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Review article

Animal models of Central Diabetes Insipidus: Human relevance of acquired beyond hereditary syndromes and the role of oxytocin

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ABSTRACT

The aim of this study was to review different animal models of Central Diabetes Insipidus, a neurobiological syndrome characterized by the excretion of copious amounts of diluted urine (polyuria), a consequent water intake (polydipsia), and a rise in the serum sodium concentration (hypernatremia). In rodents, Central Diabetes Insipidus can be caused by genetic disorders (Brattleboro rats) but also by various traumatic/surgical interventions, including neurohypophysectomy, pituitary stalk compression, hypophysectomy, and median eminence lesions. Regardless of its etiology, Central Diabetes Insipidus affects the neuroendocrine system that secretes arginine vasopressin, a neurohormone responsible for antidiuretic functions that acts trough the renal system. However, most Central Diabetes Insipidus models also show disorders in other neurobiological systems, specifically in the secretion of oxytocin, a neurohormone involved in body sodium excretion.

Although the hydromineral behaviors shown by the different Central Diabetes Insipidus models have usually been considered as very similar, the present review highlights relevant differences with respect to these behaviors as a function of the individual neurobiological systems affected. Increased understanding of the relationship between the neuroendocrine systems involved and the associated hydromineral behaviors may allow appropriate action to be taken to correct these behavioral neuroendocrine deficits.

1. General characteristics of diabetes insipidus

Diabetes refers to a wide variety of syndromes that share in common the copious production of urine (Bacic et al., 1999; Ball, 2005; Friedman et al., 1958; Holcomb, 2002; Huang and Dellmann, 1996; Ikkos et al., 1954; Laszlo and Wied, 1966; Lichardus and Ponec, 1973; Man and Hugh, 1992; O'Connor, 1950; Pickford and Ritchie, 1945; Robertson, 1995; Rose et al., 2015; Seckl and Dunger, 1992; Swaab et al., 1993; Swann, 1939 Titlebaum et al., 1996; Verbalis, 2003a,b). They include Diabetes Insipidus (DI), first described by Willis in the 17th century and characterized by the excretion of a large volume of diluted, "tasteless" urine (Ball, 2005; Deen et al., 1994; Di Iorgi et al., 2012; Fenske and Allolio, 2012; King and Agre, 1996; Laszlo and Wied, 1966; Lichardus and Ponec, 1973; Makaryus and McFarlane, 2006; Robertson, 1983; Rose et al., 2015; Schreckinger et al., 2013; Seckl and Dunger, 1992; Seckl et al., 1987; Titlebaum et al., 1960). The incidence of this disorder is around 1: 25,000 cases, with no statistically significant differences between males and females (Ball, 2005; Blevins and Wand, 1992).

The excretory response of DI individuals and animals is behaviorally associated with the intake of large amounts of water (polydipsia) (Loh and Verbalis, 2007; Rolls, 1970; Singer and Sevilla, 2003; Smith and McCann, 1962; Tisdall et al., 2006; Valtin and Schroeder, 1964; Verbalis, 2003a,b). Thus, this abnormal increased water intake of subjects with DI is secondary to excessive urine excretion (polyuria) (Ball, 2005; Di Iorgi et al., 2012; Dlouhá et al., 1982; Fenske and Allolio, 2012; Kurokawa et al., 1998; Makaryus and McFarlane, 2006; Moses et al., 1992; Robertson, 1995; Saborio et al., 2000; Seckl and Dunger, 1992; Schreckinger et al., 2013). As a result of this retention deficit, there is an increase in the serum sodium concentration (hypernatremia) (Table 1; Bacic et al., 1999; Bronstein et al., 2000; Friedman et al., 1958, 1962; Hollinshead, 1964; Huang and Dellman, 1996; Kavelaars et al., 2001; Kolmodin et al., 2013; Laszlo and Wied, 1996; Mahía et al., 2007c, 2013; Man and Hugh, 1992; O'Connor, 1950; Pivonello et al., 2000; Price and Kallenborn, 2000; Rolls, 1970; Saborio et al., 2000; Seckl and Dunger, 1992; Swann, 1939; Verbalis, 2003a,b). Thus, this marked loss of dilute fluid, which produces a rise in body sodium concentration, increases os-

Abbreviations: ANP, atrial natriuretic peptide; AQP2, aquaporin-II channels; AVP, arginine vasopressin; AVPR, arginine vasopressin receptor; CDI, Central Diabetes Insipidus; DI, diabetes insipidus; hCDI, hereditary Central Diabetes Insipidus; HPA, hypothalamic-pituitary-adrenocortical; Hypox, hypophysectomy; MBH, mediobasal hypothalamus; MEL, median eminence lesion; Neurohypox, neurohypophysectomy; NPII, neurophysin II; OT, oxytocin; PEG, polyethylene glycol; PSC, pituitary stalk compression; PVN, paraventricular nucleus; SON, supraoptic nucleus; tCDI, traumatic Central Diabetes Insipidus

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

	Diabetes insipidus	*Normal*
Urine Volume (liters/day)	Up to 20	1–1.5
Urine Osmolality (mOsm/L)	<300	300–1400
Serum Osmolality (mOsm/kg)	>300	280–300
Serum Sodium (mEq/L)	>145	135–145

motic pressures and causes osmotic thirst and the intake of large amounts of water (see Robertson, 1995).

The main model studied in pre-clinical research is hereditary DI, using Brattleboro rats; however, most central DI (CDI) disorders in humans are produced by traumatic brain injury. Furthermore, CDI is almost exclusively treated with arginine vasopressinergic substances. The objective of the present study was to review existing knowledge on other animal CDI models that involve damage to specific neurobiological systems, discussing the role of the neurohormone oxytocin, among other substances. The aim was to offer additional approaches to a more complete treatment of this neuroendocrine disorder.

2. Hypothalamic-neurohypophyseal system and central DI

Hydromineral regulation disorders in DI are mainly associated with a deficit in the production of the hormone arginine vasopressin (AVP) (central/neurogenic DI) or with a partial or total resistance to its antidiuretic effects (nephrogenic DI) (Ball, 2005; Bronstein et al., 2000; Czernichow et al., 2000; Demunbrun et al., 1954; Gonzalez-Portillo and Tomita, 1998; Greger et al., 1986; Heinbecker and White,1941; Hollinshead, 1964; Huang and Dellman, 1996; Kurokawa et al., 1998; Laszlo and Wied, 1966; Macias Batista et al., 1999; Maghnie et al., 2000; Mirsky et al., 1954; Moses et al., 1992; Robertson, 1995; Saborio et al., 2000; Seckl et al., 1987; Si-Hoe et al., 2000; Holcomb, 2002; Song et al., 1999; Swaab et al., 1993; Verbalis, 2003a,b).

The neuropeptide AVP is synthesized along with its carrier protein, neurophysin II (AVP-NPII), in the perikarya of magnocellular neurons of hypothalamic supraoptic (SON), paraventricular (PVN) and accessory neurosecretory nuclei (Armstrong, 2014; Binkley, 1995). The axons of this magnocellular complex pass through the inner part of the median eminence, forming the neurohypophyseal stalk, and terminate in the posterior hypophysis or neurohypophysis (Zimmerman and Robinson, 1976). Axonal swellings have been identified near fenestrated capillaries in the median eminence (Buma and Nieuwenhuys, 1988; Page and Dovey-Hartman, 1984; Wiegand and Price, 1980) and neurohypophysis (Armstrong, 2014; Legros, 1992; Renaud and Bourque, 1990; Saeb-Parsy et al., 2000; Swaab et al., 1993), permitting access of this neurohormone to the bloodstream for transportation to target tissues.

Hyperosmolality, hypovolemia, and hypotension are major triggers of AVP secretion (Baylis, 1987; Dunn et al., 1973; Dyball, 1968, 1971; Huang et al., 1995; Huang and Dellman, 1996; Kadekaro et al., 1995, 1997; Robertson,1987; Schiltz et al., 1997; Stricker, 1966; Treschan and Peters, 2006). The osmotic threshold for AVP release in humans is around 280–290 mOsmol/Kg. This effective system is activated when plasmatic osmolality changes by <1%, regardless of water intake fluctuations (Baylis, 1987; Robertson, 1987).

After its release into the circulatory system, AVP acts by binding to AVP receptor 2 (AVPR2) on the basal aspect of renal collecting tubule cells (King and Agre, 1996). This triggers an intracellular signaling cascade that concludes with activation of a cyclic adenosine monophosphate kinase pathway, which increases the production and insertion of aquaporin-II (AQP2) channels into the cell membrane (Fushimi et al., 1993; King and Agre, 1996; Knepper et al., 1996; Nielsen et al., 1995, 2002; Snyder et al., 1992; Star et al., 1988; Wells, 1998). This in turn leads to passive water reabsorption from the lumen of the nephron into the cells of the collecting duct along an osmotic gradient (Dumont et al., 2005; Hansell et al., 2000; Harris et al., 1991; Layton et al., 2010; Strange and Spring, 1987). The consequent excretion of concentrated urine (Jard, 1988; Rose et al., 2015; Mahía et al., 2007c) is a survival mechanism for prolonged starvation periods. Thus, the kidneys can process urine with a concentration of 1200–1400 mOsm/L (four- or five-fold higher than serum osmolality). Conversely, diluted urine is excreted in the absence of AVP (Rose et al., 2015).

Besides the aforementioned vasopressinergic neurons, this magnocellular neurosecretory system also contains cells responsible for oxytocin (OT) synthesis (Armstrong, 2014; Binkley, 1995; Leng et al., 2005; Morris, 2006). Human genes for OT-neurophysin I and AVP-neurophysin II are both on chromosome 20, separated by approximately 12 kb of intergenic sequences (Rao et al., 1992). The chemical structure of OT is highly similar to that of AVP, being also a nonapeptide and only differing in amino acids at positions 3 and 8 (Fig. 1**)** (Barberis et al., 1998; Brownstein, 1983; Brownstein et al., 1980). As in the case of AVP, OT is generated in response to increased plasmatic osmolality (hyperosmolality and hypernatremia) (Balment et al., 1980; Blackburn et al., 1995; Cheng and North, 1987; Dyball, 1968, 1971; Fitts et al., 2003; Giovanelli et al., 1992; Huang et al., 1995; Huang and Dellman, 1996; Kadekaro et al., 1997, 1992a, 1992b, 1997; Landgraf et al., 1988; McKinley et al., 1992; Morris et al., 1984; Stricker and Verbalis, 1986; Verbalis et al., 1986; Verbalis and Dohanics, 1991; Xiong and Hatton, 1996; Windle et al., 1993) and in states of hypovolemia (Blackburn et al., 1992a,b; Chiodera et al., 1998; Lang et al., 1981; Mahon et al., 1995; Stricker and Verbalis,

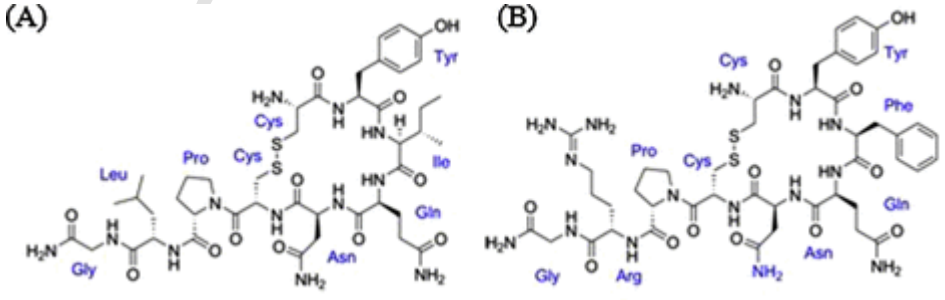

Fig. 1. Chemical structure of (A) OT and (B) AVP with labeled amino acids. OT is formed by amino acids cysteine-tyrosine-isoleucine-glutamine-asparagine-cysteine-proline-leucine-glycine-NH_2 and AVP by cysteine-tyrosine-phenylalanine-glutamine-asparagine-cysteine-proline-arginine-glycine-NH_2. In both cases, a ring of amino acids 1–6 is formed by a disulfide bond.

1986,1987; Windle et al., 1993). Finally, both neurohormones bind with high affinity to the OT receptor and AVPR2 (Han et al., 1993; Tribollet et al., 1992).

Among the regulatory processes related to hydromineral homeostasis, OT is especially involved in the excretion of body sodium (Bernal et al., 2007,2010a,b, 2015; Bourque, 2008; Conrad et al., 1986; Gimpl and Fahrenholz, 2001; Haanwinckel et al., 1995; Huang et al., 1995; Mahía et al., 2009; Sawyer, 1952; Schmidt et al., 1990; Stoeckel and Freund-Mercier, 1989; Walter et al., 2000; Windle et al., 1995, 1997), even at physiological plasma concentrations (Verbalis et al., 1991). This physiological secretion appears to be triggered by increases in glomerular filtration rate (Conrad et al., 1986) and reductions in tubular sodium reabsorption (Lippert et al., 2003) and also, indirectly, by cardiac secretion of atrial natriuretic peptide (ANP) (Haanwinckel et al., 1995). Both AVP and OT have been proposed to have synergic natriuretic effects, with their combined administration exerting an effect of greater intensity and longer duration than the sum of the effects of each neurohormone (Fig. 2**)** (Andersen et al., 1992; Windle et al., 1995).

Neurohormonal secretion is one of the main output systems related to thirst regulation and urine production. These responses depend on the integration by SON and PVN magnocellular nuclei of signals from multiple brain structures (see Bourque, 2008 for review and Betley et al., 2015; Oka et al., 2015 for new data on thirst)

3. Etiological bases of hereditary and traumatic central diabetes insipidus (CDI)

Various genetic disorders have been implicated in the development of CDI, which can also be induced by traumatic or other brain damage to magnocellular neurosecretory structures or fibers that constitute the hypothalamic-neurohypophyseal system.

3.1. Hereditary forms of CDI

Hereditary CDIs (hCDIs) account for only 1–2% of all cases (Makaryus and McFarlane, 2006). They are frequently related to mutations in the AVP-NPII gene, which encodes for AVP and neurophysin II and is located distally at the short arm of chromosome 20 (20p13), containing three exons (Christensen and Rittig, 2006; Lindholm, 2004; Mundschenk et al., 2001; Robertson, 1995; Si-Hoe et al., 2000).

More than 60 mutations of the AVP gene that encodes the AVP-NPII precursor have been identified (Babey et al., 2011), with almost all showing an autosomal dominant pattern of inheritance (Di Iorgi et al., 2012). Autosomal dominant mutations of the AVP-NPII gene lead to an accumulation of misfolded AVP fibrillar aggregates within the endoplasmic reticulum and produce the death of magnocellular neurons of the SON and PVN of the hypothalamus (Birk et al., 2009; Makaryus and McFarlane, 2006; Phulwani et al., 2011).

The discovery in the 1960s of an animal model related to this disease was a landmark finding (Saul et al., 1968; Valtin, 1967, 1974, 1982; Valtin and Schroeder, 1964; Valtin et al., 1965; Vandesande and Dierickx, 1976). The homozygous Brattleboro strain used arose from the stock of Long-Evans hooded rats, characterized by their inability to synthesize antidiuretic hormone as an autosomal recessive trait of the AVP-NPII gene (Saul et al., 1968; Schmale and Richter, 1984). These rats are homozygous due to a single base pair deletion in the second exon of the prepro-AVP-NPII gene, resulting in a frameshift mutation in the coding sequence of NPII. The mutated allele encodes a normal AVP but an abnormal NPII, which interferes with the regular transport and processing of the AVP-NPII precursor molecule (Hendy and Bichet, 1995; Schmale and Richter, 1984) without causing the death of magnocellular neurons (Fisher et al., 1982). Homozygous Brattleboro rats, as would be expected, exhibit polyuric and polydipsic responses as well as chronic hypernatremia and hyperosmolality and are therefore considered the standard model of hCDI (Babina and Lavrinenko, 2014; Baturina et al., 2013; Brimble et al., 1991; Edwards and Larochelle, 1984; Ivanova et al., 2008; Lavrinenko and Babina, 2014; Schmale and Richter, 1984; Vandesande and Dierickx, 1976).

3.2. Acquired forms of CDI

CDI syndrome can also result from traumatic brain injuries, brain neoplasms or malformations, and certain surgical procedures (Bacic et al., 1999; Bronstein et al., 2000; Hadjizacharia et al., 2008; Randall et al., 1960; Robertson, 1995; Schreckinger et al., 2013; Seckl et al., 1987; Holcomb, 2002). CDI cases generally show damage to mediobasal hypothalamus (MBH), hypophyseal stalk, infundibulum, or pituitary gland itself (Bacic et al., 1999; Ball, 2005; Bronstein et al., 2000; Robertson, 1995; Seckl et al., 1987; Verbalis, 2002, Verbalis, 2003a,b). Traumatic CDI (tCDI) can be experimentally induced in animals by surgical interventions, including median eminence lesions (MEL), sectioning of hypothalamic-neurohypophyseal tract, pituitary stalk compression (PSC), hypophysectomy (hypox), and neurohypophysectomy (neurohypox) (Antunes-Rodrigues et al., 1991; Balment et al., 1986a,b; Bernal et al., 2013; Dohanics et al., 1992; Haller et al., 1996 Huang et al., 1996; Huang and Dellmann, 1996; Mahía et al., 2007a,b, 2008, 2013; Makara et al., 1996; O'Connor, 1946; Richter and Ecker, 1935; Rolls, 1970; Smith and McCann, 1962; White and Heinbecker, 1938).

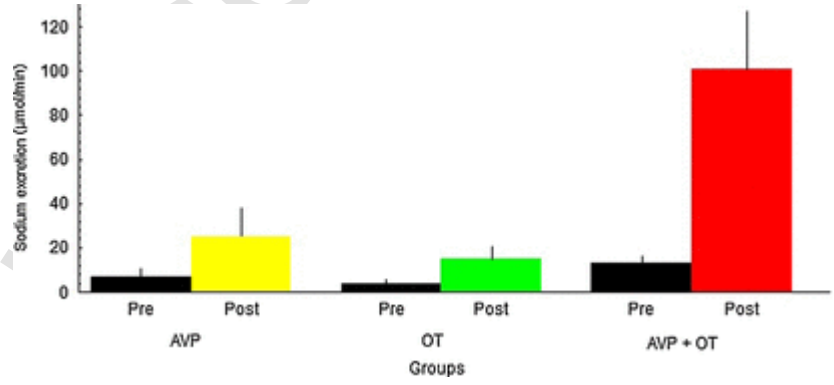

Fig. 2. Sodium excretion (µmol/min) before and after infusion of AVP, OT, or AVP plus OT (data obtained from Andersen et al. (1992).

CDI manifestations can be transient, permanent, or triphasic. Transient CDI starts with an abrupt onset of polyuria and polydipsia within 24–48 h of surgery/trauma and gradually resolves over a 3–5 day period (Dumont et al., 2005; Schreckinger et al., 2013; Seckl and Dunger, 1989). In permanent CDI, polyuric and polydipsic symptoms arise immediately and remain chronic in the absence of treatment (Fenske and Allolio, 2012; Hensen et al., 1999; Nemergut et al., 2005). Triphasic CDI was first described by Fisher and Ingram in 1936. The first phase, clinically identical to transient CDI, starts with polyuria and polydipsia within 24 h of surgery, followed by an interphase (oliguric phase), with reduction in/normalization of urine excretion volume and water intake, and finally by a persistent phase of polyuria and polydipsia (Adams et al., 2006; Bakker and Waring, 1976 ; Balment et al., 1986b; Bronstein et al., 2000; Dumont et al., 2005; Friedman et al., 1958, 1962; Hollinshead, 1964; Huang and Dellman, 1996; Laszlo and Wied, 1966; Lichardus and Ponec, 1973; O'Connor, 1946, 1950, 1952; Robertson, 1995; Rolls, 1970; Saborio et al., 2000; Seckl and Dunger, 1992; Seckl et al., 1987; Swaab et al., 1975; White and Heinbecker, 1939).

It has been proposed that the anatomical arrangement of hypothalamic-neurohypophyseal fibers may explain the regulatory and behavioral symptoms of DI animals. Thus, lesions located ventrally to the median eminence may cause CDI with only transient polydipsia (Heinbecker and White, 1941 ; O'Connor, 1946; Zimmeman et al., 1984), possibly due to secretion of the hormonal contents of SON and magnocellular PVN into the median eminence area (Buma and Nieuwenhuys, 1988; Page and Dovey-Hartman, 1984). Distinct effects are observed after damage to the whole hypothalamic-neurohypophyseal tract, which results in a consistently increased water intake from the onset (permanent CDI) (Heinbecker and White, 1941; Hollinshead, 1964; O'Connor, 1952). Finally, the presence of intact/preserved axons or the release of AVP by degenerating terminals is considered responsible for the oliguric interphase in tri-phasic CDI (Bronstein et al., 2000; Brooks and Pickford, 1958; Heinbecker and White, 1941; Hollinshead, 1964; Laszlo and Wied, 1966; Lipsett et al., 1956; O'Connor, 1946, 1952; Robertson, 1995).

4. Hereditary and acquired CDI in animals: preserved regulatory capacities and importance of OT

A lack of AVP is initially critical for the hydromineral regulation changes in both hereditary and acquired CDI. However, there are important differences among CDI types in the neurobiological systems involved and in behavioral manifestations. Thus, they appear to involve distinct neuroendocrine systems, particularly but not exclusively related to OT, generating the differential features of each neuropathological syndrome (see below).

4.1. Brattleboro homozygous rats

Brattleboro rats offer one of most specific CDI models due to their preponderant AVP synthesis deficit, although AVPR2 is preserved and is therefore reactive to AVPR2 agonists. They compensate for this deficit and the consequent excretion of excessive diluted urine by consuming large amounts of water (Fuller and Fitzsimons, 1998) and by reducing consumption and preference thresholds for salty solutions (Yirmiya et al., 1988). Nephrectomy, which prevents renal water loss, eliminates the polydipsic response of Brattleboro rats after hypertonic NaCl administration, evidencing the secondary character of drinking behavior in these animals (Fuller and Fitzsimons, 1988).

Nonetheless, the renal regulatory capacity and hydromineral behavior of Brattleboro homozygous rats can be modified by subjecting them to different hydromineral challenges, indicating that non-vasopressinergic mechanisms likely also participate in this type of regulatory response.

Wilke et al. (2005) reported reductions in urine volume and increases in urine osmolality and AQP2 channels in both Brattleboro and control rats after 72 h of food deprivation. The increased water reabsorption in Brattleboro rats under these conditions has been considered an adaptive response of the kidney to long periods of food deprivation, which may take place via AVP-independent mechanisms or, alternatively, through action on AVPR2 (Bennett and Gardiner, 1987). This preserved regulatory capacity even affects the habitual polydipsic behavior of Brattleboro rats. Thus, Wideman and Murphy (1991) observed a drastic fall in the water intake of homozygous Brattleboro rats after food restriction, while hypertonic NaCl administration was reported to markedly increase their urinary osmolality (Balment et al., 1980; Brimble et al., 1991; Edwards and La Rochelle, 1984), natriuresis (Balment et al., 1980; Brimble et al., 1991; McCann et al., 1997), and water intake (Fuller and Fitzsimons, 1988).

With respect to the possible neuroendocrine correlates that may explain these preserved regulatory capacities, it is well documented that Brattleboro rats show a sustained increase in OT mRNA in PVN and SON and increased OT plasma levels, especially under dehydration conditions (Balment et al., 1980, 1986a,b; Brimble et al., 1991; Bundzikova et al., 2008; Cheng and North, 1987; Dogterom et al., 1977; Horn et al., 1985; North et al., 1982; Pow and Morris, 1990; Sherman et al., 1988; Zelena et al., 2013). The importance of OT in dehydrated Brattleboro rats was elegantly demonstrated (Brimble et al., 1991) by blocking the natriuretic response of neurohypophysectomized Brattleboro animals after hypertonic NaCl administration and then largely re-establishing this response with subsequent OT administration (Fig. 3). This suggests that the natriuresis of Brattleboro rats after hypertonic NaCl administration may be related to OT availability in these animals.

Various studies on the effect of OT administration in Brattleboro rats have evidenced: a marked antidiuresis; increased urine osmolality; increases in AQP2, phosphorylated AQP2, and AQP3 levels in the inner and outer medulla plus cortex; and increases in the glomerular filtration rate and effective filtration fraction (Brimble et al., 1991; Chou et al., 1995a,b; Conrad et al., 1986, 1993; Li et al., 2008; Lyness et al., 1985; Pouzet et al., 2001). These OT-induced effects were blocked by treatment with the AVPR2 antagonist SR121463B (Chou et al., 1995a,b; Li et al., 2008; Lyness et al., 1985; Pouzet et al., 2001) but not by treatment with the OT receptor antagonist GW796679X (Li et al., 2008). These studies suggest that, at least under certain experimental conditions, OT may act on AVPR2, which may be relevant in antidiuresis (Adrogué and Madias, 2000; Lyness et al., 1985; Pittman, 1963; Potter, 1964; Sasaki, 2008; Wang et al., 2000). In intact animals, the antidiuretic effect of OT was accentuated in hypovolemic conditions, e.g., under states of hydromineral deficit induced by polyethylene glycol (PEG) administration (Bernal et al., 2015). This result may be comparable to the antidiuretic response of Brattleboro rats after PEG administration (Bennett and Gardiner, 1986). In other words, the antidiuretic effect observed in Brattleboro rats with the endogenous OT available after PEG administration is reproduced by OT administration in PEG-treated intact rats.

OT does not appear to be the only endocrine agent involved in the antidiuretic effects observed in Brattleboro rats. Morrissey et al. (2001) reported that prolactin, an adenohypophyseal hormone that contributes to neurohormone secretion regulation (Vega et al., 2010), reduced urinary excretion volume in Brattleboro rats with AVP deficit but not in control rats.

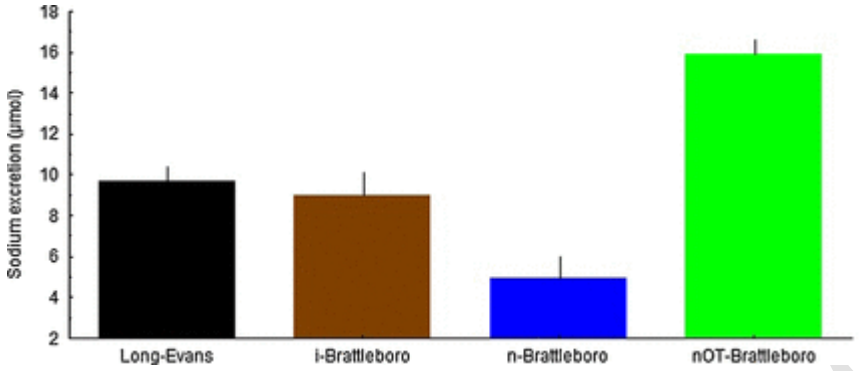

Fig. 3. Sodium excretion (µmol) induced by NaCl administration in Long-Evans, intact (i) Brattleboro, neurohypophysectomized (n) Brattleboro and neurohypophysectomized treated with Oxytocin (nOT) Brattleboro rats (data obtained from Brimble et al. (1991).

4.2. Neurohypophysectomy (neurohypox) and pituitary stalk compression (PSC)

Neurohypox interrupts the secretion of both AVP and OT, increases the flow of urine, and reduces the excretion of sodium (Balment et al., 1986b).

In neurohypophysectomized dogs, OT administration raised renal clearances (Demunbrun et al., 1954) and AVP plus OT administration increased sodium excretion (Brooks and Pickford, 1958). In neurohypophysectomized rats, Balment et al. (1986b) also found that OT administration at plasma levels within the physiological range enhanced the natriuretic response to AVP, reversing their renal sodium excretion deficit. Moreover, the combined use of lower OT and AVP doses, which individually do not promote the excretion of significant amounts of body sodium, revealed a marked synergetic natriuretic effect superior to the sum of their individual effects (Fig. 4). Hence, the reduced natriuretic capacity of neurohypox animals appears to be at least in part a consequence of the lack of both AVP and OT.

Given the technical difficulty of specific neurohypophysectomy, some authors use PSC to produce a selective deafferentation of the neurohypophysis. In these cases, compression of the pituitary stalk elicits a triphasic increase in water consumption (Dohanics et al., 1992) and urine excretion (Elias et al., 2004), and an increase in cerebrospinal fluid AVP and OT content (Haller et al., 1996). Due to the formation of an ectopic neurohypophysis, the contents of AVP and OT are redirected from the neural lobe to the pituitary stalk (portal blood), contributing to the central but not peripheral regulation of salt-water homeostasis (Makara et al., 1995).

In fact, hypertonic NaCl administration in PSC animals significantly increases their plasma osmolality but not their plasma AVP and OT levels (Dohanics et al., 1992; Elias et al., 2004). We highlight that, after salt loading, this neurosecretory deficit is maintained for 21 days post-surgery (stable phase), ruling out the possible role of hypothalamic-neurohypophyseal fiber regeneration (Raisman, 1973).

4.3. Hypophysectomy (hypox)

Sodium excretion is depressed in hypox animals (Balment et al., 1986a), but hypertonic NaCl injection into the third ventricle stimulates their sodium excretion and an antidiuretic response (Dorn et al., 1970; Morris et al., 1976). Conversely, urinary sodium output is reduced in hypox animals on low-sodium diets (Fregly and Rowland, 1989). When the neurohumoral pathway is interrupted, the parvocellular component of PVN, among others, may modulate urinary sodium and water excretion by controlling the sympathetic system *via* efferent/descending neural pathways (Johns, 2002; Nishi et al., 2015; Schramm et al., 1993; Yang and Coote, 2007). These results suggest that hypox animals maintain marked hydromineral regulation capacities in the presence of homeostatic challenges.

The intake behavior of hypox animals has been analyzed in choice tests with fluids at different osmotic concentrations. Hypox rats consumed larger amounts of NaCl solutions (and also water) than intact rats, although there were no significant differences between them in preference threshold or maximum concentrations. These data are consistent with the functional integrity of the renin-angiotensin-aldosterone system (Fregly and Rowland, 1989).

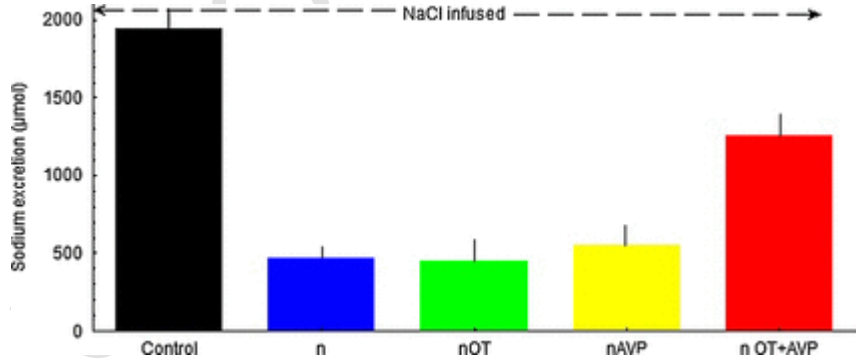

Fig. 4. Sodium excretion (µmol) in Control, neurohypophysectomized (n) and neurohypophysectomized rats treated with OT (nOT), AVP (nAVP), or OT *plus* AVP (n OT + AVP) (data obtained from Balment et al. (1986a,b).

From a neuroendocrine perspective, this surgery interrupts the hormonal secretion of both AVP and OT (Balment et al., 1984, 1986a). The administration of neurohypophyseal extracts was found to produce a major increase in the sodium excretion of hypophysectomized rats (Brunner et al., 1956). However, although combined AVP-OT treatment has synergic natriuretic effects, the peak sodium excretion of hypox animals treated with both neurohormones remains below that in intact rats (Balment et al., 1984, 1986a). Consequently, it has been proposed that the deficit produced in some adenohypophyseal hormones, such as prolactin (with its antidiuretic/hydromineral/regulatory effects in animals lacking AVP (Morrissey et al., 2001)), may be relevant in this type of CDI, given that its administration maintained plasma osmolality and plasma Na^+, Cl^- and Ca^{2+} levels in hypox fish (Jackson et al., 2005).

4.4. Median eminence lesions (MEL)

MEL interrupts both AVP and OT secretions (McCann et al., 1997; Morris et al., 1976) and generate animal models with triphasic polyuric and polydipsic CDI (see Fig. 5A) (Mahía and Puerto, 2006; Mahía et al., 2008, 2013; Rolls, 1970). This polydipsic behavior of MEL animals does not seem to depend exclusively on the loss of body fluid. A study by Smith and McCann (1962) demonstrated that the polydipsic response induced by MEL was not blocked in rats whose renal water loss was prevented by previous nephrectomy; i.e., a polydipsic response appears even in the absence of polyuria in this type of CDI.

A distinctive characteristic of MEL animals is their hyperphagia, likely attributable to damage to MBH nuclei (Bernal et al., 2013; Mahía and Puerto, 2006; Mahía et al., 2008, 2013). This suggests that food intake may be a determining factor in the hydromineral regula-

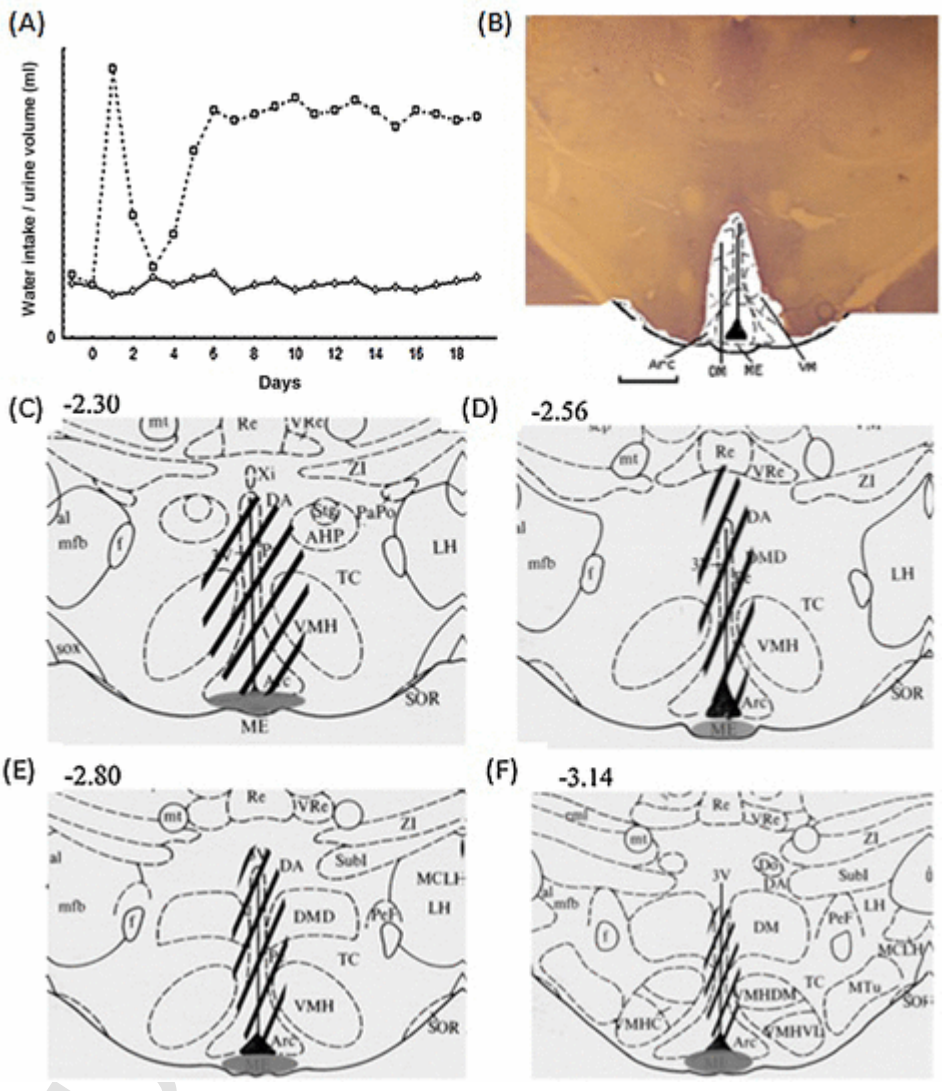

Fig. 5. DI-causing median eminence lesions. Triphasic polydipsic/polyuric pattern of the injured animals (broken line) (A). Photomicrograph of coronal brain section stained with cresyl violet at approximately −2.56 mm caudal to Bregma (B). Sequential series of schematic drawings of the smallest (gray areas) and largest (hatched areas) MEL in a representative ME-lesioned rat according to the atlas of Paxinos and Watson (1986) (C–F). Scale bar, 1 mm (Arc, arcuate nucleus; DM, dorsomedial nucleus; ME, median eminence; VMH, ventromedial nucleus). From Bernal et al. (2013) and Mahía et al. (2008) (with permission from Elsevier). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tion processes of MEL animals (Fig. 5B–F; Bernal et al., 2013; Mahía et al., 2008).

This relationship between food/water intake and urinary output in MEL animals has been analyzed in food-deprivation studies, demonstrating a drastic reduction in their urinary output and polydipsic behavior under these conditions (Bernal et al., 2013; Mahía et al., 2008, 2013). This inhibitory effect appears to depend upon the timing of the food deprivation. Thus, while deprivation during the first days post-surgery significantly reduced the magnitude of the polyuric and polydipsic response of MEL animals, deprivation during the stable DI phase completely annulled their polyuria and polydipsia (Fig. 6; Bernal et al., 2013). Moreover, the elevated blood glucose levels (diabetes mellitus) in Brattleboro rats would further increase their water intake, supporting the proposition that the polydipsia-polyuria in the late phase of the MEL model is attributable to metabolic factors rather than to the absence of AVP-OT (Zelena et al., 2006).

The sodium present in the diet may be crucial in MEL DI animals, because low-sodium diets reduce their water intake and plasma sodium concentration (Mahía et al., 2013). In other words, the increased food/sodium intake of these animals may not only exacerbate their polydipsic disorder but also increase their osmolality/plasma sodium concentration. These results are in agreement with earlier studies that established a close relationship between the sodium intake and polydipsic response of CDI animals (Curtis, 1924; Palmieri and Taleisnik, 1969; Swann, 1939; Titlebaum et al., 1960). When MEL animals could choose between a 1.5% sodium chloride solution and water, they preferentially chose (82% of total liquid consumed) the hypertonic saline solution (Mahía et al., 2008). Nevertheless, the dehydration induced by intraventricular hypertonic saline administration did not produce the expected increase in natriuretic and antidiuretic responses in MEL animals (Morris et al., 1976). This suggests the interruption of both neurohumoral pathways and activity of the autonomous nervous system (Johns, 2002; Nishi et al., 2015; Schramm et al., 1993; Yang and Coote, 2007).

Considering that MEL interrupts both AVP and OT secretion (McCann et al., 1997; Morris et al., 1976), the possibility of counteracting their deficit by OT administration has been explored. Peripheral administration of this neurohormone was found to enhance sodium excretion and to reduce the urine excretion and habitual polydipsic response of MEL animals (Bernal et al., 2013). This effect of OT is transient in *ad lib*-fed MEL animals with sodium available in their food, whereas it generates long-lasting reductions in food-deprived MEL rats (Bernal et al., 2013), suggesting that CDI may be modifiable by early intervention and the manipulation of food availability.

In this line, it should be taken into account that the plasma levels of other humoral factors, such as prolactin and β-endorphin, are also increased in animals with MBH lesions (Kiem et al., 1995).

4.5. Comparative analysis of the different CDI models

The specific neurobiological systems that appear to be affected in different types of DI animals may explain their differential behaviors, correlates, and treatments (see Table 2). Thus, a common disorder such as renal water loss deficit was prevented by nephrectomy in Brattleboro rats, suppressing their polydipsic response (Fuller and Fitzsimons, 1988), but not in MEL animals (Smith and McCann, 1962). This supports a more specific vasopressinergic circuit disorder and the preponderant secondary character of polydipsic behavior in Brattleboro animals.

Thus, choice tasks with solutions at different osmotic concentrations have revealed that Brattleboro rats preferentially consume water (Yirmiya et al., 1988), whereas hypox (Fregly and Rowland, 1989) and MEL (Mahía et al., 2008) animals consume larger amounts of both water and NaCl solutions in comparison to controls.

Besides fluid intake, a further differential behavior among CDI animal models is the hyperphagia developed by MEL (Bernal et al., 2013; Mahía and Puerto, 2006; Mahía et al., 2008, 2013) but not Brattleboro (Murphy and Wideman, 1991) or hypox (Wyndham et al., 1987) rats.

However, it is likely that one of the most important differential factors observed is related to OT, which is available in Brattleboro (Balment et al., 1980, 1986a,b; Brimble et al., 1991; Bundzikova et al., 2008; Cheng and North, 1987; Dogterom et al., 1977; Horn et al., 1985; North et al., 1982; Pow and Morris, 1990; Sherman et al., 1988; Zelena et al., 2013) but not in neurohypox (Balment et al., 1986b), PSC (Dohanics et al., 1992), hypox (Balment et al., 1986a), or MEL animals (McCann et al., 1997; Morris et al., 1976).

As reported above, there is a significant increase in plasma OT levels and in urinary osmolality and natriuresis in Brattleboro rats after hypertonic NaCl administration (Balment et al., 1980; Brimble et al., 1991; Edwards and La Rochelle, 1984; McCann et al., 1997), and OT appears responsible for the sodium excretion observed in this situation (Brimble et al., 1991). However, these hydromineral adjustments are independent of an increase in OT levels in PSC (Dohanics et al., 1992; Elias et al., 2004) and hypox (Dorn et al., 1970; Morris et al., 1976) animals. In other words, the natriuretic responses induced by NaCl solutions can be generated in the absence of AVP, OT, or anterior pituitary hormones. By contrast, no natriuresis or antidiuresis was observed in MEL animal after hypertonic NaCl administration

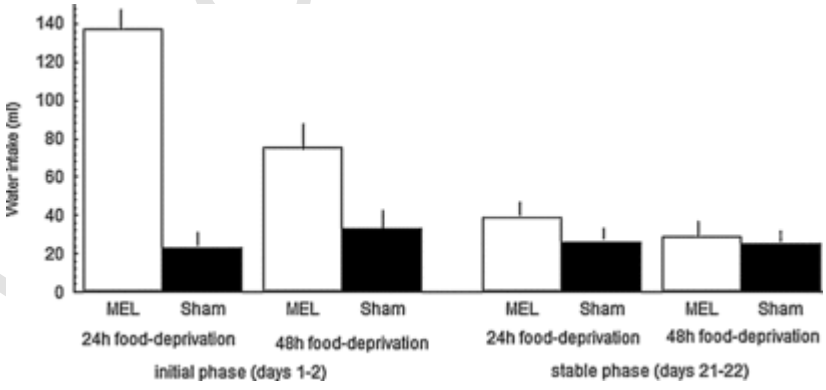

Fig. 6. Water intake (ml) of MEL and sham-operated animals after 24 or 48 h of food deprivation during the initial phase (days 1–2) and stable phase (days 21–22) (data obtained from Bernal et al. (2013).

Table 2
Neuroendocrine correlates, behavior, hypertonic NaCl, and treatment effects in animals and humans with CDI.

MAIN FINDINGS (Behavior, correlates, and treatments)		HEREDITARY CDI	ACQUIRED CDI			
		Brattleboro	Neurohypox/PSC	Hypox	MEL	CDI in humans
Neuroendocrine correlates	pOT	pOT available Balment et al. (1980); Brimble et al. (1991); Bundzikova et al. (2008); Horn et al. (1985); Zelena et al. (2013)	pOT absent Balment et al. (1986b); Dohanics et al. (1992); Elias et al. (2004)	pOT absent Balment et al. (1986a)	pOT absent McCann et al. (1997); Morris et al. (1976)	pOT absent? Fujisawa (2004)
	ANP secretion	Normal pANP Laulin and Brudieux (1990)			Lower pANP Antunes-Rodrigues et al. (1991)	Lower pANP Elias et al. (1997); Kamoi et al. (1990)
	Baseline pACTH & HPA axis regulation	Normal/lower Zelena et al. (2009)	Higher/higher levels Elias et al. (2004)		Normal/Normal Makara et al. (2001)	Normal/higher levels Elias et al. (1997); Mazza et al. (1994)
Behavior	Salt solutions (vs water) intake	Rejection Yirmiya et al. (1988)		Accepted Fregly and Rowland (1989)	Preferred Mahía et al. (2008)	
	Effects of nephrectomy on polydipsia	Polydipsic behavior inhibited Fuller and Fitzsimons (1988)			Polydipsic behavior reduced Smith and McCann (1962)	
Hypertonic NaCl administration effects		Increases Uosm, UvNa, water intake, pOT, and OT mRNA in PVN and SON Balment et al. (1980); Cheng and North (1987); Edwards and LaRochelle (1984); Sherman et al. (1988)	Increases pOsm but not pOT Dohanics et al. (1992); Elias et al. (2004)	Reduces Uv and increases UvNa but not pOT Balment et al. (1986a); Dorn et al. (1970); Morris et al. (1976)	No natriuresis, no antidiuresis, and no increases in pOT Antunes-Rodrigues et al. (2004); Morris et al. (1976)	No natriuresis, no antidiuresis Fenske and Allolio (2012)
Treatment Effects	Food or sodium deprivation	Food-deprivation (72 h) reduces Uv and increases Uosm and AQP2 expression. Food-restriction reduce water intake Wideman and Murphy (1991); Wilke et al. (2005)		Low-sodium diets reduce UvNa Fregly and Rowland (1989)	Food-deprivation reduces/ normalizes Uv and water intake. Low-sodium diets reduces Uv and pNa Bernal et al. (2013); Mahía et al. (2008, 2013)	Low sodium diets prescribed in individuals with NDI Makaryus and McFarlane, (2014); Rivkees et al. (2007)
	OT	Reduces Uv and increases UvNa, Uosm, and AQP2 excretion Brimble et al. (1991); Chou, et al. (1995a,b); Conrad et al. (1986,1993); Li et al. (2008); Lyness et al. (1985); Pouzet et al. (2001)	Physiological doses slightly increase UvNa and raise renal clearances Balment et al. (1986b); Demunbrun et al. (1954); Sawyer (1952)	Increases UvNa Balment et al. (1986a)	Potentiates UvNa and reduces Uv and water intake, especially in food-deprived animals Bernal et al. (2013)	Reduced Uv, pNa, and pOsm and increased Uosm and AQP2 excretion Joo et al. (2004)
	OT+AVP (Pituitrin or neurohypophysial extracts)		Reverses UvNa deficit Balment et al. (1986b); Brooks and Pickford (1958)	Reduces UvNa déficit Balment et al. (1984, 1986a); Brunner et al. (1956)		Reduced Uv and increased UvNa Holcomb (2002); Qureshi et al. (2014)
	PRO	Reduced Uv Morrissey et al. (2001)		Maintained pNa and pOsm Jackson et al. (2005)		

ANP: atrial natriuretic peptide; AQP2: aquaporin-II channels; AVP: arginine vasopressin; CDI: central diabetes insipidus; HPA: pituitary-adrenocortical; Hypox: hypophysectomy; MEL: median eminence lesion; NDI: nephrogenic diabetes insipidus; Neurohypox: neurohypophysectomy; pACTH plasma adrenocorticotropin; pNa plasma sodium; pOT: plasma oxytocin; pOsm: plasma osmolality; PRO: prolactin; PSC: pituitary stalk compression; PVN: paraventricular nucleus; SON: supraoptic nucleus; Uosm: urine osmolality; Uv: urine volume; UvNa: natriuresis.

(Morris et al., 1976). This suggests that MBH lesions may affect neurobiological systems whose damage interrupts the function of hypophyseal and extrahypophyseal factors, significantly reducing renal adjustment after hypertonic NaCl administration (see Antunes-Rodrigues et al., 2004).

Despite the differences among these animal models of CDI, OT administration appears to exert beneficial hydromineral effects in all of them (Brattleboro, neurohypox, hypox, and MEL animals). However, the potential therapeutic capacity of this neurohormone may depend on the type of CDI and the neurohormonal tissue affected in each case. Analysis of the synergic effects of OT and AVP in the different tCDI animal models demonstrates that their combined administration reverses renal sodium excretion deficit in neurohypophysectomized animals lacking both AVP and OT (Balment et al., 1986b) but does not completely counteract sodium excretion deficits in hypox animals with neuro- and adeno-hypophyseal hormone deficits (Balment et al., 1986a).

It therefore appears to be well established that CDI-induced abnormalities decisively involve the AVP system in all cases. Nevertheless, the different hydromineral disorders caused cannot be easily explained if only this neurohormonal system is considered. Finally, the use of AVP exclusively can be controversial, because its chronic administration may interrupt axonal regeneration of the hypothalamic-neurohypophyseal tract (Herman et al., 1987).

5. Acquired human CDI: similarities and differences with respect to diverse animal models

Fluid deprivation and hypertonic NaCl administration tests are habitually used for CDI diagnosis in humans (see Fenske and Allolio, 2012 for review). CDI is evidenced when the urine concentration fails in response to dehydration (Ball, 2005) and is diagnosed when urine osmolality is <300 mOsm/kg, i.e., lower than plasma osmolality (Di Iorgi et al., 2012; Makaryus and Mcfarlane, 2006). In addition, urine flow is persistent and natriuresis is lower during saline infusion in CDI cases (see Fenske and Allolio, 2012). These biological responses show a greater similarity to those recorded in MEL animals (Antunes-Rodrigues et al.,, 2004; Morris et al., 1976) than in other animal models of CDI **(**see Tables 2 and 3).

In general, the treatment of choice for CDI patients (see Qureshi et al., 2014 for review) is usually desmopressin (1-deamino-8-d-AVP), a synthetic analog of AVP that is selective for AVPR2 and exerts an even more potent regulatory effect than that of the neurohormone itself (Cheetham and Baylis, 2002; Fjellestad-Paulsen et al., 1993; Greger et al., 1986; Holcomb, 2002; Maghnie et al., 2000; Nemergut et al., 2005; Rembratt et al., 2004; Saborio et al., 2000; Seckl et al., 1987; Sheehan et al., 2006; Singer et al., 1997). However, other substances are also under investigation, including AC-94544 (Del Tredici et al., 2008) and OPC-51803 (Nakamura et al., 2000a), which are agonists with higher selectivity for AVPR2 but not for AVPR1a, AVPR1b, or OT receptors. Their potential usefulness in humans with CDI was suggested by observations of a dose-dependent reduction in urine volume after administration of AC-94544 in Brattleboro rats (see Del Tredici et al., 2008). In the case of OPC-51803, it not only reduced polyuria but also increased urine osmolality and reduced water intake in these rats, and its repeated administration for 4 weeks sustained an antidiuretic action similar to that of chronic treatment with AVP or AVP agonists (Nakamura et al., 2000b).

Results of research in Brattleboro rats may only be partially applicable to CDI in humans, because most hCDI human mutations involve most of the AVP gene and its regulatory sequences in the intergenic region between AVP and OT genes, which encodes the OT prohormone, affecting its secretion (Christensen et al., 2013). There have been reports of a CDI family with linkage to chromosome 20p13 but without mutations in the AVP-NPII gene (e.g. Ye et al., 2005). Likewise, in contrast to the recessive defect in the Brattleboro rat, the neurotoxicity in human hCDI denigrates the magnocellular neurons and results in dominant inheritance. Moreover, all mutations are missense, nonsense, or deletions in human hCDI, in contrast to the reading frame shifts and preserved neurons observed in Brattleboro rats (Kim and Schrier, 1998).

Magnetic resonance neuroimaging studies have revealed an attenuation of the intensity of the signal emitted by the posterior lobe of the hypophysis in individuals with diverse types of acquired CDI (Czernichow et al., 2000; Fujisawa, 2004; Fujiwara and Bichet, 2005; Maghnie et al., 2000; Saborio et al., 2000). Little research has been published on the contribution of the OT-neurophysin complex to this magnetic resonance signal, but the decreased signal intensity of the posterior lobe may also be caused by depletion of the neurosecretory vesicles that contain the OT complex (Fujisawa, 2004). Hence, the neuroendocrine correlates of human CDI may involve disorders that may be more similar to those in animals with tCDI than in Brattleboro rats (see Tables 2 and 3).

Various studies have reported the regulatory benefits of OT administration, although the natriuretic capacity of this neurohormone in humans (Andersen et al., 1998; Kostoglou-Athanassiou et al., 1994) has been questioned (Rasmussen et al., 2003; Williams et al., 1986). Rasmussen et al. (2004) subsequently confirmed that, although the excretion of body sodium is not greater in OT- versus vehicle-treated humans, this neurohormone reduces the volume of urine excretion, thereby increasing urinary osmolality and decreasing plasma sodium concentration. Accordingly, OT may be useful to counteract at least some of the symptoms of CDI due both to its antidiuretic action (Sasaki, 2008) and to its hyponatremic effect (Adrogué and Madias, 2000).

Joo et al. (2004) compared the effects of OT and desmopressin administration in CDI patients. Both treatments appear to have positive effects on urine flow reduction, serum sodium concentration, and osmolality and to increase urine osmolality and urinary AQP2 excretion without altering the urinary excretion rate of electrolytes or osmolar excretion. Four decades before Vigneaud chemically synthesized OT (du Vigneaud et al., 1953), CDI patients were treated with Pituitrin, an extract of bovine posterior pituitary hormones that contains OT and AVP (see Qureshi et al., 2014). Some authors have reported that the administration of minute amounts of Pituitrin appears to control and produce a superior fluid status with minimal adverse reactions (e.g. Holcomb 2002).

The therapeutic effects of food deprivation or low-sodium diets may also be potentially useful in CDI patients, given the above-reported findings in all animal models. In fact, low-sodium diets are frequently prescribed for patients with AVP- resistant CDI (Makaryus and McFarlane, 2007; Rivkees et al., 2007) and could be ordered for CDI patients in combination with their habitual pharmacological treatments.

Furthermore, among other possible preventive measures against CDI, Rajaratnam et al. (2003) observed that a decrease in the perioperative dose of hydrocortisone (a synthetic cortisol used for steroid cover in surgery) reduces by nearly 50% the incidence of tCDI after pituitary resection. This effect has been related to the capacity of this synthetic cortisol to inhibit AVP release (Aubry et al., 1965).

6. Other neurobiological systems differentially involved in animal and humans CDI syndromes

The main objective of this review was to examine evidence on the hydromineral regulatory capacities that are preserved in animals and humans with CDI and the neurohormonal mechanisms involved. We highlight the role of OT, although this neurohormone is not the only endocrine agent with potential relevance in CDI.

Other substances co-localized with AVP or OT in magnocellular neurons have been involved in hydromineral regulation (see Bundzikova et al., 2008 for a review). Thus, there have been diverse reports on the involvement of ANP, co-localized with OT, in natriuretic processes, especially after isotonic volume expansion (Chriguer et al., 2001; Jirikowski et al., 1986). In addition, ANP appears necessary to stimulate OT release in hyperosmolality conditions (Chriguer et al., 2001). After its release, OT may act by stimulating the release of ANP in right atrium and natriuresis (Haanwinckel et al., 1995). ANP secretion is inhibited in MEL animals (Antunes-Rodrigues et al., 1991) and humans with CDI (Kamoi et al., 1990;

Elias et al., 1997), but not in Brattleboro rats (Laulin and Brudieux, 1990) (Table 2). This is another instance of the differences between humans with CDI and Brattleboro rats and the greater similarity of the former with tCDI animals (e.g., MEL rats) (Table 3**)**.

Besides the aforementioned neurohypophyseal deficits, animals and humans with CDI often show abnormalities that affect the hypothalamic-pituitary-adrenocortical (HPA) axis. In Brattleboro rats, resting adrenocorticotropin (ACTH) plasma levels is normal but the HPA response is reduced (Zelena et al., 2009). Baseline ACTH levels are also normal in humans with CD (Elias et al., 1997), but their HPA response is enhanced (Mazza et al., 1994; Elias et al., 1997). In contrast, elevated baseline ACTH levels and HPA axis upregulation are observed in PSC animals (Elias et al., 2004). Finally, both basal plasma ACTH levels and HPA axis regulation are normal in MBH-lesioned animals (Makara et al., 2001). Hence, each of these four types of CDI has specific features in relation to the HPA axis **(**see Tables 2 and 3).

In summary, the symptoms and characteristics of animals with tCDI indicate the involvement of differential factors alongside the habitual lack of AVP, which appear to be related to the neurobiological systems affected in each case. Nevertheless, the results reviewed in this paper suggest that all types of CDI may benefit from the administration of OT and perhaps from the combination of low doses of AVP and OT.

Uncited references

Bernardis and Bellinger (1996), Bernardis and Bellinger (1993), Buckingham and Leach (1980), Edwards (1982), Flier and Maratos-Flier (1998), Kelleher and Henderson (2006), Knoers et al. (1993), Koenig et al. (1989), Llorens-Cortes and Beaudet (2005), Llorens-Cortes and Moos (2008), Meister et al. (1990), Möhring et al. (1978), Morello and Bichet (2001), Odeh and Oliven (2011), Pang et al. (1992), Paxinos and Watson (1986), Phillips (1987), Reaux et al. (2001), Rökaeus et al. (1988), Rosenior et al. (1982), Rosenthal et al. (1994), Rosenthal et al. (1992), Seibold et al. (1992), Shannon (1942), Vande Walle et al. (2007), van Lieburg et al. (1994), Willcutts et al. (1999) and Zimmeman et al. (1984).

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Table 3
Main differences among CDI models in animals and humans (see Table 2 for details).

MAIN DIFFERENCES		HEREDITARY CDI	ACQUIRED CDI			
		BRATTLEBORO ANIMALS	NEUROHYPOX/ PSC ANIMALS	HYPOX ANIMALS	MEL ANIMALS	CDI HUMANS
pOT	Baseline	↑	↓	↓	↓	↓?
	Stimulated by hypertonic NaCl administration	↑	↓	↓	↓	
ANP secretion		=			↓	↓
Baseline pACTH & HPA axis regulation		=/↓	↑/↑		=/=	=/↑
Salt solutions (vs water) intake		Reject		Accepted	Preferred	
UvNa and antidiuresis after hypertonic NaCl administration		↑/↑		↑/↑	↓/↓	↓/↓

↑ high; ↓ low; = normal; ANP: atrial natriuretic peptide; CDI: central diabetes insipidus; HPA: hypothalamic-pituitary-adrenocortical; Hypox: hypophysectomy; MEL: median eminence lesion; Neurohypox: neurohypophysectomy; pACTH: plasma corticotrophin; pOT: plasma Oxytocin; UvNa: natriuresis.

References

Adams, J.R., Blevins, L.S., Allen, G.S., Verity, D.K., Devin, J.K., 2006. Disorders of water metabolism following transsphenoidal pituitary surgery: a single institution's experience. Pituitary 9, 93–99.

Adrogué, H.J., Madias, N.E., 2000. Hyponatremia. N. Engl. J. Med. 342 (21), 1581–1589.

Andersen, S.E., Engstrom, T., Bie, P., 1992. Effects on renal sodium and potassium excretion of vasopressin and oxytocin in conscious dogs. Acta Physiol. Scand. 145, 267–274.

Antunes-Rodrigues, J., Ramalho, M.J., Reis, L.C., Menani, J.V., Turrin, M.Q., Gutkowska, J., McCann, S.M., 1991. Lesions of the hypothalamus and pituitary inhibit volume-expansion-induced release of atrial natriuretic peptide. Proc. Natl. Acad. Sci. U. S. A. 88 (7), 2956–2960.

Antunes-Rodrigues, J., de Castro, M., Elias, L.L., Valença, M.M., McCann, S.M., 2004. Neuroendocrine control of body fluid metabolism. Physiol. Rev. 84 (1), 169–208.

Armstrong, W.E., 2014. Hypothalamic supraoptic and paraventricular nuclei. In: Paxinos, G. (Ed.), The Rat Nervous System. Academic Press, San Diego, pp. 369–388.

Aubry, R.H., Nankin, H.R., Moses, A.M., Streeten, D.H., 1965. Measurement of the osmotic threshold for vasopressin release in human subjects, and its modification by cortisol. J. Clin. Endocrinol. Metab. 25 (11), 1481–1492.

Babey, M., Kopp, P., Robertson, G.L., 2011. Familial forms of diabetes insipidus: clinical and molecular characteristics. Nat. Rev. Endocrinol. 7 (12), 701–714.

Babina, A.V., Lavrinenko, V.A., 2014. Ultrastructural correlates of antidiuretic response of rat kidney. Bull. Exp. Biol. Med. 156 (5), 605–608.

Bacic, A., Gluncic, I., Gluncic, V., 1999. Disturbances in plasma sodium in patients with war head injuries. Mil. Med. 164, 214–216.

Bakker, H., Waring, H., 1976. Experimental diabetes insipidus in a marsupial macropus eugenii (desmarest). J. Endocrinol. 69, 149–157.

Ball, S., 2005. Diabetes insipidus. Medicine 33 (11), 18–19.

Balment, R.J., Brimble, M.J., Forsling, M.L., 1980. Release of oxytocin induced by salt loading and its influence on renal excretion in the male rat. J. Physiol. 308, 439–449.

Balment, R.J., Brimble, M.J., Forsling, M.L., Musabayane, C.T., 1984. Natriuretic response of the rat to plasma concentrations of arginine vasopressin within the physiological range. J. Physiol. 352, 517–526.

Balment, R.J., Brimble, M.J., Forsling, M.L., Kelly, L.P., Musabayane, C.T., 1986. A synergistic effect of oxytocin and vasopressin on sodium excretion in the neurohypophysectomized rat. J. Physiol. 381, , 453–464.

Balment, R.J., Brimble, M.J., Forsling, M.L., Musabayane, C.T., 1986. The influence of neurohypophysial hormones on renal function in the acutely hypophysectomized rat. J. Physiol. 381, , 439–452.

Barberis, C., Mouillac, B., Durroux, T., 1998. Structural bases of vasopressin/oxytocin receptor function. J. Endocrinol. 156, 223–229.

Baturina, G.S., Katkova, L.E., Ilyaskin, A.V., Solenov, E.I., Ivanova, L.N., 2013. Effect of hypoosmotic shock on the volume of renal collecting duct epithelial cells of brattleboro rats with hereditarily defective vasopressin synthesis. Dokl. Biochem. Biophys. 449, 102–104.

Baylis, P.H., 1987. Osmoregulation and control of vasopressin secretion in healthy humans. Am. J. Physiol. 253, R671–R678.

Bennett, T., Gardiner, S.M., 1986. Fluid and electrolyte handling in Long Evans and Brattleboro rats following injection of polyethylene glycol. J. Physiol. 381, 407–415.

Bennett, T., Gardiner, S.M., 1987. Water deprivation: effects on fluid and electrolyte handling and plasma biochemistry in Long-Evans and Brattleboro rats. J. Physiol. 385, 35–48.

Bernal, A., Mahía, J., Puerto, A., 2007. Oxytocin, water intake and food sodium availability in male rats. Horm. Behav. 52 (3), 289–296.

Bernal, A., Mahía, J., García del Río, C., Puerto, A., 2010. Oxytocin polyuria and polydipsia is blocked by NaCl administration in food-deprived male rats. J. Neuroendocrinol. 22, , 1043–1051.

Bernal, A., Mahía, J., Puerto, A., 2010. Potentiated effect of systemic administration of oxytocin on hypertonic NaCl intake in food-deprived male rats. Horm. Behav. 57, , 284–290.

Bernal, A., Mahía, J., Puerto, A., 2013. Differential lasting inhibitory effects of oxytocin and food-deprivation on mediobasal hypothalamic polydipsia. Brain Res. Bull. 94, 40–48.

Bernal, A., Mahía, J., Mediavilla, C., Puerto, A., 2015. Opposite effects of oxytocin on water intake induced by hypertonic NaCl or polyethylene glycol administration. Physiol. Behav. 141, 135–142.

Bernardis, L.L., Bellinger, L.L., 1993. The lateral hypothalamic area revisited: neuroanatomy, body weight regulation, neuroendocrinology and metabolism. Neurosci. Biobehav. Rev. 17 (2), 141–193.

Bernardis, L.L., Bellinger, L.L., 1996. The lateral hypothalamic area revisited: ingestive behavior. Neurosci. Biobehav. Rev. 20 (2), 189–287.

Betley, J.N., Xu, S., Cao, Z.F., Gong, R., Magnus, C.J., Yu, Y., Sternson, S.M., 2015. Neurons for hunger and thirst transmit a negative-valence teaching signal. Nature 521 (7551), 180–185.

Binkley, S.A., 1995. Vasopressin and oxytocin. In: Binkley, S.A. (Ed.), Endocrinology. Harper Collins, New York, pp. 87–106.

Birk, J., Friberg, M.A., Prescianotto-Baschong, C., Spiess, M., Rutishauser, J., 2009. Dominant pro-vasopressin mutants that cause diabetes insipidus form disulfide-linked fibrillar aggregates in the endoplasmic reticulum. J. Cell Sci. 122 (21), 3994–4002.

Blackburn, R.E., Demko, A.D., Hoffman, G.E., Stricker, E.M., Verbalis, J.G., 1992. Central oxytocin inhibition of angiotensin-induced salt appetite in rats. Am. J. Physiol. 263, , R1347–R1353.

Blackburn, R.E., Stricker, E.M., Verbalis, J.G., 1992. Central oxytocin mediates inhibition of sodium appetite by naloxone in hypovolemic rats. Neuroendocrinology 56, , 255–263.

Blackburn, R.E., Samson, W.K., Fulton, R.J., Stricker, E.M., Verbalis, J.G., 1995. Central oxytocin and ANP receptors mediate osmotic inhibition of salt appetite in rats. Am. J. Physiol. 269, R245–R251.

Blevins, L., Wand, G., 1992. Diabetes insipidus. Crit. Care Med. 20, 69–79.

Bourque, C.W., 2008. Central mechanisms of osmosensation and systemic osmoregulation. Nat. Rev. Neurosci. 9 (7), 519–531.

Brimble, M.J., Balment, R.J., Smith, C.P., Windle, R.J., Forsling, M.L., 1991. Influence of oxytocin on sodium excretion in the anaesthetized Brattleboro rat. J. Endocrinol. 129 (1), 49–54.

Bronstein, M., Malebranche, B., Cunha Neto, C., Musolino, N., 2000. Diagnosis and treatment of hypothalamic disease. In: Conn, P., Freeman, M. (Eds.), Neuroendocrinology in Physiology and Medicine. Humana Press Inc, Totowa, pp. 475–498.

Brooks, F., Pickford, M., 1958. The effect of posterior pituitary hormones on the excretion of electrolytes in dogs. J. Physiol. 142, 468–493.

Brownstein, M.J., Russell, J.T., Gainer, H., 1980. Synthesis, transport and release of posterior pituitary hormones. Science 207, 373–378.

Brownstein, M.J., 1983. Biosynthesis of vasopressin and oxytocin. Ann. Rev. Physiol. 45, 129–135.

Brunner, H., Kuschinsky, G., Peters, G., 1956. Der einfluss von oxytocin auf die renale wasser- und salzauscheidung der ratte. Arch. Exp. Path. Pharmak. 228, 457–473.

Buckingham, J.C., Leach, J.H., 1980. Hypothalamo-pituitary-adrenocortical function in rats with inherited diabetes insipidus. J. Physiol. 305, 397–404.

Buma, P., Nieuwenhuys, R., 1988. Ultrastructural characterization of exocytotic release in different layers of the median eminence of the rat. Cell Tissue Res. 252, 107–114.

Bundzikova, J., Pirnik, Z., Zelena, D., Mikkelsen, J.D., Kiss, J., 2008. Response of substances co-expressed in hypothalamic magnocellular neurons to osmotic challenges in normal and brattleboro rats. Cell. Mol. Neurobiol. 28, 1033–1047.

Cheetham, T., Baylis, P.H., 2002. Diabetes insipidus in children: pathophysiology, diagnosis and management. Paediatr. Drugs 4, 785–796.

Cheng, S.W., North, W.G., 1987. Reduced responsiveness to acute salt-loading of vasopressin-neurons and oxytocin-neurons in the heterozygous Brattleboro rat. Neuroendocrinology 45 (2), 93–98.

Chiodera, P., Volpi, R., Caiazza, A., Giuliani, N., Magotti, M.G., Coiro, V., 1998. Arginine vasopressin and oxytocin responses to angiotensin II are mediated by AT1 receptor subtype in normal men. Metab. Clin. Exp. 47 (8), 893–896.

Chou, C.L., Di Giovanni, S.R., Luther, A., Lolait, S.J., Knepper, M.A., 1995. Oxytocin as an antidiuretic hormone. II. Role of V2 vasopressin receptor. Am. J. Physiol. 269, , F78–F85 (1 Pt 2).

Chou, C.L., Di Giovanni, S.R., Mejia, R., Nielsen, S., Knepper, M.A., 1995. Oxytocin as an antidiuretic hormone. I. Concentration dependence of action. Am. J. Physiol. 269, , F70–F77 (1 Pt 2).

Chriguer, R.S., Rocha, M.J., Antunes-Rodrigues, J., Franci, C.R., 2016. 2001Hypothalamic atrial natriuretic peptide and secretion of oxytocin. Brain Res. 889 (1–2), 239–242.

Christensen, J.H., Rittig, S., 2006. Familial neurohypophyseal diabetes insipidus—an update. Semin. Nephrol. 26, 209–223.

Christensen, J.H., Kvistgaard, H., Knudsen, J., Shaikh, G., Tolmie, J., Cooke, S., Pedersen, S., Corydon, T.J., Gregersen, N., Rittig, S., 2013. A novel deletion partly removing the AVP gene causes autosomal recessive inheritance of early-onset neurohypophyseal diabetes insipidus. Clin. Genet. 83 (1), 44–52.

Conrad, K.P., Gellai, M., North, W.G., Valtin, H., 1986. Influence of oxytocin on renal hemodynamics and electrolyte and water excretion. Am. J. Physiol. 251, F290–F296.

Conrad, K.P., Gellai, M., North, W.G., Valtin, H., 1993. Influence of oxytocin on renal hemodynamics and sodium excretion. Ann. N. Y. Acad. Sci. 689, 346–362.

Curtis, G.M., 1924. The production of experimental diabetes insipidus. Arch. Intern. Med. 34 (6), 801–826.

Czernichow, P., Garel, C., Leger, J., 2000. Thickened pituitary stalk on magnetic resonance imaging in children with central diabetes insipidus. Horm. Res. 53, 61–64 (Suppl).
Deen, P.M., Verdijk, M.A., Knoers, N.V., Wieringa, B., Monnens, L.A., Vanos, C.H., Vanoost, B.A., 1994. Requirement of human renal water channel aquaporin-2 for vasopressin-dependent concentration of urine. Science 264, 92–95.
Del Tredici, A.L., Vanover, K.E., Knapp, A.E., Bertozzi, S.M., Nash, N.R., Burstein, E.S., Lameh, J., Currier, E.A., Davis, R.E., Brann, M.R., Mohell, N., Olsson, R., Piu, F., 2008. Identification of novel selective V2 receptor non-peptide agonists. Biochem. Pharmacol. 76 (9), 1134–1141.
Demunbrun, T., Keller, A., Levkoff, A., Purser, R., 1954. Pitocin restoration of renal hemodynamics to pre-neurohypophysectomy levels. Am. J. Physiol. 179, 429–434.
Di Iorgi, N., Napoli, F., Allegri, A.E.M., Olivieri, I., Bertelli, E., Gallizia, A., Rossi, A., Maghnie, M., 2012. Diabetes insipidus-diagnosis and management. Horm. Res. Paediatr. 77, 69–84.
Dlouhá, H., Krecek, J., Zicha, J., 1982. Postnatal development and diabetes insipidus in Brattleboro rats. Ann. N. Y. Acad. Sci. 394, 10–20.
Dogterom, J., Greidanus, V.W., Swaab, D.F., 1977. Evidence for the release of vasopressin and oxytocin into the cerebrospinal fluid, measurements in plasma and CSF of intact and hypophysectomized rats. Neuroendocrinology 24, 108–118.
Dohanics, J., Hoffman, G.E., Smith, M.S., Verbalis, J.G., 1992. Functional neurolobectomy induced by controlled compression of the pituitary stalk. Brain Res. 575 (2), 215–222.
Dorn, J., Antunes-Rodrigues, J., McCann, S.M., 1970. Natriuresis in the rat following intraventricular carbachol. Am. J. Physiol. 219 (5), 1292–1298.
Dumont, A.S., Nemergut, E.C., Jane Jr., J.A., Laws Jr., E.R., 2005. Postoperative care following pituitary surgery. J. Intensive Care Med. 20, 127–140.
Dunn, F.L., Brennan, T.J., Nelson, A.E., Robertson, G.L., 1973. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J. Clin. Invest. 52, 3212–3219.
Dyball, R.E.J., 1968. Stimuli for the release of neurohypophysial hormones. Br. J. Pharmacol. Chemother. 33, 319–328.
Dyball, R.E.J., 1971. Oxytocin and AVP secretion in relation to electrical activity in antidromically identified supraoptic and paraventricular units. J. Physiol. 214, 245–256.
Edwards, B.R., La Rochelle, F.T., 1984. Antidiuretic effect of endogenous oxytocin in dehydrated Brattleboro homozygous rats. Am. J. Physiol. 247, F453–465.
Edwards, B.R., 1982. Water balance in the Brattleboro rat: single or multiple defects?. Ann. N. Y. Acad. Sci. 394, 414–423.
Elias, L.L., Antunes-Rodrigues, J., Elias, P.C., Moreira, A.C., 1997. Effect of plasma osmolality on pituitary-adrenal responses to corticotrophin-releasing hormone and atrial natriuretic peptide changes in central diabetes insipidus. J. Clin. Endocrinol. Metab. 82 (4), 1243–1247.
Elias, P.C.L., Elias, L.L.K., Castro Antunes-Rodrigues, M.J., Moreira, A.C., 2004. Hypothalamic–pituitary–adrenal axis up-regulation in rats submitted to pituitary stalk compression. J. Endocrinol. 180, 297–302.
Fenske, W., Allolio, B., 2012. Current state and future perspectives in the diagnosis of diabetes insipidus: a clinical review. J. Clin. Endocrinol. Metab. 97 (10), 3426–3437.
Fisher, C., Ingram, W.R., 1936. The effect of interruption of the supraoptico–hypophyseal tracts on the antidiuretic, pressor and oxytocic activity of the posterior lobe of the hypophysis. Endocrinology 20, 762–768.
Fisher, A.W.F., Lederis, K., Redstone, P., 1982. The possibility of topographical organization of nerve terminals within the neural lobe of Brattleboro rat. Ann. N. Y. Acad. Sci. 394, 96–101.
Fitts, D.A., Thronton, S.N., Ruhf, A.A., Zierat, D.K., Johnson, A.K., Thunhorst, R.L., 2003. Effects of central oxytocin receptor blockade on water and saline intake, mean arterial pressure, and c-Fos expression in rats. Am. J. Physiol. 285, R1331–R1339.
Fjellestad-Paulsen, A., Paulsen, O., Agay-Abensour, L., Lundin, S., Czernichow, P., 1993. Central diabetes insipidus: oral treatment with dDAVP. Regul. Pept. 45, 303–307.
Flier, J.S., Maratos-Flier, E., 1998. Obesity and the hypothalamus: novel peptides for new pathways. Cell 92 (4), 437–440.
Fregly, M.J., Rowland, N.E., 1989. Preference threshold for NaCl solutions and sodium homeostasis in hypophysectomized rats. Physiol. Behav. 45 (4), 825–829.
Friedman, S.M., Scherrer, H.F., Nakashima, M., Friedman, C.L., 1958. Extrarenal factors in diabetes insipidus in the rat. Am. J. Physiol. 192 (2), 401–404.
Friedman, S.M., Sréter, F., Nakashima, M., Friedman, C., 1962. Adrenal cortex and neurohypophyseal deficiency in salt and water homeostasis of rats. Am. J. Physiol. 203, 697–701.
Fujisawa, I., 2004. Magnetic resonance imaging of the hypothalamic-neurohypophyseal system. J. Neuroendocrinol. 16 (4), 297–302.
Fujiwara, T.M., Bichet, D.G., 2005. Molecular biology of hereditary diabetes insipidus. J. Am. Soc. Nephrol. 16, 2836–2846.
Fuller, L., Fitzsimons, J.T., 1988. Thirst in brattleboro rats. Am. J. Physiol. 255, R217–R225.
Fushimi, K., Uchida, S., Hara, Y., Hirata, Y., Marumo, F., Sasaki, S., 1993. Cloning and expression of apical membrane water channel of rat kidney collecting tubule. Nature 361 (6412), 549–552.
Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system, structure, function and regulation. Physiol. Rev. 81, 629–683.
Giovanelli, L., Shiromani, P.J., Jirikowski, G.F., Bloom, F.E., 1992. Expression of c-fos protein by immunohistochemically identified oxytocin neurons in the rat hypothalamus upon osmotic stimulation. Brain Res. 588, 41–48.
Gonzalez-Portillo, G., Tomita, T., 1998. The syndrome of inappropriate secretion of antidiuretic hormone, an unusual presentation for childhood craniopharyngioma: report of three cases. Neurosurgery 42, 917–922.
Greger, N., Kirkland, R., Clayton, G., Kirkland, J., 1986. Central diabetes insipidus. AJDC 140, 551–554.
Haanwinckel, M.A., Elias, L.K., Favaretto, A.L., Gutowska, J., McCann, S.M., Antunes-Rodrigues, J., 1995. Oxytocin mediates atrial natriuretic peptide release and natriuresis after volume expansion in the rat. Proc. Natl. Acad. Sci. U. S. A. 92, 7902–7906.
Hadjizacharia, P., Beale, E.O., Inaba, K., Chan, L.S., Demetriades, D., 2008. Acute diabetes insipidus in severe head injury: a prospective study. J. Am. Coll. Surg. 207 (4), 477–484.
Haller, J., Makara, G.B., Barna, I., Kovács, K., Nagy, J., Vecsernyés, M., 1996. Compression of the pituitary stalk elicits chronic increases in CSF vasopressin, oxytocin as well as in social investigation and aggressiveness. J. Neuroendocrinol. 8 (5), 361–365.
Han, J.S., Maeda, Y., Knepper, M.A., 1993. Dual actions of vasopressin and oxytocin in regulation of water permeability in terminal collecting duct. Am. J. Physiol. 265, F26–F34.
Hansell, P., Göransson, V., Odlind, C., Gerdin, B., Hällgren, R., 2000. Hyaluronan content in the kidney in different states of body hydration. Kidney Int. 58 (5), 2061–2068.
Harris, H.W., Zeidel, M.L., Hosselet, C., 1991. Quantitation and topography of membrane proteins in highly water-permeable vesicles from AVP-stimulated toad bladder. Am. J. Physiol. 261, C143–C153.
Heinbecker, P., White, H., 1941. Hypothalamic-hypophysial system and its relation to water balance in the dog. Am. J. Physiol. 133, 582–593.
Hendy, G.N., Bichet, D.G., 1995. Diabetes insipidus. Bailliere's Clin. Endocrinol. Metab. 9 (3), 509–524.
Hensen, J., Henig, A., Fahlbusch, R., Meyer, M., Boehnert, M., Buchfelder, M., 1999. Prevalence, predictors and patterns of postoperative polyuria and hyponatraemia in the immediate course after transsphenoidal surgery for pituitary adenomas. Clin. Endocrinol. (Oxf.) 50, 431–439.
Herman, J.P., Marciano, F.F., Wiegand, S.J., Gash, D.M., 1987. Selective cell death of magnocellular vasopressin neurons in neurohypophysectomized rats following chronic administration of vasopressin. J. Neurosci. 7 (8), 2564–2575.
Holcomb, S.S., 2002. Diabetes insipidus. Dimens. Crit. Care Nurs 21 (3), 94–97.
Hollinshead, W., 1964. The interphase of diabetes insipidus. Mayo Clin. Proc. 39, 92–100.
Horn, A.M., Robinson, I.C., Fink, G., 1985. Oxytocin and vasopressin in rat hypophysial portal blood: experimental studies in normal and Brattleboro rats. J. Endocrinol. 104 (2), 211–224.
Huang, Y.S., Dellmann, H.D., 1996. Chronic intermittent salt loading enhances functional recovery from polydipsia and survival of vasopressinergic cells in the hypothalamic supraoptic nucleus following transection of the hypophysial stalk. Brain Res. 732, 95–105.
Huang, W., Lee, S.L., Sjoquist, M., 1995. Natriuretic role of endogenous oxytocin in male rats infused with hypertonic NaCl. Am. J. Physiol. 268, R634–R640.
Ikkos, D., Luft, R., Olivecrona, H., 1954. Hypophysectomy in man: effect on water excretion during the first two postoperative months. J. Clin. Endocrinol. Metabol. 15, 553–567.
Ivanova, L.N., Lavrinenko, V.A., Babina, A.V., Khegay, I.I., 2008. Structure and concentration capacity of the kidneys in brattleboro rats under conditions of long-term vasopressin treatment. Bull. Exp. Biol. Med. 146 (5), 642–646.
Jackson, L.F., McCormick, S.D., Madsen, S.S., Swanson, P., Sullivan, C.V., 2005. Osmoregulatory effects of hypophysectomy and homologous prolactin replacement in hybrid striped bass. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 140 (2), 211–218.
Jard, S., 1988. Vasopressin receptors. A historical survey. Adv. Exp. Med. Biol. 449, 1–13.
Johns, E.J., 2002. The autonomic nervous system and pressure-natriuresis in cardiovascular-renal interactions in response to salt. Clin. Auton. Res. 12 (4), 256–263.
Joo, K.W., Jeon, U.S., Kim, G.H., Park, J., Oh, Y.K., Kim, Y.S., Ahn, C., Kim, S., Kim, S.Y., Lee, J.S., Han, J.S., 2004. Antidiuretic action of oxytocin is associated with increased urinary excretion of aquaporin-2. Nephrol. Dial. Transplant. 19 (10), 2480–2486.
Kadekaro, M., Summy-Long, J.Y., Freeman, S., Harris, J., Terrell, M.L., Eisenberg, H.M., 1992. Cerebral metabolic responses and vasopressin and oxytocin secretions during progressive water deprivation in rats. Am. J. Physiol. 262, , R310–R317.

Kadekaro, M., Summy-Long, J.Y., Harris, J.S., Terrell, M.L., Freeman, S., Eisenberg, H.M., 1992. Cerebral metabolic and vasopressin and oxytocin responses during osmotic stimulation in conscious rats. J. Neuroendocrinol. 4 (2), 217–222.
Kadekaro, M., Harris, J., Freeman, S., Terrell, M.L., Koehler, E., Summy-Long, J.Y., 1995. Water intake and activity of hypothalamoneurohypophysial system during osmotic and sodium stimulation in rats. Am. J. Physiol. 268, R651–R657.
Kadekaro, M., Liu, H., Terrell, M.L., Gestl, S., Bui, V., Summy-Long, J.Y., 1997. Role of NO on vasopressin and oxytocin release and blood pressure responses during osmotic stimulation in rats. Am. J. Physiol. 273, R1024–R1030.
Kamoi, K., Ebe, T., Kobayashi, O., Ishida, M., Sato, F., Arai, O., Tamura, T., Takagi, A., Yamada, A., Ishibashi, M., Yamaji, T., 1990. Atrial natriuretic peptide in patients with the syndrome of inappropriate antidiuretic hormone secretion and with diabetes insipidus. J. Clin. Endocrinol. Metab. 70 (5), 1385–1390.
Kavelaars, J., Tamsma, J., Meinders, A., 2001. Hypernatremia in a non insulin dependent (type 2) diabetic patient with central diabetes insipidus. Neth. J. Med. 58, 150–154.
Kelleher, H.B., Henderson, S.O., 2006. Severe hyponatremia due to desmopressin. J. Emerg. Med. 30, 45–47.
Kiem, D.T., Barna, I., Koenig, J.I., Makara, G.B., 1995. Adrenocorticotropin, prolactin and beta-endorphin stimulatory actions of alpha-2-adrenoceptor antagonists. Neuroendocrinology 61 (2), 152–158.
Kim, J.K., Schrier, R.W., 1998. Vasopressin processing defects in the Brattleboro rat: implications for hereditary central diabetes insipidus in humans?. Proc. Assoc. Am. Physicians 110 (5), 380–386.
King, L.S., Agre, P., 1996. Pathophysiology of the aquaporin water channels. Annu. Rev. Physiol. 58, 619–648.
Knepper, M.A., Wade, J.B., Terris, J., Ecelbarger, C.A., Nielsen, S., Knepper, M.A., 1996. Renal aquaporins. Kidney Int. 49, 1712–1717.
Knoers, N., van den Ouweland, A., Dreesen, J., Verdijk, M., Monnens, L.A., van Oost, B.A., 1993. Nephrogenic diabetes insipidus: identification of the genetic defect. Pediatr. Nephrol. 7, 685.
Koenig, J.I., Hooi, S., Gabriel, S.M., Martin, J.B., 1989. Potential involvement of galanin in the regulation of fluid homeostasis in the rat. Regul. Pept. 24, 81–86.
Kolmodin, L., Sekhon, M.S., Henderson, W.R., Turgeon, A.F., Griesdale, D.E.G., 2013. Hypernatremia in patients with severe traumatic brain injury: a systematic review. Ann. Intensive Care 3, 35.
Kostoglou-Athanassiou, I., Treacher, D.F., Forsling, M.L., 1994. Is oxytocin natriuretic in man?. J. Endocrinol. 143 (Suppl. O) (39).
Kurokawa, H., Fujisawa, I., Nakano, Y., Kimura, H., Akagi, K., Ikeda, K., Uokawa, K., Tanaka, Y., 1998. Posterior lobe of the pituitary gland, correlation between signal intensity on T1-weighted MR images and vasopressin concentration. Radiology 207, 79–83.
Landgraf, R., Neumann, R.I., Schwarzberg, H., 1988. Central and peripheral release of vasopressin and oxytocin in the conscious rat after osmotic stimulation. Brain Res. 457, 219–225.
Lang, R.E., Rascher, W., Heil, J., Unger, T.H., Wiedman, G., Ganten, D., 1981. Angiotensin stimulates oxytocin release. Life Sci. 29, 1425–1428.
Laszlo, F., Wied, D., 1966. Antidiuretic hormone content of the hypothalamoneurohypophysial system and urinary excretion of antidiuretic hormone in rats during the development of diabetes insipidus after lesions in the pituitary stalk. J. Endocrinol. 36, 125–137.
Laulin, J.P., Brudieux, R., 1990. Atrial natriuretic factor is unlikely to be involved in the reduced aldosterone production in the Brattleboro rat. Regul. Pept. 31 (3), 157–165.
Lavrinenko, V.A., Babina, A.B., 2014. Analysis of the efficiency of osmotic concentration in Wistar and Brattleboro rats under the effect of Desmopressin. Bull. Exp. Biol. Med. 156 (5), 624–626.
Layton, A.T., Pannabecker, T.L., Dantzler, W.H., Layton, H.E., 2010. Functional implications of the three-dimensional architecture of the rat renal inner medulla. Am. J. Physiol. 298 (4), F973–F987.
Legros, J.J., 1992. Neurohypophyseal peptides and psychopathology. Horm. Res. 37 (Suppl. 3), 16–21.
Leng, G., Caquineau, C., Sabatier, N., 2005. 2005 Regulation of oxytocin secretion. Vitam. Horm. 71, 27–58.
Li, C., Wang, W., Summer, S.N., Timothy, D., Brooks, W.D.P., Falk, S., Schrier, R.W., 2008. Molecular mechanisms of antidiuretic effect of oxytocin. J. Am. Soc. Nephrol. 19, 225–232.
Lichardus, B., Ponec, J., 1973. On the role of the hypophysis in the renal mechanism of body fluid volumes regulation. Endokrinologie 61, 403–412.
Lindholm, J., 2004. Diabetes insipidus: historical aspects. Pituitary 7, 33–38.
Lippert, T.H., Mueck, A.O., Seeger, H., Pfaff, A., 2003. Effects of oxytocin outside pregnancy. Horm. Res. 60, 262–271.
Lipsett, M., McLean, J., West, C., Li, M.C., Pearson, O., 1956. An analysis of the polyuria induced by hypophysectomy in man. J. Clin. Endocrinol. Metabol. 16, 183–195.
Llorens-Cortes, C., Beaudet, A., 2005. Apelin, a neuropeptide that counteracts vasopressin secretion. Med. Sci. (Paris) 21, 741–746.
Llorens-Cortes, C., Moos, F., 2008. Opposite potentiality of hypothalamic coexpressed neuropeptides, apelin, and vasopressin in maintaining body-fluid homeostasis. Prog. Brain Res. 170, 559–570.
Loh, J.A., Verbalis, J.G., 2007. Diabetes insipidus as a complication after pituitary surgery. Nat. Clin. Pract. Endocrinol. Metab. 3, 489–494.
Lyness, J., Robinson, A.G., Sheridan, M.N., Gash, D.M., 1985. Antidiuretic effects of oxytocin in the Brattleboro rat. Experientia 41, 1444–1446.
Möhring, J., Kohrs, G., Möhring, B., Petri, M., Homsy, E., Haack, D., 1978. Effects of prolonged vasopressin treatment in Brattleboro rats with diabetes insipidus. Am. J. Physiol. 234 (2), F106–F111.
Macias Batista, A., Martinez, P., De Pablos Velasco, P., 1999. Diabetes insípida e hipernatremia adípsica en un paciente con craneofaringioma. Ann. Med. Intern. 16, 87–88.
Maghnie, M., Cosi, G., Genovese, E., Manca-Bitti, M., Cohen, A., Zecca, S., Tinelli, C., Gallucci, M., Bernasconi, S., Boscherini, B., Severi, F., Aricò, M., 2000. Central diabetes insipidus in children and young adults. N. Engl. J. Med. 343, 998–1007.
Mahía, J., Puerto, A., 2006. Lesions of tuberomammillary nuclei induce differential polydipsic and hyperphagic effects. Eur. J. Neurosci. 23 (5), 1321–1331.
Mahía, J., Bernal, A., Puerto, A., 2007. Dipsogenic potentiation by sodium chloride but not by sucrose or polyethylene glycol in tuberomammillary-mediated polydipsia. Exp. Brain Res. 183 (1), 27–39.
Mahía, J., Bernal, A., Puerto, A., 2007. Hyperphagia and increased body weight induced by lesions of the ventral tuberomammillary system. Behav. Brain Res. 181 (1), 147–152.
Mahía, J., Bernal, A., Puerto, A., 2007. Trastornos del comportamiento regulatorio, polidipsia primaria, polidipsia secundaria y su tratamiento. Int. J. Clin. Health Psychol. 7 (2), 511–527.
Mahía, J., Bernal, A., Puerto, A., 2008. NaCl preference and water intake effects of food availability in median eminence polidipsia. Neurosci. Lett. 447, 7–11.
Mahía J, Mahía, A. Bernal, C. García del Río, A. Puerto, The natriuretic effect of oxytocin blocks medial tuberomammillary polydipsia and polyuria in male rats, Eur. J. Neurosci. 29 (2009) 1440–1446.
et al., 2009.
Mahía, J., Bernal, A., Puerto, A., 2013. Inhibition of natriuresis in median eminence polydipsia: effects after intake of diets with different osmolalities and after hypertonic NaCl administration. Acta Neurobiol. Exp. 73, 326–337.
Mahon, J.M., Allen, M., Herbert, J., Fitzsimons, J.T., 1995. The association of thirst, sodium appetite and vasopressin release with c-fos expression in the forebrain of the rat after intracerebroventricular injection of angiotensin II, angiotensin-(1–7) or carbachol. Neuroscience 69 (1), 199–208.
Makara, G.B., Sutton, S., Otto, S., Plotsky, P.M., 1995. Marked changes of arginine vasopressin, oxytocin, and corticotropin-releasing hormone in hypophysial portal plasma after pituitary stalk damage in the rat. Endocrinology 136 (5), 1864–1868.
Makara, G.B., Kiss, A., Lolait, S.J., Aguilera, G., 1996. Hypothalamic-pituitary corticotrophine function after shunting of magnocellular vasopressin and oxytocin to the hypophyseal portal circulation. Endocrinology 137 (2), 580–586.
Makara, G.B., Harbuz, M.S., Coventry, T.L., Jessop, D.S., Zelena, D., Lightman, S.L., 2001. The effect of hypothalamic lesions on hypothalamo-pituitary-adrenal axis activity and inflammation in adjuvant-induced arthritis. Stress 4 (1), 25–37.
Makaryus A.N., McFarlane S.I., Diabetes insipidus, diagnosis and treatment of a complex disease, Clevel. Clin. J. Med. 73 (2006) 65–71.
Makaryus and McFarlane, 2006
Man, S., Hugh, C., 1992. Disorders of sodium metabolism, hypernatremia and hyponatremia. Crit. Care Med. 20, 94–103.
Mazza, E., Goffi, S., Barchi, P., Arvat, E., Bellone, J., Limone, P., Ghigo, E., Camanni, F., 1994. Enhanced adrenocorticotrophic hormone and cortisol responses to corticotrophin-releasing hormone in central idiopathic diabetes insipidus. Eur. J. Endocrinol. 130 (2), 121–124.
McCann, S.M., Franci, C.R., Favaretto, A.L., Gutkowska, J., Antunes-Rodrigues, J., 1997. Neuroendocrine regulation of salt and water metabolism. Braz. J. Med. Biol. Res. 30 (4), 427–441.
McKinley, M.J., Bicknell, R.J., Hards, D., McAllen, R.M., Vivas, L., Weisinger, R.S., Oldfield, B.J., 1992. Efferent neural pathways of the lamina terminallis subserving osmoregulation. Prog. Brain Res. 91, 395–402.
Meister, B., Cortes, R., Villar, M.J., Schalling, M., Hökfelt, T., 1990. Peptides and transmitter enzymes in hypothalamic magnocellular neurons after administration of hyperosmotic stimuli: comparison between messenger RNA and peptide/protein levels. Cell Tissue Res. 260, 279–297.
Mirsky, A., Paulisch, G., Stein, M., 1954. The antidiuretic activity of the plasma of adrenalectomized, hypophysectomized and adrenalectomized-hypophysectomized rats. Am. J. Physiol. 54, 691–697.
Morello, J.P., Bichet, D.G., 2001. Nephrogenic diabetes insipidus. Annu. Rev. Physiol. 63, 607–630.

Morris, M., McCann, S.M., Orias, R., 1976. Evidence for hormonal participation in the natriuretic and kaliuretic responses to intraventricular hypertonic saline and norepinephrine. Proc. Soc. Exp. Biol. Med. 152 (1), 95–98.
Morris, M., Barnard, R., Sain, L., 1984. Osmotic mechanisms regulating cerebrospinal fluid vasopressin and oxytocin in the conscious rat. Neuroendocrinol 39, 377–383.
Morris, J.F., 2006. Vasopressin and oxytocin. In: Kastin, A.J. (Ed.), Handbook of Biologically Active Peptides. Academic Press, San Diego, pp. 621–627.
Morrissey, S.E., Newth, T., Rees, R., Barr, A., Shora, F., Laycock, J.F., 2001. Renal effects of recombinant prolactin in anaesthetized rats. Eur. J. Endocrinol. 145 (1), 65–71.
Moses, A., Clayton, B., Hochhauser, L., 1992. Use of T1-weighted MR imaging to differentiate between primary polydipsia and central diabetes insipidus. Am. J. Neuroradiol. 13, 1273–1277.
Mundschenk, J., Rittig, S., Siggaard, C., Hensen, J., Lehnert, H., 2001. A new mutation of the arginine vasopressin neurophysin II gene in a family with autosomal dominant neurohypophyseal diabetes insipidus. Exp. Clin. Endocrinol. Diabetes 109 (8), 406–409.
Murphy, H.M., Wideman, C.H., 1991. Vasopressin deficiency and the modulation of consummatory behavior. Peptides 12 (2), 319–322.
Nakamura, S., Hirano, T., Tsujimae, K., Aoyama, M., Kondo, K., Yamamura, Y., Mori, T., Tominaga, M., 2000. Antidiuretic effects of a nonpeptide vasopressin V(2)-receptor agonist, OPC-51803, administered orally to rats. J. Pharmacol. Exp. Ther. 295 (3), 1005–1011.
Nakamura, S., Yamamura, Y., Itoh, S., Hirano, T., Tsujimae, K., Aoyama, M., Kondo, K., Ogawa, H., Shinohara, T., Kan, K., Tanada, Y., Teramoto, S., Sumida, T., Nakayama, S., Sekiguchi, K., Kambe, T., Tsujimoto, G., Mori, T., Tominaga, M., 2000. Characterization of a novel nonpeptide vasopressin V(2)-agonist OPC-51803, in cells transfected human vasopressin receptor subtypes. Br. J. Pharmacol. 129 (8), 1700–1706.
Nemergut, E.C., Zuo, Z., Jane Jr., J.A., Laws Jr., E.R., 2005. Predictors of diabetes insipidus after transsphenoidal surgery, a review of 881 patients. J. Neurosurg. 103, 448–454.
Nielsen, S., Chou, C.L., Marples, D., Christensen, E.I., Kishore, B.K., Knepper, M.A., 1995. Vasopressin increases water permeability of kidney collecting duct by inducing translocation of aquaporin-CD water channels to plasma membrane. Proc. Natl. Acad. Sci. U. S. A. 92, 1013–1017.
Nielsen, S., Frøkiaer, J., Marples, D., Kwon, T.H., Agre, P., Knepper, M.A., 2002. Aquaporins in the kidney: from molecules to medicine. Physiol. Rev. 82, 205–244.
Nishi, E.E., Bergamaschi, C.T., Campos, R.R., 2015. The crosstalk between the kidney and the central nervous system: the role of renal nerves in blood pressure regulation. Exp. Physiol. 100 (5), 479–484.
North, W.G., Gellai, M., Hardy, G., 1982. Oxytocin and oxytocin-associated neurophysin evaluation by RIA in the Brattleboro rat: turnover. Ann. N. Y. Acad. Sci. 394, 167–172.
O'Connor, W., 1946. The effect of section of the supraoptic-hypophyseal tracts on the inhibition of water diuresis by emotional stress. Q. J. Exp. Physiol. 33, 149–161.
OConnor, W., 1950. The role of the neurohypophysis of the dog in determining urinary changes, and the antidiuretic activity of urine, following the administration of sodium chloride or urea. Q. J. Exp. Physiol. 36, 21–48.
O'Connor, W., 1952. The normal interphase in the polyuria which follows section of the supraoptico-hypophysial tracts in the dog. Q. J. Exp. Physiol. 37, 1–10.
Odeh, M., Oliven, A., 2011. Coma and seizures due to severe hyponatremia and water intoxication in an adult with intranasal desmopressin therapy for nocturnal enuresis. J. Clin. Pharmacol. 41, 582–584.
Oka, Y., Ye, M., Zuker, C.S., 2015. Thirst driving and suppressing signals encoded by distinct neural populations in the brain. Nature 520 (7547), 349–352.
Page, R.B., Dovey-Hartman, B.J., 1984. Neurochemical contact in the internal zone of the rabbit median eminence. J. Comp. Neurol. 226, 274–288.
Palmieri, G.M., Taleisnik, S., 1969. Intake of NaCl solution in rats with diabetes insipidus. J. Comp. Physiol. Psychol. 68 (1), 38–44.
Pang, Y., Metzenberg, A., Das, S., Jing, B., Gitschier, J., 1992. Mutations in the V2 vasopressin receptor gene are associated with X-linked nephrogenic diabetes insipidus. Nat. Genet. 2, 103–106.
Paxinos, G., Watson, C., 1986. The Rat Brain in Stereotaxic Coordinates. Academic Press, New York.
Phillips, M.I., 1987. Functions of angiotensin in the central nervous system. Annu. Rev. Physiol. 49, 413–435.
Phulwani, N., Pandey, T., Khatri, J., Raghu, H., Ramakrishnaiah, T.P., Chetan, C.S., 2011. Imaging manifestations and techniques in diabetes insipidus. In: Kamoi, K. (Ed.), Diabetes Insipidus. InTech, Rijeka, pp. 109–140.
Pickford, M., Ritchie, A., 1945. Experiments on the hypothalamic-pituitary control of water excretion in dogs. J. Physiol. 104, 105–128.
Pittman, J.G., 1963. Water intoxication due to oxytocin. N. Engl. J. Med. 68 (1963), 481–482.
Pivonello, R., Faggiano, A., Arrichiello, P., Di Sarno, A., Di Osma, C., Ferone, D., Lombardi, G., Colao, A., 2000. Central diabetes insipidus and heart: effect of acute arginine vasopressin deficiency and replacement treatment with desmopressin on cardiac performance. Clin. Endocrinol. 54, 97–106.
Potter, R.R., 1964. Water retention due to oxytocin. Obstet. Gynecol. 23, 699–702.
Pouzet, B., Serradeil-Le, G.C., Bouby, N., Maffrand, J.P., Le, F.G., Bankir, L., 2001. Selective blockade of vasopressin V2 receptors reveals significant V2-mediated water reabsorption in Brattleboro rats with diabetes insipidus. Nephrol. Dial. Transplant. 16, 725–734.
Pow, D.V., Morris, J.F., 1990. Ontogeny of diabetes insipidus in the Brattleboro rat, morphological and physiological correlates. J. Neuroendocrinol. 2 (2), 233–239.
Price, T., Kallenborn, J., 2000. Infant hypernatremia. J. Emerg. Med. 19, 153–157.
Qureshi, S., Galiveeti, S., Bichet, D.G., Roth, J., 2014. Diabetes insipidus: celebrating a century of vasopressin therapy. Endocrinology 155 (12), 4605–4621.
Rökaeus, A., Young, W.S., Mezey, E., 1988. Galanin coexists with vasopressin in the normal rat hypothalamus and galanin's synthesis is increased in the Brattleboro (diabetes insipidus) rat. Neurosci. Lett. 90, 45–50.
Raisman, G., 1973. Electron microscopic studies of the development of new neurohaemal contacts in the median eminence of the rat after hypophysectomy. Brain Res. 55 (2), 245–261.
Rajaratnam, S., Seshadri, M.S., Chandy, M.J., Rajshekhar, V., 2003. Hydrocortisone dose and postoperative diabetes insipidus in patients undergoing transsphenoidal pituitary surgery: a prospective randomized controlled study. Br. J. Neurosurg. 17 (5), 437–442.
Rao, V.V., Löffler, C., Battey, J., Hansmann, I., 1992. The human gene for oxytocin-neurophysin I (OXT) is physically mapped to chromosome 20p13 by in situ hybridization. Cytogenet. Cell Genet. 61 (4), 271–273.
Rasmussen, M.S., Simonsen, J.A., Sandgaard, N.C., Høilund-Carlsen, P.F., Bie, P., 2003. Mechanisms of acute natriuresis in normal humans on low sodium diet. J. Physiol. 546 (Pt. 2), 591–603.
Rasmussen, M.S., Simonsen, J.A., Sandgaard, N.C., Høilund-Carlsen, P.F., Bie, P., 2004. Effects of oxytocin in normal man during low and high sodium diets. Acta Physiol. Scand. 181 (2), 247–257.
Reaux, A., De Mota, N., Skultetyova, I., Lenkei, Z., El Messari, S., Gallatz, K., Corvol, P., Palkovits, M., Llorens-Cortes, C., 2001. Physiological role of a novel neuropeptide, apelin, and its receptor in the rat brain. J. Neurochem. 77, 1085–1096.
Rembratt, A., Graugaard-Jensen, C., Senderovitz, T., Norgaard, J.P., Djurhuus, J.C., 2004. Pharmacokinetics and pharmacodynamics of desmopressin administered orally versus intravenously at daytime versus night-time in healthy men aged 55–70 years. Eur. J. Clin. Pharmacol. 60, 397–402.
Renaud, L., Bourque, C., 1990. Neurophysiology and neuropharmacology of hypothalamic magnocellular neurons secreting vasopressin and oxytocin. Prog. Neurobiol. 36, 131–169.
Richter, C.P., Ecker, J.F., 1935. Further evidence for the primacy of polyuria in diabetes insipidus. Am. J. Physiol. 113, 578–581.
Rivkees, S.A., Dunbar, N., Wilson, T.A., 2007. The management of central diabetes insipidus in infancy: desmopressin, low renal solute load formula, thiazide diuretics. J. Pediatr. Endocrinol. Metab. 20 (4), 459–469.
Robertson, G.L., 1983. Thirst and vasopressin function in normal and disordered states of water balance. J. Lab. Clin. Med. 101, 351–371.
Robertson, G.L., 1987. Physiology of AVP secretion. Kidney Int. 32 (Suppl. 21), S20–S26.
Robertson, G.L., 1995. Diabetes insipidus. Endocrinol. Metab.Clin. North Am. 24, 549–572.
Rolls, B.J., 1970. Drinking by rats after irritative lesions in the hypothalamus. Physiol. Behav. 5, 1385–1393.
Rose, B.D., Post, T., Stokes, J., 2015. Clinical Physiology of Acid Base and Electrolyte Disorders. McGraw-Hill, New York.
Rosenior, J.C., North, W.G., Moore, G.J., 1982. Biosynthesis of oxytocin and oxytocin-neurophysin in homozygous Brattleboro rats. Ann. N. Y. Acad. Sci. 394, 183–187.
Rosenthal, W., Seibold, A., Antaramian, A., Lonergan, M., Arthus, M.F., Hendy, G.N., Birnbaumer, M., Bichet, D.G., 1992. Molecular identification of the gene responsible for congenital nephrogenic diabetes insipidus. Nature 359, 233–235.
Rosenthal, W., Seibold, A., Antaramian, A., Gilbert, S., Birnbaumer, M., Bichet, D.G., Arthus, M.F., Lonergan, M., 1994. Mutations in the vasopressin V2 receptor gene in families with nephrogenic diabetes insipidus and functional expression of the Q-2 mutant. Cell. Mol. Biol. 40, 429–436.
Saborio, P., Tipton, G., Chan, J., 2000. Diabetes insipidus. Pediatr. Rev. 21, 122–129.
Saeb-Parsy, K., Lombardelli, S., Khan, F.Z., McDowall, K., Au-Yong, I.T., Dyball, R.E., 2000. Neural connections of hypothalamic neuroendocrine nuclei in the rat. J. Neuroendocrinol. 12, 635–648.
Sasaki, S., 2008. 2008 Is oxytocin a player in antidiuresis?. J. Am. Soc. Nephrol. 19, 189–193.
Saul, G.B.I.I., Garrity, E.B., Benirschke, K., Valtin, H., 1968. Inherited hypothalamic diabetes insipidus in the Brattleboro strain of rats. J. Hered. 59, 113–117.
Sawyer, W.H., 1952. Posterior pituitary extracts and excretion of electrolytes by the rat. Am. J. Physiol. 169 (3), 583–587.
Schiltz, J.C., Hoffman, G.E., Stricker, E.M., Sved, A.F., 1997. Decreases in arterial pressure activate oxytocin neurons in conscious rats. Am. J. Physiol. 273, R1474–R1483.

Schmale, H., Richter, D., 1984. Single base deletion in the vasopressin gene is the cause of diabetes insipidus in Brattleboro rats. Nature 308, 705–709.
Schmidt, A., Jard, S., Dreifuss, J.J., Tribollet, E., 1990. Oxytocin receptors in rat kidney during development. Am. J. Physiol. 259, F872–F881.
Schramm, L.P., Strack, A.M., Platt, K.B., Loewy, A.D., 1993. Peripheral and central pathways regulating the kidney: a study using pseudorabies virus. Brain Res. 616 (1–2), 251–262.
Schreckinger, M., Szerlip, N., Mittal, S., 2013. Diabetes insipidus following resection of pituitary tumors. Clin. Neurol. Neurosurg. 115, 121–126.
Seckl, J.R., Dunger, D.B., 1989. Postoperative diabetes insipidus. BMJ 298, 2–3.
Seckl, J.R., Dunger, D.B., 1992. Diabetes insipidus: current treatment recommendations. Drugs 44 (2), 216–224.
Seckl, J., Dunger, D., Lightman, S., 1987. Neurohypophyseal peptide function during early postoperative diabetes insipidus. Brain 110, 737–746.
Seibold, A., Brabet, P., Rosenthal, W., Birnbaumer, M., 1992. Structure and chromosomal localization of the human antidiuretic hormone receptor gene. Am. J. Hum. Genet. 51, 1078–1083.
Shannon, J.A., 1942. The control of the renal excretion of water: I and II. J. Exp. Med. 76, 371–386.
Sheehan, J.M., Sheehan, J.P., Douds, G.L., Page, R.B., 2006. DDAVP use in patients undergoing transsphenoidal surgery for pituitary adenomas. Acta Neurochir. 148, 287–291.
Sherman, T.G., Day, R., Civelli, O., Douglass, J., Herbert, E., Akil, H.I., Watson, S.J., 1988. Regulation of hypothalamic magnocellular neuropeptides and their mRNAs in the brattleboro rat: coordinate responses to further osmotic challenge. J. Neurosci. 8 (10), 3785–3796.
Si-Hoe, S., De Bree, F., Nijenhuis, M., Davies, J., Howell, L., Tinley, H., Waller, S.J., Zeng, Q., Zalm, R., Sonnemans, M., Van Leeuwen, F.W., Burbach, J.P., Murphy, D., 2000. Endoplasmic reticulum derangement in hypothalamic neurons of rats expressing a familial neurohypophyseal diabetes insipidus mutant vasopressin transgene. FASEBS J. 14, 1680–1684.
Singer, P.A., Sevilla, L.J., 2003. Postoperative endocrine management of pituitary tumors. Neurosurg. Clin. N. Am. 14, 123–138.
Singer, I., Oster, J., Fishman, L., 2016. The management of diabetes insipidus in adults. Arch. Intern. Med. 157, 1293–1301.
Smith, R.W., McCann, C.S., 1962. Alterations in food and water intake after hypothalamic lesions in the rat. Am. J. Physiol. 203, 366–370.
Snyder, H.M., Noland, T.D., Breyer, M.D., 1992. cAMP-dependent protein kinase mediates hydrosmotic effect of vasopressin in collecting duct. Am. J. Physiol. 263 (1 Pt 1), C147–C153.
Song, J., Eskridge, J., Niakan, C., Winn, R., 1999. Diabetes insipidus arising from hypothalamic diffuse axonal injury. J. Neurosurg. 90, 1141–1142.
Star, R.A., Nonoguchi, H., Balaban, R., Knepper, M.A., 1988. Calcium and cyclic adenosine monophosphate as second messengers for vasopressin in the rat inner medullary collecting duct. J. Clin. Invest. 81, 1879–1888.
Stoeckel, M.E., Freund-Mercier, M.J., 1989. Autoradiographic demonstration of oxytocin-binding sites in the macula densa. Am. J. Physiol. 257, F310–F314.
Strange, K., Spring, K.R., 1987. Absence of significant cellular dilution during ADH-stimulated water reabsorption. Science 235 (4792), 1068–1070.
Stricker, E.M., Verbalis, J.G., 1986. Interaction of osmotic and volume stimuli in regulation of neurohypophyseal secretion in rats. Am. J. Physiol. 250, R267–R275.
Stricker, E.M., Verbalis, J.G., 1987. Central inhibitory control of sodium appetite in rats: correlation with pituitary oxytocin secretion. Behav. Neurosci. 101 (4), 560–567.
Stricker, E.M., 1966. Extracellular fluid volume and thirst. Am. J. Physiol. 211, 232–238.
Swaab, D.F., Pool, C.W., Nijveldt, F., 1975. Immunofluorescence of vasopressin and oxytocin in the rat hypothalamo-neurohypophypopseal system. J. Neural Transm. 36 (3–4), 195–215.
Swaab, D.F., Hofman, M.A., Lucassen, P.J., Purba, J.S., Raadsheer, F.C., Van De Nes, J.A., 1993. Functional neuroanatomy and neuropathology of the human hypothalamus. Anat. Embriol. 187, 317–330.
Swann, H.G., 1939. Sodium chloride and diabetes insipidus. Science 90 (2325), 67–68.
Tisdall, M., Crocker, M., Watkiss, J., Smith, M., 2006. Disturbances of sodium in critically ill adult neurologic patients: a clinical review. J. Neurosurg. Anesthesiol. 18, 57–63.
Titlebaum, L., Falk, J., Mayer, J., 1960. Altered acceptance and rejection of NaCl in rats with diabetes insipidus. Am. J. Physiol. 199, 22–24.
Treschan, T.A., Peters, J., 2006. The vasopressin system: physiology and clinical strategies. Anesthesiology 105, 444–445.
Tribollet, E., Dubois-Dauphin, M., Dreifuss, J.J., 1992. Oxytocin receptors in the central nervous system. N. Y. Acad. Sci. 652, 29–38.
Valtin, H., Schroeder, H.A., 1964. Familial hypothalamic diabetes insipidus in rats (Brattleboro Strain). Am. J. Physiol. 206, 425–430.
Valtin, H., Sawyer, W.H., Sokol, H.W., 1965. Neurohypophysial principles in rats homozygous and heterozygous for hypothalamic diabetes insipidus (Brattleboro strain). Endocrinology 77, 701–706.
Valtin, H., 1967. Hereditary hypothalamic diabetes insipidus in rats (Brattleboro strain): A useful experimental model. Am. J. Med. 42, 814–827.
Valtin, H., 1974. Genetics models in biomedical investigation. N. Engl. J. Med. 290, 670–675.
Valtin, H., 1982. The discovery of the Brattleboro rat, recommended nomenclature, and the question of proper controls. Ann. N. Y. Acad. Sci. 394, 1–9.
Vande Walle, J., Stockner, M., Rase, A., Nørgaard, J.P., 2007. Desmopressin 30 years in clinical use, a safety review. Curr. Drug Saf. 2, 232–238.
Vandesande, F., Dierickx, K., 1976. Immuno-cytochemical demonstration of the inability of the homozygous Brattleboro rat to synthesize vasopressin and vasopressin-associated neurophysin. Cell Tissue Res. 165 (3), 307–316.
Vega, C., Moreno-Carranza, B., Zamorano, M., Quintanar-Stéphano, A., Méndez, I., Thebault, S., Martínez de la Escalera, G., Clapp, C., 2010. Prolactin promotes oxytocin and vasopressin release by activating neuronal nitric oxide synthase in the supraoptic and paraventricular nuclei. Am. J. Physiol. 299 (6), R1701–R1708.
Verbalis, J.G., Dohanics, J., 1991. Vasopressin and oxytocin secretion in chronically hyposmolar rats. Am. J. Physiol. 261, R1028–R1038.
Verbalis, J.G., Baldwin, E.F., Robinson, A.G., 1986. Osmotic regulation of plasma vasopressin and oxytocin after sustained hyponatremia. Am. J. Physiol. 250, R444–R451.
Verbalis, J.G., Mangione, M.P., Stricker, E.M., 1991. Oxytocin produces natriuresis in rats at physiological plasma concentrations. Endocrinology 128, 1317–1322.
Verbalis, J.G., 2003. Diabetes insipidus. Rev. Endocr. Metab. Disord. 4, , 177–185.
Verbalis, J.G., 2003. Disorders of body water homeostasis. Best Pract. Res. Clin. Endocrinol. Metab. 17, , 471–503.
Walter, M.F., Forsling, M.L., Shirley, D.G., 2000. Contribution of endogenous oxytocin to sodium excretion in anaesthetized, surgically operated rats. J. Endocrinol. 165, 19–24.
Wang, J.Y., Lin, S.H., Lin, Y.F., Chen, H.Y., Yu, F.C., Fu, M.T., 2000. An unforgotten cause of acute hyponatremia, water intoxication due to oxytocin administration in a pregnant woman. Nephron 86 (3), 342–343.
Wells, T., 1998. Vesicular osmometers, vasopression secretion and aquaporin-4: A new mechanism for osmoreception?. Mol. Cell. Endocrinol. 136, 103–107.
White, H., Heinbecker, P., 1938. Observations on creatinine and urea clearances on response to water ingestion and on concentrating power of kidneys in normal diabetes insipidus and hypophysectomized dogs. Am. J. Physiol. 123, 566–576.
Wideman, C.H., Murphy, H.M., 1991. Effects of vasopressin replacement during food-restriction stress. Peptides 12 (2), 285–288.
Wiegand, S.J., Price, J.L., 1980. Cells of origin of the afferent fibers to the median eminence in the rat. J. Comp. Neurol. 192, 1–19.
Wilke, C., Sheriff, S., Soleimani, M., Amlal, H., 2005. Vasopressin-independent regulation of collecting duct aquaporin-2 in food deprivation. Kidney Int. 67 (1), 201–216.
Willcutts, M.D., Felner, E., White, P.C., 1999. Autosomal recessive familial neurohypophyseal diabetes insipidus with continued secretion of mutant weakly active vasopressin. Hum. Mol. Genet. 8, 1303–1307.
Williams, T.D., Abel, D.C., King, C.M., Jelley, R.Y., Lightman, S.L., 1986. Vasopressin and oxytocin responses to acute and chronic osmotic stimuli in man. J. Endocrinol. 108 (1), 163–168.
Windle, R.J., Forsling, M.L., Smith, C.P., Balment, R.J., 1993. Patterns of neurohypophysial hormone release during dehydration in the rat. J. Endocrinol. 137, 311–319.
Windle, R.J., Judah, J.M., Forsling, M.L., 1995. Do vasopressin and oxytocin have synergistic renal effects in the conscious rat?. J. Endocrinol. 144, 441–448.
Windle, R.J., Judah, J.M., Forsling, M.L., 1997. Effect of oxytocin receptor antagonists on the renal actions of oxytocin and vasopressin in the rat. J. Endocrinol. 152, 257–264.
Wyndham, J.R., Everitt, A.V., Eyland, A., Major, J., 1987. Inhibitory effect of hypophysectomy and food restriction on glomerular basement membrane thickening, proteinuria and renal enlargement in aging male Wistar rats. Arch. Gerontol. Geriatr. 6 (4), 323–337.
Xiong, J.J., Hatton, G.I., 1996. Differential responses to oxytocin and vasopressin neurons to the osmotic and stressful components of hypertonic saline injections, a Fos protein double labelling study. Brain Res. 719, 143–153.
Yang, Z., Coote, J.H., 2007. Paraventricular nucleus influence on renal sympathetic activity in vasopressin gene-deleted rats. Exp. Physiol. 92 (1), 109–117.
Ye, L., Li, X., Chen, Y., Sun, H., Wang, W., Su, T., Jiang, L., Cui, B., Ning, G., 2005. Autosomal dominant neurohypophyseal diabetes insipidus with linkage to chromosome 20p13 but without mutations in the AVP-NPII gene. J. Clin. Endocrinol. Metab. 90 (7), 4388–4393.
Yirmiya, R., Holder, M.D., Derdiarian, A., 1988. Salt preference in rats with hereditary hypothalamic diabetes insipidus (Brattleboro strain). Behav. Neurosci. 102 (4), 574–579.
Zelena, D., Filaretova, L., Mergl, Z., Barna, I., Tóth, Z.E., Makara, G.B., 2006. Hypothalamic paraventricular nucleus, but not vasopressin, participates in chronic hyperactivity of the HPA axis in diabetic rats. Am. J. Physiol. Endocrinol. Metab. 290 (2), E243–E250.

Zelena, D., Domokos, A., Jain, S.K., Jankord, R., Filaretova, L., 2009. The stimuli-specific role of vasopressin in the hypothalamus-pituitary-adrenal axis response to stress. J. Endocrinol. 202 (2), 263–278.

Zelena, D., Pintér, O., Langnaese, K., Richter, K., Landgraf, R., Makara, G.B., Engelmann, M., 2013. Oxytocin in brattleboro rats: increased synthesis is contrasted by blunted intrahypothalamic release from supraoptic nucleus neurones. J. Neuroendocrinol. 25, 711–718.

Zimmeman, M.B., Nilavier, G., Hou-Yu, A., Silverman, A.J., 1984. Vasopressinergic and oxytocinergic pathways in central nervous system. Feed. Proc. 43, 91–96.

Zimmerman, E.A., Robinson, A.G., 1976. Hypothalamic neurons secreting vasopressin and neurophysin. Kidney Int. 10, 12–24.

du Vigneaud, V., Ressler, C., Swan, C.J.M., Roberts, C.W., Katsoyannis, P.G., Gordon, S., 1953. The synthesis of an octapeptide amide with the hormonal activity of oxytocin. J. Am. Chem. Soc. 75 (19), 4879–4880.

van Lieburg, A.F., Verdijk, M.A., Knoers, V.V., van Essen, A.J., Proesmans, W., Mallmann, R., Monnens, L.A., van Oost, B.A., van Os, C.H., Deen, P.M., 1994. Patients with autosomal nephrogenic diabetes insipidus homozygous for mutations in the aquaporin 2 water-channel gene. Am. J. Hum. Genet. 55 (4), 648–652.