fluid intake*

Typically, treatments that activate the RAAS in adulthood induce thirst and sodium appetite (Fitzsimons, 1998). However, challenges to or alterations of the RAAS during ontogeny by experimental or external factors have profound and long-lasting effects; ANG II, in particular, appears to play a critical role in thirst and sodium appetite programming. For example, ANG II contributes to kidney development, at least in the rat (Langley-Evans, 2009), because the effect of RAAS blockade during the developmental period caused long-term changes in water and salt intake in adult rats

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that were at least partially attributable to chronic alterations in renal morphophysiology (Butler *et al.*, 2002, Mecawi *et al.*, 2010; Marin *et al.*, 2011). In fact, RAAS blockade with enalapril from birth until 24 - 28 days of age induced evident abnormalities in neonatal rats at 3 or 4 weeks of age. These rats exhibited impaired renal hemodynamics with a reduced filtration rate, and, with respect to effective renal plasma flow, they showed elevated renal vascular resistance and impaired tubular reabsorption of water and sodium (Guron, 2005). Thus, the RAAS is clearly involved in kidney organogenesis apart from its classic role in maintaining cardiovascular and hydromineral homeostasis (Guron, 2005; Cooper *et al.*, 2006; Gomez *et al.*, 1993; Friberg *et al.*, 1994; Shanmugam *et al.*, 1994).

Water drinking responsiveness to dipsogenic stimuli has a well-known sequential activation pattern, and changes in the ontogeny of drinking behavior after manipulation of the RAAS during pregnancy have already been reported (Perillan et al., 2004, 2007, 2008). In this context, offspring exposed to extracellular dehydration *in utero* did not respond to either cellular dehydration at 2 days of age or extracellular dehydration at 4 days of age (Perillan et al., 2008). Additionally, rats that developed in a hyperreninemic ambiance during gestation were more sensitive to thirst induced by isoproterenol (β-adrenergic agonist); this seems to be independent of the RAAS system because captopril pre-treatment did not alter the increased water intake induced by isoproterenol (Perillan et al., 2004).

On the other hand, according to Mecawi *et al.* (2010), RAAS blockade during all of pregnancy and lactation via maternal oral administration of an ACE inhibitor did not change the spontaneous water and salt intake in adult male rats (despite the apparent renal injury). In contrast, Butler *et al.* (2002) found that blockage of the AT_1 receptors in rat dams only during pregnancy (from gestational day 2 to 19) resulted in female offspring displaying significantly increased water intake and hypertonic saline under basal conditions in adulthood. This apparent discrepancy between the results obtained by Butler *et al.* (2002) and Mecawi *et al.* (2010) might be due to the duration of treatment, the RAAS inhibitor used in each protocol, or differences by gender. Moreover, Mecawi et al. (2010) observed a decreased response to strong stimuli such as cellular dehydration (hypertonic sodium chloride), extracellular dehydration (PEG), β-adrenergic RAAS stimulation (isoproterenol), or brain ANG II production stimulation (with a low dose of an oral ACE inhibitor). Using the same approach, Mecawi *et al.*

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(2009) demonstrated that ACE inhibition during pregnancy and lactation could lead to changes in other behavioral patterns such as locomotor activity, pain perception, and social interaction, all of which might be related to the observed changes in feeding behavior in adulthood.

As previously discussed, maternal dehydration during pregnancy has been associated with homeostatic changes in sodium appetite (Nicolaidis *et al*., 1990), thirst (Zhang *et al*., 2011), and the pressor response to ANG II (Gomez *et al*., 1993) in adult offspring. In all cases, the effects have been attributed to alterations of the RAAS components, suggesting that the development of the fetal RAAS is sensitive to maternal-fetal hydration. This is supported by Guan *et al*. (2009) and Zhang *et al*. (2011), whose works describe increased expression of the AT_1 and AT_2 receptors in the offspring of dehydrated mothers. Thus, maternal dehydration alters the RAAS sensitivity of adult offspring.

Follow-up RAAS studies focusing on hypertensive mothers showed that total aortic ligation between the renal arteries produces a sharp rise in renin secretion, generally accompanied by a deleterious side effect on the rat's health (Rojo-Ortega and Genest, 1968). Thus, partial aortic ligation (Costales *et al*., 1984) is a modified model that produces animals with polydipsia and natriophilia along with adequate health. This experimental pathophysiological paradigm provides the opportunity to study the influence of environmental factors such as an endogenously modified RAAS during pregnancy on the hydromineral homeostasis of the offspring. In this context, progeny from dams subjected to partial aortic ligation showed a long-term modification in their ingestive behavior, exhibiting an increased appetite for hypotonic saline solutions compared with control rats and an increase in their salt/water intake ratio following two different thirst challenges (24 hours of fluid deprivation or sodium depletion by furosemide treatment; Arguelles *et al*., 2000). Thus, it was shown that while pups from dams with hypocaloric-induced hypertension were insensitive to the hypertensive effects of sodium chloride (Langley-Evans and Jackson, 1996; Arguelles *et al*. 2000; Perillan *et al*. 2004; 2012), the offspring of hyperreninemic, hypertensive and natriophilic rat mothers had modified ingestive behaviors.

In view of the diversity of the experimental results, it seems obvious that the RAAS is involved in several aspects of the development of mechanisms that are responsive to hydrosaline imbalances. The apparent discrepancies might be due to the

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variety of experimental protocols used, thus highlighting the need for further studies. These findings suggest that a hydrosaline- and RAAS-altered environment during pregnancy might modify some thirst and sodium appetite responses later in life.

3.4. *Steroid hormones and the programming of fluid intake*

Very few studies have directly assessed the effects of glucocorticoids and mineralocorticoids on thirst programming. Perillan *et al*., (2007) demonstrated there were no effects on the offspring of rat dams treated with deoxycorticosterone on thirst induced by hypertonic saline at two days old, by PEG at four days old, or by isoproterenol at six days old. In adulthood, the offspring from dams treated with cortisol or dexamethasone showed no significant differences in need-free water intake compared to the controls. Additionally, when submitted to sodium overload, prenatally cortisol-treated offspring showed a tendency to increase their water intake and urinary volume compared with controls (Moritz *et al*. 2011). Thus, there seems to be no significant effects of treatment with adrenal corticoids hormones during the developmental period on thirst programming, although some reports described hypertensive patterns in the adult offspring of dams treated with glucocorticoids (Wyrwoll et al., 2007; Tang et al., 2011).

In humans, a congenital deficiency of the 21-hydroxylase enzyme, which is involved in cortisol and aldosterone (ALD) synthesis, is responsible for a severe reduction in plasma cortisol and ALD levels, leading to the early development of adrenal hyperplasia and, in the most severe cases, renal salt wasting. Kochli *et al*. (2005) evaluated the salt appetite of young patients with a salt wasting form of congenital adrenal hyperplasia. They demonstrated an increased salt appetite in non-therapeutic normalized salt wasting patients compared with healthy control subjects. These authors suggested that the increased salt appetite in salt wasting patients is due to three factors: i) an adaptive response mediated by the RAAS to maintain the bodily sodium balance, ii) an innate predisposition to eat salt, and iii) an imprinting by hyponatremic events due to the absence of ALD. However, more experimental and clinical studies are needed to understand the impact of developmental alterations of adrenal hormones on the programming of behavioral responses related to the hydromineral balance in adulthood.

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In addition to the role of androgens, estrogens and progestogens in sexual differentiation, behavior and reproduction, the influence of gonadal steroid hormones on cardiovascular and hydromineral homeostasis in adult life is well established (Mecawi *et al*., 2007, 2008; Dalmasso *et al*., 2011; Caeiro *et al.*, 2011; Antunes-Rodrigues *et al*., 2013; Dadam *et al*., 2014). In view of this, SWR/J mice are known to develop nephrogenic *diabetes insipidus*, with a higher polydipsia in females than in males. Schmalbach and Kutscher (1975) performed a gonadectomy in SWR/J male and female mice before puberty to verify whether gonadal hormones were responsible for programming sexual differences in fluid intake. They showed that that an ovariectomy significantly reduced polydipsia in females, whereas castration had no effect in males. Moreover, the castration of SWR/J males resulted in a lower intake of isotonic NaCl solution, whereas females showed no significant differences in salt intake.

Similarly, a neonatal female rat ovariectomy markedly reduced need-free saline drinking in adulthood, with intake values comparable to those found in male rats. Moreover, the treatment of male newborn rats with estradiol led to increased intake of hypertonic saline in adulthood in relation to vehicle-treated animals (Krecek, 1978). Additionally, Alan Epstein's group showed that newborn gonadectomized male rats drank 3% NaCl in adulthood in both need-free and need-induced states, whereas the ovariectomized female rats that were given neonatal testosterone showed a decrease in 3% NaCl intake in need-free conditions (Chow *et al*., 1992). On the other hand, when newborn ovariectomized rats were treated with nonaromatizable androgen (dihydrotestosterone, the biologically active form of testosterone), changes were not observed in either need-free or need-induced 3% NaCl intake in adulthood (Chow *et al*., 1992). This result suggests that the effect of testosterone on sodium intake seems to be governed by the conversion of testosterone to estrogen in the brain.

Although using a non-invasive approach, Ferguson *et al*. (2003; 2009) confirmed the abovementioned findings, showing that estrogen during the developmental period leads to increased salt intake in adulthood. The research showed that male and female offspring from mothers that received chow with ethinyl estradiol (a semisynthetic estrogen) after gestational day 7 consumed more 3% sodium chloride-flavored solution than same-sex controls (Scallet *et al*., 2003). This group also demonstrated a similar effect on salt intake using phytoestrogen genistein, but only in higher doses and with an unclear transgenerational effect (Ferguson *et al*., 2003).

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These studies have shown that developmental exposure to gonadal steroid hormones leads to an increased sodium appetite in adult life, which is in contrast to adulthood exposure, for which adult female ovariectomized rats treated with estradiol for 2 weeks showed a significant reduction in hypertonic saline intake in need-free and need-induced conditions compared with vehicle-treated rats (Mecawi *et al*., 2007; 2009; Dalmasso *et al*., 2011). This opposite effect of gonadal hormones given during development or in adulthood might reveal a possible difference in the epigenetic programming effects of gonadal hormones during development versus in a matured and sexually dimorphic phase of life.

3.5.   *Other developmental influences on the programming of fluid intake*

Several other changes during ontogeny influence drinking behavior. Partial maternal separation during lactation, for example, impacts adult fluid intake. Leshem et al. (1996) demonstrated that rats separated from their dams for 24 hours on the 15th day of lactation only increased need-free saline intake when they had no access to saline during the separation period. These results indicate that maternal separation affects salt intake in adulthood only as a secondary outcome when there is also sodium deprivation. Furthermore, it should not be overlooked that salt ingestion during suckling deprivation might attenuate the stress effects of maternal separation.

The overconsumption of sugar throughout pregnancy might cause metabolic and cardiovascular problems in offspring in adulthood (Grande, 1975). Likewise, high sugar exposure during fetal development can also program fluid intake in adult life. Studies have shown that fetal exposure to a high sucrose solution at the end of pregnancy induced increased expression of the AT_1 and AT_2 receptor proteins in the forebrain in adult animals, although there were no significant differences in water or hypertonic saline intake compared with controls in need-free conditions (Wu *et al*., 2011). However, after water deprivation, the animals exposed to a high sucrose solution in early life showed increased water and 1.8% NaCl intake, as a result of their extracellular volume losses (as indicated by the higher hematocrit), and c-Fos protein expression in neurons from the SFO, PVN and SON compared with control rats. Thus, the excessive consumption of sugar during pregnancy can alter offspring hydromineral balance regulation in adulthood in response to homeostatic challenges, including essential

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neuroendocrine and renal changes, and cause greater sensitivity of the forebrain RAAS mechanisms that control body fluids. In addition, maternal diabetes mellitus induces increased plasma aldosterone concentrations in dams as well as in newborn (Cugini et al., 1987). Future studies are necessary to more closely investigate the influence of these disturbances on body fluid homeostasis.

Another issue of concern is hypoxia during gestation, a common complication during pregnancy that could lead to several morphological and functional changes related to cardiovascular diseases in adult life (Rueda-Clausen *et al*., 2009). Fetal hypoxia induces changes in the need-induced sodium appetite in adult life. Rat offspring from mothers affected by hypoxia during pregnancy show a reduced expression of AT_2 (but not AT_1) ANG II receptors in the forebrain, associated with an increased sodium appetite in response to subcutaneous hypertonic saline or ICV ANG II injection (Yang *et al*., 2010). Additionally, ICV ANG II injection induced higher c-Fos expression in the SFO, MnPO, PVN and SON nuclei among rats submitted to fetal hypoxia compared with control animals, suggesting a higher sensitivity among those animals to the RAAS and, consequently, to the adjustments to challenges (Yang *et al*., 2010).

Prenatal exposure to the abuse of drugs such as alcohol and nicotine can program the offspring's hydromineral balance in adulthood. Rats exposed to alcohol during pregnancy showed seven-fold greater AVP plasma concentrations than control animals, as well as significantly elevated levels of need-free water consumption (Dow-Edwards *et al*., 1989). These results indicate that prenatal alcohol exposure causes a long-term disruption in the central mechanisms regulating AVP release and water intake in rats. Conversely, male and female pups from mothers exposed to nicotine during gestation or during both gestation and lactation showed a significant increase in hypertonic saline intake after 24 hours of water deprivation in adulthood, without a significant alteration in salt intake in need-free conditions (Hui *et al*., 2009). On the other hand, female but not male rats exposed to nicotine during development showed a significant increase in water intake and a decrease in AT_1 and AT_2 receptor expression in the forebrain after water deprivation (Hui *et al*., 2009). Furthermore, offspring of dams exposed to nicotine had a significantly increased renal AT_1/AT_2 ratio (Mao *et al.*, 2009). Because the available results are scarce or discrepant, more studies are necessary to elucidate the consequences of the gestational use of illicit and licit drugs on the hydromineral balance of offspring.

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4.   Epigenetic mechanisms and hydromineral balance

Several studies have been conducted to understand how changes during the biological developmental stages of mammals could lead to severe phenotype modifications in adulthood without individual DNA sequence alterations (for review, see Fig. 3). The increase in our knowledge of the epigenetic control of gene expression provides a broader view of our current understanding of developmental plasticity and the relationships between the environment and changes in gene expression (Hochberg *et al*., 2011).

Spontaneously hypertensive rats (SHR) drink more water and hypertonic saline than Wistar rats, and this phenotype also seems to be related to increased expression of RAAS components in the brain and periphery (Harrap *et al*., 1984). Erkadius *et al*. (1996) and Di Nicolantonio *et al*. (2005), using an elegant model of SHR embryo transfer from an SHR female donor to a Wistar female recipient, demonstrated that the development of an exaggerated sodium appetite in SHR rats is dependent on prenatal SHR fetal environmental programming. In addition, some research had demonstrated that epigenetic changes in SHR rats correlated with increased RAAS activity. For example, in the kidneys of SHR rats, pro-renin mRNA and protein are overexpressed compared with their expression in Wistar rats; this overexpression was associated with increased histone acetylation, increased methylation in activating histone codes, and decreased methylation of suppressive histone codes (Lee *et al*., 2012b). Additionally, several tissues from SHR rats also show higher levels of ACE mRNA and protein expression correlated with ACE gene promoter hypomethylation and histone code modifications (Lee *et al*., 2012a). Therefore, RAAS inhibition by peripheral and central ACE administration decreases sodium intake and blood pressure in SHR rats (Antonaccio *et al*., 1979; Di Nicolantonio *et al*., 1982).

In this context, SHR rats display lower serotonin turnover in the forebrain and midbrain structures (Kim and Ko, 1998; Kubo *et al*., 1990). Additionally, reduced serotonergic activity is commonly associated with depression in adulthood (Blier and Montigny, 1998). Booij et al. (2013) and Albert and Benkelfat (2013) argue that the DNA methylation status at several key genes of the serotonergic system, accompanied early life stress, constitutes a risk factor for depression. The origin of the serotonergic

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system in the DRN has been shown to be an important neuronal circuit that is implicated in renal sodium excretion and sodium appetite regulation (Reis, 2007; Mecawi *et al.* 2013). Overall, the developmental epigenome of the serotonergic system might be an early critical programming effect implicated in the efficiency of adult cardiovascular and hydromineral phenotype control when faced with environmental challenges.

Exposure to nicotine during pregnancy reduces AT_2 expression in association with increased AT_2 gene promoter methylation in the brains of offspring (Li *et al.*, 2012). Relatedly, pre- and/or postnatal nicotine exposure also increases sodium intake in adulthood after water deprivation (Hui *et al.*, 2009). Another example of maternal environmental epigenetics changing RAAS compounds is the maternal protein restriction approach, in which increased adrenal AT_1 receptor expression and decreased gene promoter methylation occur in adulthood (Bogdarina *et al.*, 2007). Additionally, offspring from mothers fed a low-protein diet show increased ACE and reduced AT_2 receptor expression associated with hypomethylation of the ACE gene promoter and reduced expression of the miRNA mmu-mir-330, which putatively regulates AT_2 translation (Goyal *et al.*, 2010).

The enzyme 11 beta-hydroxysteroid dehydrogenase type 2 (HSD2) is expressed only in ALD target cells, in which it confers ALD selectivity to the mineralocorticoid receptor, thereby inactivating glucocorticoids (Geerling *et al.*, 2006). The differential expression of HSD2 is also correlated to the range in HSD2 gene promoter methylation levels. The tissues that show high expression of HSD2 also show less methylation of the same gene than tissues that show little or no expression of the HSD2 enzyme (Alikhani-Koopaei *et al.*, 2004). Because the central classical ALD action of inducing sodium appetite is dependent on HSD2 expression (Geerling *et al.*, 2006), epigenetic changes to the gene encoding this enzyme might also be responsible for sodium appetite programming.

In addition to the RAAS, other systems related to hydromineral balance are epigenetically modulated. Murgatroyd *et al.*, (2009) showed that early life stress in mice leads to high corticosterone plasma levels and PVN AVP mRNA expression and is related to AVP gene hypomethylation in adulthood. In humans, disturbances in volume-regulating mechanisms are associated with eating disorders and alcohol abstinence; the AVP and ANP have been possibly implicated in this allosteric state (Frieling *et al.*

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2008; Hillemacher *et al*., 2009). Frieling *et al*., (2008) demonstrated that women with bulimic disorders also had significantly lower ANP mRNA expression accompanied by hypermethylation of the promoter region of the ANP gene in peripheral blood cells. Furthermore, alcohol-abstinent patients submitted to a detoxification treatment showed decreased ANP mRNA expression and increased methylation of the ANP gene promoter region. This study also revealed decreased methylation of the AVP gene promoter region but no changes in AVP mRNA expression (Hillemacher *et al*., 2009). Because AVP and ANP affect the hydromineral balance, these epigenetic changes caused by developmental or adult life events could also lead to changes in osmotic and volume regulation, which might in turn affect thirst and sodium appetite.

Thus, it is reasonable to assume that pre- and postnatal challenges associated with changes in chromatin structure and, therefore, in the expression of a differentiated epigenome might be responsible for the expression of a new phenotype in adulthood, especially for hydromineral balance. Some studies have shown the importance of epigenetic modulation in several systems implicated in hydromineral homeostatic control. Many studies have also explored the phenomenon of the developmental programming of drinking behavior, but only recently have we had a breakthrough in understanding the molecular mechanisms potentially responsible for this phenomenon. Thus, it is extremely important to associate molecular biology techniques that allow for the study of epigenetic alterations with the study of physiological and behavioral mechanisms that are programmed by developmental environmental changes. This approach will allow us to explain which systems are involved in the programming of the adult phenotype and at what level of organization (genetic, epigenetic, cellular or systemic) these changes are occurring.

5.   Clinical aspects of the developmental programming of fluid intake

As previously mentioned, much information is being collected about the developmental programming of hydromineral balance (Curtis *et al*., 2004; Galaverna *et al*., 1995; Contreras and Kosten, 1983; Contreras and Ryan, 1990; Mouw *et al*., 1978; Butler *et al*., 2002; Nicolaidis *et al*., 1990), and several studies have shown evidence of these programming effects in humans (Crystal and Bernstein, 1995 and 1998; Leshem, 2009a; 2009b; Shirazki *et al*., 2007). Imprinting research in humans, therefore, acquires

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a greater importance, considering the high frequency of maternal and offspring sodium status alterations that result from morning sickness, high sodium intake and/or hyponatremia events, among others.

Taking into account the diverse modifications that might occur in the sodium status of the body during the prenatal and postnatal periods caused by environmental alterations and the implications of these modifications for development, it is interesting to evaluate the effects of i) neonatal diuretic therapy and ii) dehydration/hypernatremia in infants or neonates fed by breastfeeding alone.

For example, studies performed in children who had received neonatal diuretic therapy found that they have, together with an increased salt preference, a greater fractional excretion of sodium than their matched controls, suggesting that neonatal serum sodium loss might be related to a greater salt appetite in children 8–15 years later (Leshem *et al*., 1998).

On the other hand, sodium loss in premature infants is defined as hyponatremia if serum sodium falls below 130 mmol; this can naturally occur in the first postnatal days due to decreased fluid delivery to the distal nephron-diluting segments, often caused by the decreased glomerular filtration rate of the underdeveloped kidneys. Additionally, hyponatremia in the latter half of the first month of life (late onset) is most commonly due to excessive renal losses related to i) the high fractional excretion of sodium, particularly in infants born before 28 weeks of gestation, ii) inadequate sodium intake, iii) the retention of free water from excessive AVP release, iv) renal failure or, less commonly, v) edematous disorders (Al-Dahhan *et al*., 2002; Fanaroff and Martin, 2000).

In addition to the evidence of the programming effects of hyponatremic and vomiting episodes during pregnancy (Nicolaidis *et al*., 1990; Crystal and Bernstein, 1995, 1998; Galaverna *et al*., 1995), it is possible to expect and assume that these events could also model the fluid intake behavior and central circuit activity responsible for hydromineral balance maintenance.

Another possible situation is the occurrence of a hypernatremic-dehydration event during the first days of life caused by breastfeeding alone. There is no doubt that breastfeeding is the best and safest way of nurturing infants, and its advantages are well-recognized; however, dehydration caused by especially bad breastfeeding might occur in the first weeks of life (American Academy of Pediatrics, 1997). Reports of

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dehydration and hypernatremia in exclusively breastfed term infants have appeared in the literature (Sofer *et al*., 1993; Paul *et al*., 2000). It has been demonstrated that good breastfeeding establishes a decrease in the sodium concentration in breast milk to normal physiological levels. However, if a woman fails to establish good breastfeeding, the normal physiological decrease in the breast milk sodium concentration does not occur (Morton, 1994), resulting in the occurrence of mild hypernatremia in the mother and, consequently, in the babies, as well. Moreover, observations made by Kusuma (2009) showed an interesting correlation between a higher sodium concentration in breast milk and hypernatremic babies; for every 1 mEq/L of breast milk sodium level enhancement, there is a 1.8-fold increase in the baby's natremia. Additionally, hypernatremia in these babies is due not only to the high sodium content in the breast milk but also to inadequate milk intake and consequent dehydration and weight loss in near-term newborns (Kusuma *et al*., 2009; Sofer *et al*., 1993; Paul *et al*., 2000; Cooper *et al*., 1995; Oddie *et al*., 2001; Maayan-Metzger *et al*., 2003; Dewey *et al*., 2003).

Although healthy humans do not show a pronounced sodium appetite (Leshem, 2009a), we can formulate some plausible hypotheses about how perinatal experiences might alter water and salt intake in adulthood: i) perinatal experiences might lead to several physiological changes in the endocrine, renal and cardiovascular systems throughout development, and these changes might be responsible for an imbalance in sodium and water excretion, leading to their excess or deficiency and, consequently, an increased or reduced water and salt intake; ii) the complex neural network involved in the perception and determination of the thresholds for the induction of thirst and sodium appetite (taste, central integration and neuroendocrine responses) can be epigenetically programmed to be hyper- or hypo-responsive to dipsogenic and/or natriorexigenic stimuli; and iii) conditioning and learning by the cultural environment in early childhood should influence the pleasure of eating salt and, consequently, the amount of salt intake in adulthood (for a review, see Leshem, 2009a). Finally, the long-term programming effects of the developmental environment and changes in the pattern of fluid intake among elderly humans might be very interesting to explore (Cowen *et al.,* 2013; Hendi & Leshem, 2014). Several studies show that aging rats are deficient in thirst and salt appetite responses to homeostatic challenges compared with young rats, suggesting a deficit in dehydration signals in the elderly (Phillips *et al*., 1984; 1991; Silver, 1990; Adams, 1988). This represents a health hazard for a steadily increasing

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elderly population and might be accentuated by the programming effects originated during the pre- and/or postnatal periods.

6. Conclusions

To summarize, the studies and findings presented here indicate that several developmental complications, not necessarily related to hydromineral or cardiovascular disturbances (such as hypoxia), in addition to the lifestyle (such as smoking, alcohol consumption, undernutrition and an excess of sugars in the diet) and the cultural environment, can program the neuroendocrine systems that are directly implicated in the control of thirst and sodium appetite in adult offspring, thereby changing their behavioral responses in adulthood. It is also suggested that cardiovascular and renal diseases might coexist in these altered phenotypes. Thus, because the lifestyle during pregnancy (among other issues) causes abnormalities in fluid intake in adult life, it is important that health professionals are critically aware of the need for caution during pregnancy. It is also extremely important that there is careful and close monitoring of the feeding, weight and urination frequency of neonate babies to prevent the development of severe dehydration and hypernatremic conditions. More studies are needed to evaluate how the different situations of hypernatremic-dehydration induced by breastfeeding, hypovolemia/hyponatremia from diuretic treatment and vomiting episodes during pregnancy can program and affect the offspring. Furthermore, it is essential to study the alterations caused by changes during the early stages of life to advance the establishment of efficient therapeutic strategies for the prevention and the treatment of related pathologies.

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Figure Legends

Graphical Abstract: Scheme showing the possible consequence of several environmental factors (lifestyle, hydromineral balance and/or challenges, neuroendocrine disturbances, dietary composition and drug use) at different stages of the developmental programming of thirst and sodium appetite, as well as the

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predisposition to pathological conditions such as hypertension and/or kidney damage.

Figure 1. Schematic representation of the neurochemical circuits involved in fluid balance regulation [Adapted from Vivas *et al.*, 2013].

Figure 2. Effects of furosemide-induced sodium depletion (2 doses: Low-Furo and High-Furo) on the number of Fos-immunoreactive (Fos-ir) cells in (A) the subfornical organ (SFO), (B) the nucleus of the solitary tract (NTS), and (C) the supraoptic nucleus (SON) and the lateral magnocellular subdivision of the paraventricular nucleus (PaLM) of the two perinatal manipulated (PM) groups. The PM-Na group had voluntary access to a hypertonic sodium chloride solution (0.45 M NaCl), water and a standard diet, whereas the PM-Ctrol group had free access to water and a standard diet only. (D) The average number of Fos/vasopressin-immunoreactive (Fos/AVP-ir) double-labeled cells in the SON and the PaLM subdivision of the paraventricular nucleus of both PM groups after injection with the two different doses of furosemide. Values are the means±SE. (*) $p < 0.05$, significantly different from the PM-Ctrol group. (E) Photomicrographs showing the pattern of Fos-immunoreactivity in the subfornical organ (SFO, I–II) and immunoreactive double-labeled cells (Fos-AVP) in the supraoptic nucleus (III–IV) among PM-Ctrol (I, III) and PM-Na (II, IV) animals after the injection of a high dose of furosemide. The small squares in plates C and D show higher magnifications (40×) of cells in 10X plates. Scale bar=100 μm [Adapted from Macchione *et al*., 2012].

Figure 3. Epigenetic programming of the morphofunctional phenotype by environmental factors. **1.** Several external or internal environmental factors are able to interact with biological systems and change the expression/activity of the enzymatic machinery responsible for catalyzing covalent changes in DNA and histones, remodeling chromatin and modulating gene expression. **2.** The enzymes that mediate changes in the histone acetylation (Ac) pattern are histone acetyltransferases (which catalyze the acetylation) that promote chromatin unpacking and histone deacetylases (which catalyze the deacetylation) that promote chromatin packaging. **3.** DNA methylation (M) is catalyzed by DNA methyltransferases (thereby reducing gene expression), whereas DNA demethylation could be passive or active; in the latter case, demethylation is mediated by DNA demethylase enzymes (thereby increasing gene

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expression). **4.** Both increased chromatin packing and increased DNA methylation reduce gene expression by hindering the interaction of transcription factors (TF) and RNA polymerase with target genes, whereas chromatin unpacking and DNA methylation reduction facilitate gene expression. **5.** Thus, these epigenetic changes in specific genes are able to increase or decrease the expression of mRNA and its related proteins, inducing the morphofunctional programming of physiological systems.

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Figure 1

Figure 2

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Figure 3