*Swaab/The Human Hypothalamus: Hypothalamus and Neuroendocrine Disorders*

**ANIMAL MODELS FOR DIABETES INSIPIDUS**

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**ABSTRACT**

The hormone arginine vasopressin (AVP) is a nonapeptide synthesized by hypothalamic magnocellular nuclei and secreted from the posterior pituitary into the bloodstream. It binds to AVP receptor 2 (AVPR2) in the kidney to promote the insertion of aquaporin channels (AQP2) and antidiuretic responses. AVP secretion deficits produce central diabetes insipidus (CDI), while renal insensitivity to the antidiuretic effect of AVP causes nephrogenic diabetes insipidus (NDI). Hereditary and acquired forms of CDI and NDI generate hypotonic polyuria, polydipsia, hyperosmolality, and hypernatremia. The AVP mutant (Brattleboro) rat is the principal animal model of hereditary CDI, while neurohypophysectomy, pituitary stalk compression, hypophysectomy, and mediobasal hypothalamic lesions produce acquired CDI. In animals, hereditary NDI is mainly caused by mutations in AVP2R or AQP2 genes, while acquired NDI is most frequently induced by lithium. We report here on determinants of the intake and excretion of water and mineral salts and on the different types of DI in humans. We then describe the hydromineral characteristics of these animal models and the responses observed after administration of hypertonic NaCl or when they are fed with low-sodium diets. Finally, we report on the effects of drugs such as AVP analogues and/or oxytocin, another neuropeptide that increases sodium excretion in animal models and humans with CDI, and sildenafil, a compound that increase the expression and function of AQP2 channels in animal models and humans with NDI.

**Keywords:** Central diabetes insipidus; nephrogenic diabetes insipidus; polyuria; polydipsia; hypernatremia; mutations; hypothalamic-neurohypophyseal system damage; arginine vasopressin, oxytocin, aquaporins.

1.- **DETERMINANTS OF THE INTAKE AND EXCRETION OF WATER AND MINERAL SALTS**

Diabetes Insipidus (DI) affects hydromineral homeostasis. In order to understand this syndrome, it is useful to consider the factors that determine fluid intake, sodium appetite, and diuresis (reviewed by Stricker and Sved, 2000; de Souza Mecawi et al., 2015; Stanhewicz and Kenney, 2015; Gizowski and Bourque, 2018; Hughes et al., 2018; Kenefick, 2018).

Water is the largest component of the human body and is lost through breathing, sweating, and the production of feces and urine. Total body water comprises extracellular fluid (ECF) and intracellular fluid (ICF), each with specific concentrations of solutes (Stricker and Sved, 2000). The most abundant solute in the ECF is sodium, and the primary ions are chloride and bicarbonate, representing almost all of the osmotically active components of this fluid. The most abundant solute in the ICF is potassium. ECF and ICF are separated by cell membranes that are selectively permeable to solutes but freely permeable to water. Thus, water passes by osmosis through membranes from areas of lower to higher solute concentration, thereby equalizing osmotic ECF and ICF concentrations (de Souza Mecawi et al., 2015).

Homeostatic thirst and sodium appetite are related to changes in the volume and composition of ECF and ICF and are mainly produced by two distinct biological mechanisms (Fitzsimons, 1979; Gizowski and Bourque, 2018). One mechanism results from an increase in the concentration of solutes in ECF and is designated osmotic thirst (Gizowski and Bourque, 2018; Hughes et al., 2018), produced in particular by the intake of sodium chloride-rich food. The accumulation of NaCl in the extracellular space causes the loss of water from the cell (cell dehydration) (Kenefick, 2018). In order to compensate for these effects and return to the set point, the sodium appetite is inhibited and the natriuretic response is enhanced. Simultaneously, the intake of water is stimulated at the same time as the diuresis is reduced (Figure 1, upper).

Another mechanism that stimulates water intake is volemic thirst (Gizowski and Bourque, 2018). In this case, the intake is a consequence of the loss of intravascular fluid, which forms part of the ECF. Hypovolemia is defined by a net loss of ECF volume, which triggers compensatory neuroendocrine reactions to conserve body fluids (antidiuretic response to retain water and antinatriuretic response to preserve salt) and maintain an optimal blood pressure (vasoconstrictor response) (Kenefick, 2018). These circumstances also produce a thirst and appetite for sodium, especially the intake of isotonic drinks that contain sodium chloride at the same concentration as in the intravascular fluid (0.15 Molar). The goal of all of these responses is to restore the volume deficit (Figure 1, lower). Diarrhea, vomiting, hemorrhages, renal disease, and cardiovascular disorders are sometimes accompanied by major volume losses that mandate the consumption of liquids and salt (Stricker and Sved, 2000).

**PLEASE INSERT FIGURE 1 ABOUT HERE**

**2.- DIABETES INSIPIDUS: CHARACTERISTICS AND TYPES**

Diabetes insipidus (DI) was first described in the 17th century as the excretion of abnormally high volumes of dilute urine (hypotonic polyuria). This retention deficit leads to rises in serum sodium concentration (hypernatremia) and osmolality (hyperosmolality) that are responsible for increased osmotic pressures, osmotic thirst and, frequently, a high compensatory water intake (polydipsia) (see Table 1, Fenske and Allolio, 2012; Arima et al., 2016; Kalra et al., 2016; Robertson, 2016; Bernal et al., 2016, 2017; Bockenhauer and Bichet, 2017; Schernthaner-Reiter et al., 2017; Christ-Crain et al., 2019; Kavanagh and Uy, 2019).

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The excretion of urine and electrolytes by the kidneys is mainly regulated by the hormone arginine vasopressin (AVP), which is encoded by the AVP‑neurophysin II gene (AVP‑NPII) (Kalra et al., 2016; Bankir et al., 2017; Schernthaner-Reiter et al., 2017). This neuropeptide is synthesized in the somata of magnocellular neurons of hypothalamic paraventricular (PVN), supraoptic (SON), and accessory neurosecretory nuclei alongside its carrier protein, neurophysin II. The precursor of AVP and NPII is processed within the endoplasmic reticulum and Golgi apparatus and stored in neurosecretory vesicles, where AVP and NPII are cleaved by dipeptidases during its migration down the axons. Axons of this magnocellular complex pass through the median eminence (ME), forming the neurohypophyseal stalk, and terminate in the neurohypophysis or posterior pituitary. Axonal swellings are observed close to fenestrated capillaries in the ME and posterior pituitary, allowing this neurohormone to enter the bloodstream (Armstrong, 2014; Qureshi et al., 2014). After its release into the circulation, AVP binds to AVP receptor 2 (AVPR2) on renal collecting tubule cells (King and Agre, 1996) (Figure 2). This triggers an intracellular signaling cascade that results in the increased production and insertion of aquaporin-II (AQP2) channels in the cell membrane (Bech et al., 2018; Yingjie et al., 2017), leading to passive water reabsorption from the nephron lumen into cells of the collecting duct along an osmotic gradient. Next, water leaves the cell towards the interstitium *via* AQP3 and AQP4, expressed on the basolateral collecting duct membrane (Ando et al., 2018; Loonen et al., 2008; He and Yang, 2019).

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Numerous factors can influence the secretion of AVP, although the most potent stimulus under physiological conditions is increased plasma sodium levels and osmolality. There is a linear relationship between plasma osmolality and circulating AVP concentrations (Bankir et al., 2017; Hughes et al., 2018). Another strong stimulus of AVP secretion is hypovolemia. Plasma AVP was found to increase exponentially with a higher degree of hypovolemia in rats (Bankir et al., 2017).

The magnocellular neurosecretory system also contains cells responsible for oxytocin (OT) synthesis (Armstrong, 2014). The OT gene is situated close to the AVP-NII gene on chromosome 20, separated by 12 kb of intergenic sequences (Rao et al., 1992), and the chemical structures of AVP and OT are very similar, being nonapeptides that only differ in amino acids at positions 3 and 8 (Figure 3) (Brownstein et al., 1980). In addition, they both bind with high affinity to AVPR2 and OT receptors (Qureshi et al., 2014). Given these structural similarities, it is not surprising that OT exerts an effect on urinary concentrations, and it is particularly related to natriuretic processes (Balment et al., 1980; Verbalis et al., 1991). It has also been proposed that AVP and OT have synergistic natriuretic effects (Andersen et al., 1992). Other substances that are co-localized within magnocellular OT or AVP neurons participate in hydromineral homeostasis (see Bundzikova et al., 2008 for a review). For instance, atrial natriuretic peptide (ANP), co-localized with OT, has been reported to play a role in the excretion of body sodium, especially in response to isotonic volume expansion (Chriguer et al., 2001).

**PLEASE INSERT FIGURE 3 ABOUT HERE**

Among the four recognized types of DI (Christ-Crain et al., 2019; Kalra, Zargar, Jain et al., 2016; Robertson, 2016), the most widespread is central, neurogenic or neurohypophyseal DI (CDI) (Arima et al., 2016; Christ-Crain et al., 2019; Lu, 2017), which is caused by deficient AVP production. The most frequent CDI is acquired CDI, caused by brain injury or surgery in the pituitary, hypophyseal stalk, infundibulum, or mediobasal hypothalamus (MBH) (Wijetilleka et al., 2016; Mahía et al., 2019). By contrast, congenital CDI, which can be due to autosomal dominant or autosomal recessive mutations, accounts for only 1-2 % of CDI cases (Schernthaner-Reiter et al., 2017; Rutishauser et al., 2019; Morishita and Arvan, 2020, see <https://omim.org>). Heterozygous infants with dominant mutations are healthy at birth but develop DI at a later age (Christ-Crain et al., 2019), due to the progressive death of AVP-producing neurons (see below).

Nephrogenic diabetes insipidus (NDI) is a less frequent type of DI that results from renal insensitivity to the antidiuretic effects of AVP and is characterized by reduced urine osmolality and increased urine volume despite the availability of AVP (Kalra, et al., 2016; Robertson, 2016; Bockenhauer and Bichet, 2017; Lu, 2017; Schernthaner-Reiter et al., 2017; Balla and Hunyady, 2019; Christ-Crain et al., 2019; Kavanagh and Uy, 2019). The congenital form of NDI is rare (1 per 100,000 human births). A high number of mutations in AVPR2 have been identified, including deletions and insertions, missense and nonsense mutations. Other mutations affect the AQP2 gene. Most are missense or nonsense mutations that cause autosomal recessive nephrogenic DI (see Christ-Crain et al., 2019 for review). It appears early in life, being produced in 90% of cases, mainly in males, by X‑linked recessive mutations in the gene of the AVP2R localized in chromosome Xq28, and in the remaining 10% of cases by autosomal-recessive and -dominant mutations in the gene that encodes AQP2, localized in chromosome 12q13 (Boone and Deen, 2008; Loonen et al., 2008; Lu, 2017; Milano et al., 2017; Ando et al., 2018). The acquired form of NDI, induced in adults by drugs such as lithium, is more frequent. Lithium is prescribed for bipolar disorders and is associated with renal injury, including impaired urine concentration capacity (Nielsen et al., 2002; Loonen et al., 2008; Kalra et al., 2016; Lu, 2017: Poulsen et al., 2017; de Groot, et al., 2019).

A third type of DI, gestational DI, is due to a deficiency of plasma levels of AVP through its increased degradation by cysteine aminopeptidase, an enzyme produced in the placenta. Gestational DI typically onsets in the third trimester but spontaneously resolves at 2–3 weeks postpartum. The pathophysiology of gestational DI is similar to that of CDI except for its resistance to AVP treatment (Siristatidis et al., 2004; Kalra et al., 2016; Robertson, 2016; Lu, 2017; Christ-Crain et al., 2019). A fourth type of DI (primary polydipsia) is produced by the suppression of AVP secretion due to excessive fluid intake (Kalra et al., 2016; Robertson, 2016; Christ-Crain et al., 2019). It is commonly related to psychiatric disorders (psychogenic primary polydipsia) such as schizophrenia and compulsive behavior, and it is usually accompanied by an explicit denial of thirst (Verghese, et al., 1993, 1996). In other cases (dipsogenic primary polydipsia), regulatory anomalies can result from a wide variety of diseases involving different regions of the central nervous system, including meningitis, neurosarcoidosis, traumatic brain injury, or brain damage due to the consumption of chemical products such as lithium or alcohol, among others (Christ-Crain et al., 2019).

**3.- ANIMAL MODELS OF CENTRAL AND NEPHROGENIC DI**

Animal models have proven highly useful to determine the neurobiological substrate of neurogenic and nephrogenic DI and to develop possible therapeutic approaches. This chapter describes the animal models of central and nephrogenic DI listed in Table 2.

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3.1. Animal models of Central Diabetes Insipidus (CDI).

* + 1. Hereditary CDI

The first natural knock-out model of hereditary CDI spontaneously appeared in the Long-Evans hooded strain in a laboratory in West Brattleboro, Vermont (Valtin and Schroeder, 1964). The polydipsia and polyuria of Brattleboro rats derive from their incapacity to synthesize AVP due to an autosomal recessive variant of the AVP-NII gene (Nielsen et al., 2002; Baturina et al., 2016). The mutated allele encodes normal AVP but abnormal NII, thereby interfering with the transport and processing of the AVP-NII precursor molecule (see Fujiwara and Bichet, 2005). As expected, homozygous Brattleboro rats produce a ten-fold higher volume of hypotonic urine than normal, being polydipsic with chronic hypernatremia and hyperosmolality and showing a reduced consumption of salty solutions (Sokol and Valtin, 1982; Yirmiya et al., 1988; Füller and Fitzsimons, 1998). Although vasopressin synthesis is impaired, OT, the other structurally similar neurohypophyseal peptide hormone, is synthesized in Brattleboro rats (see Sokol and Valtin, 1982).

Renal water loss is averted by bilateral nephrectomy, which eliminates the hyperdipsic response of Brattleboro rats after hypertonic NaCl administration, demonstrating the primary nature of polyuria in these rats (Füller and Fitzsimons, 1988). Nevertheless, various hydromineral challenges can modify the hydromineral regulatory behavior of homozygous Brattleboro rats. For example, food deprivation is followed by a reduction in the polyuric (Wilke et al., 2005) and polydipsic (Wideman and Murphy, 1991; Wilke et al., 2005) responses that accompany increases in urinary osmolality and in the expression of AQP2 channels (Wilke et al., 2005). Likewise, Brattleboro rats respond appropriately to hypertonic NaCl administration, increasing the natriuretic response (Balment et al., 1980; Brimble et al., 1991), the urine concentration (Balment et al., 1980; Edwards and La Rochelle, 1984; Brimble et al., 1991), and the intake of water (Füller and Fitzsimons, 1988). This conservation of the regulatory capacities of Brattleboro rats may be related to their increased plasma levels of OT (Brimble et al., 1991; Zelena et al., 2013) and prolactin, an adenohypophyseal hormone that promotes OT release and antidiuresis in these rats (Morrissey et al., 2001).

Animal models of CDI inherited in an autosomal dominant pattern have been developed by inserting mutations into the AVP-NII gene (knock-in or KI models). For instance, C98X-KI mice were produced by replacing a Cys residue at position 98 of the AVP-NII gene with a stop codon. C98X-KI mice replicate various features of human autosomal dominant mutations, including a delayed onset and progressive worsening of the disease. These characteristics have been related to the accumulation of aggregates of mutant AVP precursors in the endoplasmic reticulum and to the subsequent progressive death of AVP-producing neurons (Russell et al., 2003; Hagiwara et al., 2014; Ariyasu et al., 2017).

* + 1. Acquired CDI

Neurohypophysectomy, pituitary stalk compression or electrolytic lesion, hypophysectomy, and damage to mediobasal hypothalamic (MBH) structures, can reduce the secretion of AVP and lead to the onset of CDI (see Antunes-Rodrigues et al., 1991; Mahía et al., 2008, 2013, 2019; Bernal et al., 2013; Arima et al., 2016; Wijetilleka et al., 2016; Lu, 2017; Feng et al., 2018; Rutishauser et al., 2019; Morishita and Arvan, 2020).

3.1.2.1 Neurohypophysectomy, pituitary stalk compression, and pituitary stalk electrolytic lesion

The neurohypophysis is removed by making a small incision in the caudal tip of the anterior lobe of the pituitary gland exposed *via* a parapharyngeal approach (Merrill et al., 1986), then extracting the underlying posterior pituitary lobe by suction. A specific neurohypophysectomy (neurohypox) is technically challenging, and some authors use pituitary stalk compression (PSC; Dohanics et al., 1992), mounting anesthetized rats on a stereotaxic frame with nose down 3.3 mm and excising a small square of bone from the skull. Next, a triangle-shaped wire is lowered in coronal plane 4.0 mm caudal to bregma in the midline down to the skull floor, maintained in place for 30 s, and then removed. A 3D-printed lesion knife was recently designed for incorporation into the stereotaxic instrument. A pituitary stalk electrolytic lesion (PSEL) was produced by applying a cathodic current of 500 μA for 40 s at the skull floor at 3.8 mm caudal to bregma (Feng et al., 2018). Histological examination of the pituitaries after PSC, or PSEL showed no significant anatomic tissue damage to either the anterior or the intermediate lobes.

Neurohypox, PSC and PSEL, increase polyuria and water intake, and decrease sodium excretion (Balment et al., 1986a; Dohanics et al., 1992; Haller et al., 1996; Elias et al., 2004; Feng et al., 2018). PSC reduces AVP and OT contents in the neurointermediate pituitary lobe but not in the ME. However, despite this availability, plasma AVP and OT responses to intravenous hypertonic NaCl infusion were blunted in PSC rats (Dohanics et al., 1992).

In earlier studies with neurohypox animals, AVP administration reduced their urine flow and increased their sodium excretion (Balment et al., 1986a). This natriuretic response to AVP was enhanced by the administration of OT, which corrected the renal sodium excretion deficit of neurohypox animals (Balment et al., 1986a). This finding is consistent with the synergic natriuretic effects produced by the joint administration of the two neurohormones (Andersen et al., 1992) and suggests that the absence of both AVP and OT may be responsible for the lesser natriuretic ability of neurohypox animals.

* + - 1. Hypophysectomy

In anesthetized animals, the pituitary gland is exposed *via* a parapharyngeal approach, the base of the skull is penetrated using a dental drill, and the anterior and posterior lobes are then removed by gentle suction (Neilson et al., 2019; Smith, 1930). Hypophysectomy (hypox) reduces urinary sodium excretion and increases urinary output, serum sodium concentration and water intake (Balment et al., 1986b; Fregly and Rowland, 1989). Hypox animals frequently have severe body sodium regulation disorders and, unlike in the case of Brattleboro rats, the consumption of NaCl solutions is higher by hypox rats than by sham-operated rats (Fregly and Rowland, 1989).

The deficient natriuretic response of hypox animals is only partially corrected by the joint administration of AVP and OT, remaining lower than that of intact rats (Balment et al., 1984; 1986b). Hence, it has been proposed that low levels of some adenohypophyseal hormones, including prolactin, may play an important role when AVP secretion is impaired (Morrisey et al., 2001). In contrast, the administration of hypertonic NaCl to hypox animals increased their urinary sodium excretion (Dorn et al., 1970), which was reduced by a low sodium diet (Fregly and Rowland, 1989). These findings indicate the functional integrity of the renin-angiotensin-aldosterone system in hypox rats (Fregly and Rowland, 1989).

* + - 1. Mediobasal hypothalamic lesion

Lesions to the mediobasal hypothalamic (MBH) region were produced by placing anesthetized rats in a stereotaxic apparatus for the bilateral application of an anodic current of 1.5 mA for 15 s with a stainless-steel electrode that was insulated except at the tip (Rolls, 1970; Antunes-Rodrigues et al., 1991; Mahía et al., 2008, 2013, 2019; Bernal et al., 2013) Stereotaxic coordinates in Wistar rats were 2.56 mm caudal to bregma, 0.4 mm lateral to midline, and 9.8 mm ventral to bregma. All lesioned animals showed extensive MBH lesions in the rostral-caudal dimension with total damage of the ME region, also observing partial injury of the arcuate, ventromedial, and dorsomedial hypothalamic nuclei in most of the rats. There was no damage to supraoptic or paraventricular nuclei (Mahía et al., 2008, 2013, 2019; Bernal et al., 2013) (Figure 4).

**PLEASE INSERT FIGURE 4 ABOUT HERE**

MBH lesions in animals produce a triphasic polyuric and polydipsic CDI with hypernatremia. The process begins with polyuria and polydipsia for 24-48 h, followed by an interphase (oliguric phase) of a few days with reduced urine excretion and water intake, and a final chronic phase of polyuria and polydipsia (Rolls, 1970; Morris et al., 1976; Antunes-Rodrigues et al., 1991; Mahía et al., 2008, 2013; Bernal et al., 2013). The hydromineral behavior of MBH-lesioned animals is characterized by hyperphagia, which is not found in hypox rats (Bernal et al., 2013; Mahía et al., 2008, 2013), and damage to the arcuate and/or ventromedial hypothalamic nuclei is likely to be responsible for this behavior (see Schwartz et al. 2000). As in other models, AVP secretion is interrupted in MBH-lesioned animals; however, unlike in Brattleboro animals, MBH lesions also stop the secretion of OT and atrial natriuretic peptide (Antunes-Rodrigues et al., 1991; McCann et al., 1997) and increase the consumption of salty solutions (Mahía et al., 2008). In addition, nephrectomy does not abolish the polydipsic response of MBH-lesioned animals (Smith and McCann, 1962), suggesting that the ingestive behavior of these animals is not solely secondary to renal fluid loss.

One factor that may account for this hyperdipsic response is diabetic hyper-natremia/osmolality, and this would also not be exclusively the result of hypotonic excretion. This is consistent with the proposal that lesions of the ME area may affect brain circuits that regulate sodium levels (Antunes-Rodrigues et al., 2004) and also with classic studies suggesting a relationship between diabetic hyperdipsia and the amount of sodium consumed in the diet (e.g., Curtis, 1924; Swann, 1939). In line with this proposition, studies of hydromineral regulation in our laboratory have confirmed that OT administration, food deprivation (Bernal et al., 2013; Mahía et al., 2019), and low-sodium diets (Mahía et al., 2013), which all reduce serum sodium concentrations (Fitzsimons, 1979), reduces the diabetic polydipsic response of MBH-lesioned animals. These effects were greater when OT was administered to food-deprived MBH-lesioned rats during the initial diabetic phase and when MBH-lesioned animals were food-deprived during the chronic phase (Bernal et al., 2013).

3.2.- Animal models of NDI

As in the case of CDI, NDI can also result from genetic and acquired factors (Kwon et al., 2000; Boone and Deen, 2008; Loonen et al., 2008; Bockenhauer and Bichet, 2017; Milano et al., 2017; Poulsen et al., 2017; Balla and Hunyady, 2019; Kavanagh and Uy, 2019) (see Table 2).

3.2.1. Hereditary NDI

The first viable mouse model of human X-NDI was recently developed by deleting the AV2PR gene in adult mouse kidneys in a conditional manner by standard mouse gene-targeting techniques (Li et al., 2009; Milano et al., 2017). The gene was modified by inserting two loxP sites for excision of the flanked (floxed) gene segment through Cre-mediated recombination. The conditional mutant mice were then generated by crossing the floxed strain with a Cre transgenic line so that the target gene is inactivated *in vivo* within the expression domain of Cre. An adequate supply of CreER(T2) transgenic mice permitted the inducible inactivation of AVPV2R floxed alleles in adult mice by administering tamoxifen (0.5 mg i.p/mouse) for 6 consecutive days (Li et al., 2009). The resulting AVP2R-KO mice demonstrated the key symptoms of X-NDI, including polyuria and polydipsia, and a marked reduction in renal AQP2 and AQP3 expression (Li et al., 2009). Studies of this new mouse model have led to the development of highly effective drugs for X-NDI. Thus, the prolonged treatment of AVP2R-KO mice with ONO -AE1-329, a selective EP4 PGE2 receptor agonist, was found to increase renal AQP2 levels and urine osmolality and reduce urine excretion and water intake (Li, et al., 2009; Olesen et al., 2011; Gao et al., 2015).

Recently developed autosomal NDI mouse models have yielded new and relevant *in vivo* information on the role of AQP2 in water conservation under physiological and pathological conditions (Boone et al., 2008; Loonen et al., 2008; Milano et al., 2017). Rojek et al. (2006), used Cre/loxP technology to generate mice lacking functional AQP2 in collecting ducts (AQP2-CD-KO) by inserting LoxP sites into AQP2 introns 2 and 3. Cre recombinase activity leads to deletion of the AQP2 gene exon 3, suppressing channel function. Specifically, AQP2-CD-KO mice with a virtually complete absence of AQP2 in cortical collecting duct cells survived to adulthood and showed a more extreme renal phenotype of NDI than is usually observed in humans (Li et al., 2009; Milano et al., 2017).

Nitric oxide (NO) has been proposed as a key messenger in the pathogenesis of nephrogenic diabetes insipidus, based on mouse studies in which genes for all three NO synthases (NOSs) were deleted. Because NOSs promote vasopressin-induced APQ2 expression in the collecting duct, these triple NOSs null mice evidenced prominent polyuria, polydipsia, and blunted renal responsiveness to exogenous AVP (Tsutsui et al., 2015).

3.2.2. Acquired NDI

Lithium-induced NDI is the most frequent acquired form of NDI and is estimated to affect 1 in 1000 patients with bipolar disorders under long-term treatment with lithium salts, and around a quarter of these suffer from serious adverse effects such as polyuria, polydipsia, and a limited renal response to AVP (Nielsen et al., 2002; Loonen et al., 2008; Poulsen et al., 2017; de Groot et al., 2019). The effects of a 25-day treatment with oral lithium treatment have been studied in Wistar rats (Marples et al., 1995; Kwon et al., 2000). In these studies, lithium chloride was added to their diet at a final concentration of 40 or 60 mM lithium/Kg of dry food, containing food with 40 mM lithium/Kg for the first 10 days and 60 mM lithium/kg thereafter, thereby achieving therapeutic serum lithium concentrations and minimizing lithium-induced weight loss (Christensen and Agner, 1982). All lithium-treated rats also had access to a solid NaCl block in order to obtain sufficient NaCl, avoiding lithium intoxication and a negative sodium balance. This lithium treatment progressively reduced their AQP2 and AQP3 levels to 5% of control levels at 25 days (Marples et al., 1995; Kwon et al., 2000). The downregulation of AQP2 expression was accompanied by the progressive development of severe hypotonic polyuria and highly elevated water intake (Marples et al., 1995; Kwon et al., 2000; Nielsen et al., 2002).

The fact that lithium-treated patients vary in their susceptibility to these lithiopathies indicates a possible genetic predisposition (de Groot et al., 2019). Genome-wide association studies of animals have described eight loci with different candidate genes related to lithium-induced NDI. For instance, Acer2-KO mice, which lack a highly conserved protein segment of the alkaline ceramidase family expressed in the collecting duct, were at greater risk of lithium-induced NDI. These knockout mice, generated using CRISPR/Cas9 technology, were administered with 40 mM lithium chloride/Kg daily for 8 days and showed a significant increase in urine output and decrease in urine osmolality at the end of this treatment (Li et al., 2018), when a reduction in AQP2 expression was also observed (de Groot et al., 2019).

The above studies confirm that genetic variation plays a major role in the susceptibility of mice to lithium-induced adverse effects and have identified genes that may help to identify susceptibility genes in humans (de Groot et al., 2019).

**4. From animal models to emerging human therapies for DI**

A deficit in AVP, which produces the excretion of a high volume of dilute urine, is a necessary and sufficient condition for the onset of CDI, as demonstrated in the Brattleboro rat (Sokol and Valtin, 1982; Yirmiya et al., 1988; Füller and Fitzsimons, 1998; Fujiwara and Bichet, 2005). For this reason, the current standard of care for patients with CDI is treatment with desmopressin (1-deamino-8-d-AVP), a synthetic analog of AVP selective for AVPR2 that has an increased and prolonged antidiuretic effect (see Qureshi et al., 2014 for review).

However, the symptoms of most patients with acquired CDI, are more similar to those recorded in MBH-lesioned animals than to those observed in other animal models of CDI (see Bernal et al., 2016; Christ-Crain et al., 2019 for review). In particular, all of the animal models of acquired CDI described above suggest that the secretion of OT may also be affected (Balment et al., 1986a,b; Antunes-Rodrigues et al., 1991; Dohanics et al., 1992).

Although there has been inadequate research on involvement of the oxytocinergic magnocellular system in patients with CDI, some findings have pointed in this direction. For example, Christensen et al. (2013) identified a mutation that produces CDI and involves the majority of the AVP gene and its regulatory sequences in the intergenic region between AVP and OT genes, which encodes the OT prohormone. We highlight the recent report by Aulinas et al. (2019) of low plasma OT levels in patients with CDI.

These results support the usefulness of these animal models to study human CDI and suggest that, as in animals (Balment et al., 1986a, b; Bernal et al., 2013; Mahía et al., 2019), OT might also prove useful for the treatment of humans with CDI. Indeed, one study of seven patients with CDI reported that both OT and desmopressin reduced their urine volume and free water clearance and increased their urine osmolality and AQP2 excretion (Joo et al., 2004).

Moreover, studies of animal models of CDI have also demonstrated that a more potent natriuretic response is obtained by the combined *versus* separate administration of AVP and OT (Balment et al., 1986a,b). Nevertheless, although patients with CDI were treated with neurohypophyseal extracts containing both AVP and OT at the beginning of the last century (Farini, 1913; von den Velden, 1913), these were withdrawn soon afterwards due their oxytocic activity (see Qureshi et al., 2014). More recently, researchers reported using small doses of a bovine posterior pituitary hormone extract (Pituitrin) containing OT and AVP to produce a superior fluid status to that achieved by desmopressin, and with minimal adverse effects (see Holcomb, 2002). Thus, it appears possible that the synergic effects of OT and AVP (Andersen et al., 1992) may allow a reduction in the dose and therefore in the risk of adverse effects.

Besides the administration of drugs, the utilization of food-deprivation and sodium-deficient diets have demonstrated therapeutic efficacy in animal models (Fregly and Rowland, 1989; Wideman and Murphy, 1991; Wilke et al., 2005; Mahía et al., 2008, 2013; Bernal et al., 2013) and in humans (Rivkees et al., 2007) with CDI.

Mutant C98X-KI mice were recently treated with chemical chaperones such as 4-phenylbutylate (4-PBA), which reduces the accumulation of mutant AVP in the endoplasmic reticulum, increasing AVP secretion and reducing polyuria in these mice (Tochiya et al., 2018). However, no data are yet available on the effects of chaperones in patients with autosomal dominant CDI.

For patients with NDI, current treatment approaches are mainly limited to sodium-deficient diets and the administration of thiazide diuretics that decrease distal tubule reabsorption of sodium inducing natriuresis, but these measures are only partially effective (Sands and Klein, 2016; Milano et al., 2017; Ando and Uchida, 2018; Bech et al., 2018). Novel therapeutic options have been inspired by experimental findings on the molecular physiology and signaling pathways that regulate water transport and urine-concentrating mechanisms. Their aim is to stimulate AVP-independent water reabsorption pathways (Sands and Klein, 2016; Milano et al., 2017; Ando and Uchida, 2018; Bech et al., 2018). Functional abnormalities in the AQP2 water channel are not observed in patients with congenital NDI due to AVP2R mutation or with acquired NDI due to lithium. For this reason, the goal of most treatments has been to increase AQP2 expression and function (Sands and Klein, 2016; Ando and Uchida, 2018). In this regard, Sands and Klein (2016) reviewed the effects on AVP-independent urine concentration mechanisms of sildenafil, metformin, and simvastatin, three commercially available drugs with very good long-term safety records. Sildenafil, currently approved for erectile dysfunction and pulmonary hypertension, is reported to have a positive effect on urine concentration. Sildenafil increases cyclic guanosine monophosphate, which promotes the insertion of AQP2 water channels into the apical membrane (Sands and Klein, 2016; Bech et al., 2018) and reduced polyuria in a rat model of lithium-induced NDI (Sanchez et al., 2012). Moreover, Assadi and Sharbaf (2015) reported that a 10-day course of sildenafil increased urine osmolality and reduced the urine output in a child with a X-linked NDI induced by a mutation in the AVP2R gene in comparison to the usual treatments. Metformin, currently approved for patients with polycystic ovary syndrome or diabetes mellitus, enhances phosphorylation and accumulation of AQP2, increasing urine osmolality in AVP2R-KO mice (Efe et al. 2016; Klein et al. 2016; Milano et al., 2017). Simvastatin is a cholesterol-lowering drug, which was reported to increase AQP2 expression in renal tubules (Bech et al., 2018). In this context, increases in urinary AQP2 and urine osmolality were recorded in hypercholesterolemic patients who started treatment with simvastatin (Procino et al. 2016). Simvastatin was also found to increase the apical membrane expression of AQP2 and urine osmolality in Brattleboro rats (Li et al., 2011), but no data are yet available on the effects of this drug in patients with CDI or NDI.

A further promising approach to congenital and lithium-induced NDI may be to activate EP4 prostanoid receptors on collecting duct cells. The EP4 receptor is an independent regulator of urinary concentration in renal collecting ducts under physiological conditions (Gao et al., 2015). Agonists of EP4 receptors, such as ONO-AE1-329, attenuated polyuria and polydipsia in a mouse model of X-NDI (Li et al., 2009). However, although their activation might compensate for the lack of renal AVP2R activity, the solubility of ONO is limited and it is relatively unstable in aqueous solution. Hence, a more stable EP4 receptor agonist is required before the clinical application of this approach (Li et al., 2009).

In summary, the study of animal models in the laboratory is a key element in the development of advances in the prevention and treatment of human diseases such as diabetes insipidus. Even if these complementary treatments cannot decrease urine output to normal levels, its reduction can markedly improve the quality of life of patients with DI and reduce their risk of severe dehydration.

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**Conflicts of Interest**

The authors declare no conflicts of interest.

**Table and Figure legends**

**Figure 1.** Behavioral and physiological kidney mechanisms to maintain the osmolality/natremia (upper) and volemia (lower) of extracellular fluid (ECF). Reductions in ECF osmolality/natremia inhibit water intake and promote diuresis, inducing sodium appetite and suppressing natriuresis. Conversely, increased ECF osmolality (or natremia) induces water intake and reduces diuresis, suppressing sodium appetite and increasing natriuresis. ECF hypovolemia increases water and sodium intakes and reduces diuresis and natriuresis, whereas ECF hypervolemia reduces water and sodium intakes and increases diuresis and natriuresis.

***Approximate size: full page.***

**Table 1.** General characteristics of patients with DI in comparison to a healthy population.

**Figure 2.** Upper: Sagittal section of brain (left) and kidney (right). Lower (magnified insets): AVP and OT neurosecretory system (left) and simplified structure of a nephron (right) (adapted from Bernal et al., 2017, with permission).

***Approximate size: ½ page.***

**Figure 3.** Chemical structure of (A) AVP and (B) OT. AVP is formed by the amino acids cysteine-tyrosine-phenylalanine-glutamine-asparagine-cysteine-proline-arginine-glycine-NH2 and OT by cysteine-tyrosine-isoleucine-glutamine-asparagine-cysteine-proline-leucine-glycine-NH2. In both cases, a ring of amino acids 1–6 is formed by a disulfide bond (S-S) (adapted from Bernal et al., 2017, with permission).

***Approximate size: ¼ page.***

**Table 2.** Main animal models of nephrogenic and neurogenic diabetes insipidus (DI).

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(Abbreviations: AVP2R-KO, X‑linked recessive mutations in the gene of the arginine vasopressin receptor 2; AQP2-CD-KO, autosomal-recessive and -dominant mutations in the gene of aquaporin-II channel in the collecting ducts; C98X-KI, autosomal-dominant mutation in the gene of arginine vasopressin-neurophysin II; MBH-lesion, mediobasal hypothalamic lesion; NOS-KO, triple nitric oxide synthases null mice).

**Figure 4.** Extent of mediobasal hypothalamic (MBH) damage after median eminence (ME) lesions in rats. Upper: sequential series of schematic drawings of the smallest (black areas) and largest (hatched areas) MBH lesions. Plates correspond to coronal sections at −2.30, −2.56, −2.80 and −3.14 mm caudal to bregma (atlas of Paxinos and Watson, 1997). Scale bar, 1mm. Lower: sagittal section showing antero-posterior level of the coronal sections (Arc, arcuate hypothalamic nucleus; DM, dorsomedial hypothalamic nucleus; ME, median eminence; VM, ventromedial hypothalamic nucleus).

***Approximate size: 1/3 page.***

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