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Chapter 4

Animal Models of Central Diabetes Insipidus: Oxytocin and Low-Sodium Diets as Complementary Treatments

Antonio Bernal, Javier Mahía and Amadeo Puerto

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Abstract

Human central diabetes insipidus (CDI) is a neurobiological syndrome characterized by the presence of hypotonic polyuria, hypernatremia, and polydipsia. CDI can be acquired (aCDI) as the result of brain damage to magnocellular neurosecretory cells or fibers that constitute the hypothalamic-neurohypophyseal system or can be caused by genetic disorders (hereditary CDI). aCDI can be experimentally induced by various surgical interventions, including neurohypophysectomy, pituitary stalk compression (PSC), hypophysectomy, and hypothalamic mediobasal lesions. CDI has been associated with a deficient production of arginine vasopressin (AVP) (the antidiuretic hormone secreted by magnocellular system), while more recently, aCDI animal studies also suggest the possible involvement of oxytocin (OT) (a natriuretic-promoting hormone secreted by neurosecretory systems) and other factors related to serum fluid concentration. Both humans and animals with aCDI may benefit from the combined administration of AVP and OT and, importantly, from a low-sodium diet. Moreover, increased OT levels are observed in Brattleboro rats (with mutated AVP gene), which may explain the regulatory hydromineral capacity shown by these animals after hydromineral challenges. In short, the symptoms shown by the different CDI animal models suggest the involvement of additional factors besides the absence of AVP, which appear to depend on the particular neurobiological systems affected in each case.

Keywords: central diabetes insipidus, hypophysectomy, neurohypophysectomy, pituitary stalk compression, mediobasal hypothalamic lesion, arginine vasopressin, oxytocin, hypernatremia, low-sodium diet

1. Introduction

The term diabetes refers to a wide variety of syndromes, including diabetes insipidus (DI), which share in common the copious production of urine (polyuria). DI is characterized by the

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excretion of abundant diluted, "tasteless" urine and was first described by Willis in the seventeenth century. The incidence of this disorder is around 1:25,000 cases, with no statistically significant differences between males and females.

In general, two main DI types can be distinguished: one that is related to deficient secretion of the antidiuretic hormone arginine vasopressin (AVP), which is better documented and referred to as central, neurogenic, neurohypophyseal, or hypothalamic DI, and another characterized by renal insensitivity to the antidiuretic effect of AVP, designated nephrogenic DI [1–5].

This chapter starts with a description of the general characteristics of central diabetes insipidus (CDI), including its symptoms, the brain systems involved, and the etiologies of acquired and hereditary CDI. We then review the main animal models of acquired (neurohypophysectomy, pituitary stalk compression (PSC), hypophysectomy, and hypothalamic mediobasal lesions) and hereditary (Brattleboro rats) CDI. Finally, data from animal and human studies are discussed in relation to the therapeutic usefulness of oxytocin and a low-sodium diet.

2. Central diabetes insipidus: an overview

2.1. General characteristics of human central diabetes insipidus

CDI is a neurobiological syndrome characterized by the excretion of copious amounts of diluted urine, i.e., containing a reduced concentration of electrolytes (mainly Na^+). The excretory response in CDI is associated with a rise in serum osmolality (hyperosmolality) and sodium concentration (hypernatremia) and with the intake of large amounts of water (polydipsia) (see **Table 1**) [2, 5, 6].

2.2. Neuroendocrine control of antidiuresis and electrolyte excretion

Urine and electrolyte excretions by the kidneys are related to the hormones AVP and oxytocin (OT), among other endocrine mechanisms [7, 8]. AVP and OT have similar chemical structures and are both nonapeptides, differing in amino acids at positions 3 and 8 (**Figure 1**). They are synthesized with their corresponding carriers, neurophysins I and II, respectively,

	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

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

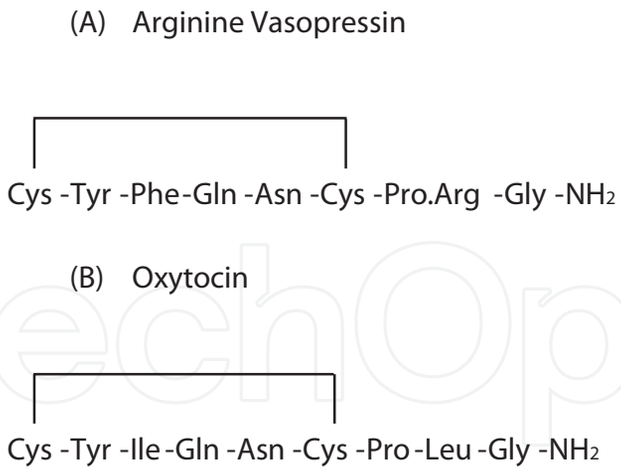

Figure 1. Chemical structure of (A) AVP and (B) OT. AVP is formed by amino acids cysteine-tyrosine-phenylalanine-glutamine-asparagine-cysteine-proline-arginine-glycine-NH_2 and OT by cysteine-tyrosine-isoleucine-glutamine-asparagine-cysteine-proline-leucine-glycine-NH_2. In both cases, a ring of amino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

and human genes for OT-neurophysin I and AVP-neurophysin II are both on chromosome 20, separated by only 12 kb of intergenic sequences [9].

Both hormones are synthesized in the perikarya of the magnocellular neurons of hypothalamic paraventricular (PVN) and supraoptic nuclei (SON). There is a predominance of AVP-producing cells in the SON, while oxytocinergic cells are confined to the rostral and dorsal nucleus region. For its part, the magnocellular PVN possesses a similar number of oxytocinergic and vasopressinergic neurons; its anteromedial portion contains mostly OT neurons, whereas its anterolateral portion contains an inner part with AVP neurons, surrounded by a ring of OT neurons. Less densely packed groups of AVP and OT neurons are found in posterior PVN. The axons of this complex (magnocellular PVN and SON) pass through the inner part of the median eminence, forming the neurohypophyseal stalk, and terminate in the neurohypophysis. Axonal swellings have been identified near fenestrated capillaries in both the median eminence and neurohypophysis, permitting access of these neurohormones to the bloodstream [10].

Hyperosmolality, hypernatremia, and hypovolemia (isotonic loss of fluid and electrolytes) are the main triggers of AVP and OT secretion [7, 11, 12]. After AVP is released into the blood, it acts by binding to AVP receptor 2 (AVPR2) on the basal surface of renal collecting tubule cells, triggering an intracellular signaling cascade. This concludes with activation of a cyclic adenosine monophosphate kinase pathway, increasing the production and insertion of aquaporin-II (AQP2) channels into the cell membrane. This in turn leads to passive water resorption from the lumen of the nephron into the cells of the collecting duct along an osmotic gradient [12–15]. The consequent excretion of concentrated urine is a survival mechanism for prolonged starvation periods. Conversely, diluted urine is excreted in the absence of AVP [8]. The neurohormone OT is especially involved in the excretion of body sodium or natriuresis [11, 16–20]. This secretion appears to be stimulated by increases in the glomerular filtration rate [21] and reductions in tubular sodium reabsorption [22]. These effects are mediated by actions on OT receptors present in the kidney and also, indirectly, by cardiac secretion of

atrial natriuretic peptide (ANP) [11]. OT may also act on AVPR2 to exert antidiuretic effects (**Figure 2**) [23, 24].

Both AVP and OT have been proposed to have synergic effects, with the natriuretic effect of their combined administration having a greater intensity and longer duration than the sum of the effects of each neurohormone [25, 26].

It has been reported that other hormones are involved in hydromineral regulatory processes, such as ANP co-localized with OT in hypothalamic magnocellular neurons (see Bundzikova et al. [27] for a review).

2.3. Etiological bases of human CDI

2.3.1. Acquired CDI

The most common CDI follows brain injury or surgery in the region of the pituitary and hypothalamus with damage to mediobasal hypothalamus (MBH), hypophyseal stalk, infundibulum, or the pituitary gland itself [28–32].

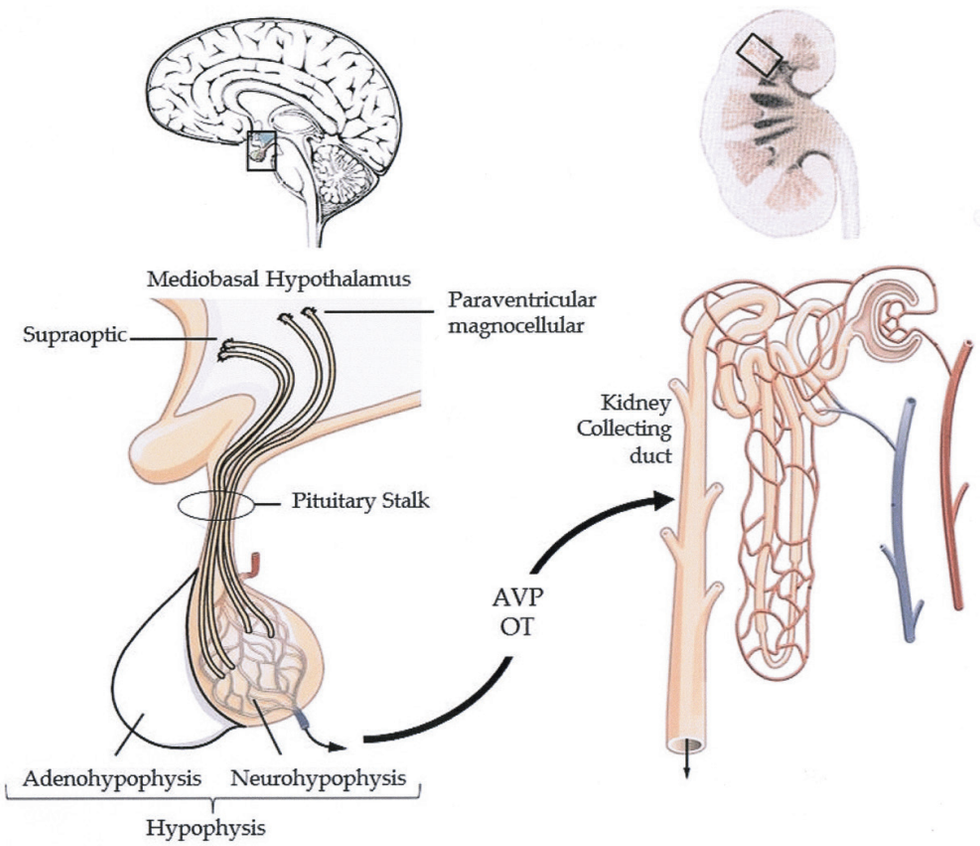

Figure 2. *Upper*: Sagittal section of the brain (*left*) and kidney (*right*). *Lower* (*magnified insets*): AVP and OT neurosecretory system (*left*) and simplified structure of a nephron (*right*).

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- to 5-day period [13, 30]. In permanent CDI, polyuric and polydipsic symptoms arise immediately and remain chronic in the absence of treatment [2, 33]. Triphasic CDI (**Figure 3**) was first described by Fisher and Ingram [35]. 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 a reduction in urine excretion volume and water intake, and a final persistent phase of polyuria and polydipsia [13, 28, 36].

The regulatory and behavioral symptoms of CDI may be explained by the arrangement of hypothalamic-neurohypophyseal fibers. In this way, CDI with only transient polydipsia may be produced by lesions located ventrally to the median eminence, possibly attributable to secretion into the median eminence area of the hormonal contents of magnocellular PVN and SON neurons. 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). Finally, the presence of intact/preserved axons or the release of AVP by degenerating terminals is considered responsible for the oliguric interphase in triphasic CDI [28, 37, 38].

2.3.2. Hereditary CDI

Hereditary CDI (hCDI) accounts for only 1–2% of all cases [5, 39]. It is frequently related to mutations in the AVP-neurophysin II gene, located distally at the short arm of chromosome 20 (20p13) and containing three exons. The signal peptide AVP and the NH_2-terminal region of

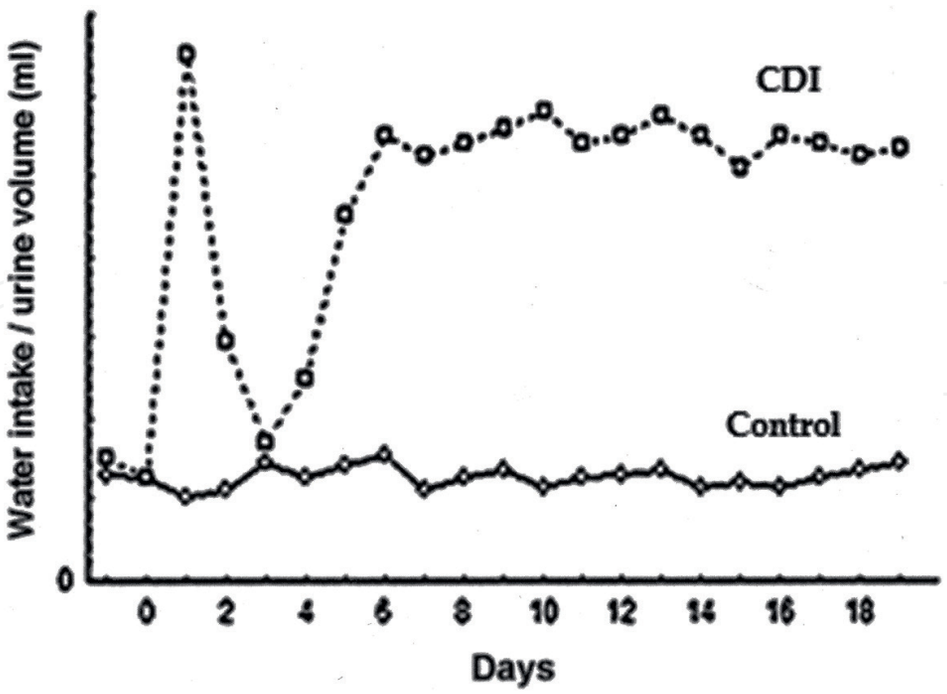

Figure 3. Water intake and urine volume in triphasic CDI (adapted from Ref. [34] with permission from Elsevier).

neurophysin II are encoded by exon A of the AVP-neurophysin II gene, and the central region of neurophysin II is encoded by exon B, while the COOH-terminal region of neurophysin II and glycopeptide are encoded by exon C.

More than 50 AVP mutations segregating with autosomal dominant or autosomal recessive CDI have been described (see http://omim.org/entry/125700). Limited capacity to secrete AVP during severe dehydration is maintained by patients with autosomal dominant CDI, whose polyuric-polydipsic symptoms generally appear after the age of 1 year, when adults are more likely to comprehend the child's requests for water. There have also been reports of three families with autosomal recessive neurohypophyseal DI in which the patients were homozygous or compound heterozygotes for AVP mutations. Two of these families were phenotypically characterized by severe polyuria, polydipsia, dehydration, and early onset in the first 3 months of life.

3. Animal models of CDI

3.1. Animal models of acquired CDI

Acquired CDI (aCDI) can be experimentally induced in animals by surgical interventions that produce a deficit in the secretion of both AVP and OT, including mediobasal hypothalamic (MBH) lesions, sectioning of hypothalamic-neurohypophyseal tract, pituitary stalk compression, hypophysectomy, and neurohypophysectomy (see Bernal et al. [34] for a review).

3.1.1. Neurohypophysectomy and pituitary stalk compression

After exposure of the pituitary gland through a parapharyngeal approach, a small incision is made in the caudal tip of the anterior lobe. This reveals the underlying posterior pituitary lobe, which is then removed by gentle suction. Given the technical difficulty of a specific neurohypophysectomy (neurohypox), selective deafferentation of the neurohypophysis has been induced by some authors (pituitary stalk compression). For this purpose, anesthetized rats are mounted on a stereotaxic frame with nose down 3.5 mm, the skull is opened by removing a small square of the bone, and a triangle-shaped wire is then lowered in coronal plane 4.0 mm caudal to bregma in the midline until it reached the skull floor. The wire is held against the skull for 30 s and then removed, evaluating the absence of tissue damage to the anterior pituitary lobe by microscopic examination and measurements of plasma levels of adenohypophyseal hormones in terminal blood samples.

Neurohypox and pituitary stalk compression (PSC) have been found to interrupt the secretion of AVP and OT, increase urine excretion and water intake, and reduce the excretion of sodium [40, 41]. In addition, salt loading (administration of hypertonic NaCl) increased serum osmolality to a greater degree in PSC animals than in sham-operated animals [42].

In earlier studies in neurohypox dogs, OT administration raised renal clearances [43] and AVP plus OT administration increased sodium excretion [44]. In a study of neurohypox rats, Balment and associates [40] found that AVP administration reduced urine flow and produced a small increase in sodium excretion. Importantly, however, OT administration within the physiological

range enhanced the natriuretic response to AVP, reversing the renal sodium excretion deficit in neurohypox rats. Moreover, the combined use of OT and AVP at low doses that do not separately promote significant body sodium excretion revealed a marked synergic natriuretic effect superior to the sum of their individual effects. Consequently, the reduced natriuretic capacity of neurohypox animals appears to be attributable to a lack of both AVP and OT.

3.1.2. Hypophysectomy

In anesthetized rats, the pituitary gland is exposed by parapharyngeal approach, and a dental drill is used to penetrate the base of the skull. The whole pituitary (anterior and posterior lobes) is then removed by suction.

Hypophysectomy (hypox) interrupts the hormonal secretion of both AVP and OT, depresses sodium excretion, and increases serum sodium concentration and water intake [45]. However, the peak sodium excretion of hypox animals treated with both neurohormones (AVP and OT) remains below that of intact rats, despite the synergic natriuretic effects of the combined treatment. Consequently, it has been proposed that the deficit produced in some adenohypophyseal hormones, such as prolactin (with antidiuretic effects in animals lacking AVP [46], may be relevant in this type of CDI.

Besides their hormone deficit, hypox animals often show marked disorders in their body sodium regulation. Thus, hypox rats consumed larger amounts of NaCl solutions than intact rats [47], an unexpected behavior considering that these animals are hypernatremic. However, hypox animals maintain an adequate hydromineral regulation capacity under homeostatic challenges. Thus, hypox animals significantly reduced their urinary sodium outputs on low-sodium diets [47], while hypertonic NaCl injection into the third ventricle stimulated their sodium excretion and antidiuresis [48, 49]. Given that these capacities could not have been activated by the secretion of AVP or OT, these and other data have been considered to demonstrate the functional integrity of the renin-angiotensin-aldosterone system in hypox rats [47].

3.1.3. Mediobasal hypothalamic (MBH) lesion

Anesthetized rats are mounted on a stereotaxic frame to bilaterally apply an anodic current (1.5 mA) for 15 s through a stainless steel electrode insulated except at the tip. In Wistar rats, stereotaxic coordinates are 6.44 mm anterior to interaural line, 0.4 mm lateral to midline, and 0.2 mm dorsal to interaural line; the extent of lesions is usually estimated by using the rat brain atlas of Paxinos and Watson [50]. Generally, all lesioned animals show extensive MBH lesions in the rostrocaudal dimension with complete damage of the median eminence region. However, partial injury of the arcuate (Arc), ventromedial (VM), and dorsomedial hypothalamic nuclei has also been observed in most rats (**Figure 4**) [51–53].

MBH lesions in animals generate hypernatremia with triphasic polyuric and polydipsic CDI. A distinctive characteristic of MBH-lesioned animals is hyperphagia [51–53], which is not observed in hypox rats [54]. This greater food intake is likely attributable to damage to the Arc and/or VM hypothalamic nuclei [55]. From a neuroendocrine perspective, MBH lesions interrupt AVP, OT, and ANP secretions [49, 56, 57].

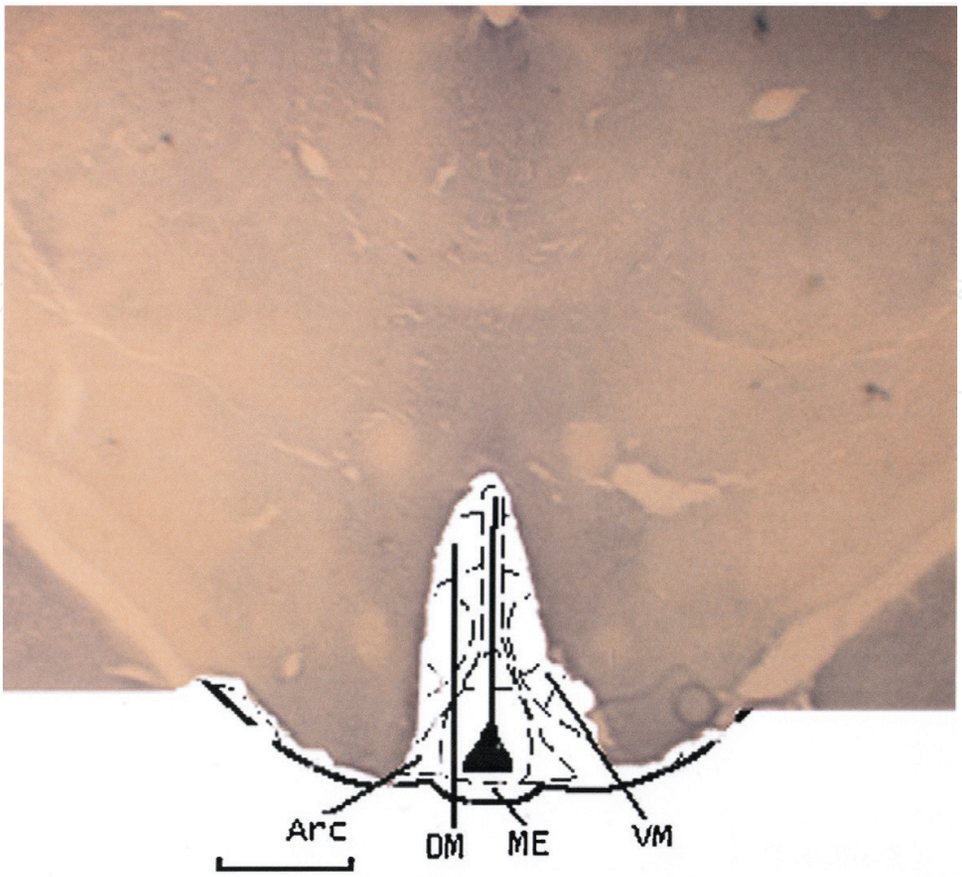

Figure 4. Photomicrograph of coronal brain section of an MBH-lesioned animal stained with cresyl violet at approximately −2.56 mm caudal to bregma. Scale bar, 1 mm (Arc, arcuate nucleus; DM, dorsomedial nucleus; ME, median eminence; VM, ventromedial nucleus) (from Ref. [51] with permission from Elsevier).

Systemic OT administration was found to enhance sodium excretion and reduce urine excretion and the standard polydipsic response of MBH-lesioned animals. However, concomitant food deprivation is necessary to show this effect, and OT-treated MBH animals with food available ad libitum showed no reduction in water intake or urine excretion. Likewise, the effects of OT were only observed when it was administered during the initial diabetic phase, not during the stable phase [51].

Hence, the regulatory capacity of MBH-lesioned animals is closely related to food availability. Specifically, it has been observed that food deprivation generates a transient reduction in water intake of MBH-lesioned animals during the initial DI phase but completely annuls their polyuria and polydipsia during the stable DI phase [51, 52]. According to these results, MBH-lesioned animals appear to retain some antidiuretic capacity, at least under food deprivation conditions. Furthermore, food deprivation on days 20–22 postsurgery was found to produce a lasting reduction in the hyperphagia (besides polydipsia) of MBH animals during the days that followed, when food was available ad libitum. This suggests that the magnitude of the polydipsic response observed after the food deprivation period may be related to the amount of food consumed. This dependence on food intake is in agreement with earlier studies suggesting that the severity of the polydipsia and polyuria of DI is approximately proportional to the amount of sodium ingested in food [58–60].

Given that nephrectomy, which prevents water loss, does not eliminate the polydipsic response of MBH-lesioned animals [61], it seems likely that this response is not exclusively a secondary effect of renal fluid loss. Thus, studies of hydromineral regulation in our laboratory have confirmed that OT administration and food deprivation can reduce water intake without a significant decrease in urine volume [62]. The possible importance of body sodium regulation disorders in the polydipsic behavior of these diabetic animals is supported by findings that low-sodium diets reduce the serum sodium concentration and water intake of MBH-lesioned animals [53] and that OT administration reduces the serum sodium concentration and water intake of food-deprived MBH-lesioned animals [51].

Unlike in hypox animals [48, 49], salt loading did not increase the natriuretic and antidiuretic responses of MBH-lesioned animals [49], suggesting an interruption of neuroendocrine pathways and of autonomous nervous system activity [63–65]. Nevertheless, when MBH-lesioned animals could choose between a hypertonic NaCl solution and water, they preferentially selected the saline solution [52]. These results are consistent with suggestions by other authors that lesions in the median eminence region might affect brain circuits that control body sodium levels [66].

In summary, it appears to be well established that food deprivation reduces body sodium accumulation and consequently the diabetic polydipsia of this animal model. Thus, the combination of the natriuretic effect of OT and the food deprivation may have a normalizing effect on the hypernatremia of MBH animals.

3.2. Animal model of hereditary CDI: the Brattleboro rat

The standard model of hereditary CDI is the homozygous Brattleboro rat, first reported by the Valtin group in the 1960s [67]. This strain was developed from Long-Evans hooded rats, which are unable to synthesize antidiuretic hormone as an autosomal recessive trait of the AVP-neurophysin II gene. The mutated allele encodes a normal AVP but an abnormal neurophysin II, which interferes with the regular transport and processing of the AVP-neurophysin II precursor molecule [39]. Homozygous Brattleboro rats, as would be expected, exhibit polyuric and polydipsic responses as well as chronic hypernatremia and hyperosmolality. However, AVPR2 is preserved in Brattleboro rats, which are therefore reactive to AVPR2 agonists [68].

Nephrectomy, which prevents renal water loss, was found to block the polydipsic response of Brattleboro rats after hypertonic NaCl administration, evidencing the primary character of polyuria in these animals [69], in contrast to the aforementioned observations in nephrectomized MBH-lesioned animals [61]. Thus, it has been observed that Brattleboro rats compensate for the excretion of excessive diluted urine by consuming large amounts of water [69] and reducing their consumption of salty solutions [70], in contrast to hypox and MBH-lesioned animals [47, 52].

However, various hydromineral challenges have been found to modify the renal regulatory capacity and hydromineral behavior of Brattleboro rats. Thus, Wilke and associates [71] reported reductions in urine volume and increases in urine osmolality and AQP2 channels after food deprivation or restriction, whereas Wideman and Murphy [72] observed a drastic fall in the water intake of Brattleboro animals. Conversely, hypertonic NaCl administration

was found to markedly increase their urinary osmolality [73–75], natriuresis [57, 73, 74], and water intake [69]. These preserved regulatory capacities of Brattleboro rats have been related to the presence of increased OT plasma levels [27, 40, 45, 73, 74, 76, 77], in contrast to the AVP and OT deficit of neurohypox, hypox, and MBH-lesioned animals [40, 41, 45, 49, 57].

The OT-induced antidiuretic effect in Brattleboro rats was blocked by treatment with AVPR2 antagonist [23, 78–81] but not by OT receptor antagonist [80], suggesting that OT may act on AVPR2 of Brattleboro rats to activate the antidiuretic response [23, 24, 82]. However, OT does not appear to be the only hormone involved in the antidiuretic effects observed in Brattleboro rats. Morrissey et al. [46] reported that prolactin, an adenohypophyseal hormone that contributes to neurohormone secretion regulation [83], reduced urinary excretion volume in Brattleboro but not control rats.

OT also appears to be critical for the natriuretic capacity of Brattleboro rats. Thus, the suppression of OT secretion by neurohypox greatly diminished sodium excretion rates in Brattleboro rats; moreover, OT administration produced a substantial and sustained natriuresis in the neurohypophysectomized animals [74].

Besides increasing the antidiuretic and natriuretic capacity of Brattleboro rats, OT increases their urine osmolality, AQP2, glomerular filtration rate, and effective filtration fraction [21, 23, 74, 78–81, 84].

Other animal models have been developed in later studies. Thus, it has been found that mutations in the AQP2 gene that interfere with its cellular processing can produce autosomal recessive nephrogenic diabetes insipidus [85]. In addition, the transgenic rat TGR(ASrAOGEN)680, characterized by a transgene-producing antisense RNA against angiotensinogen in the brain and a reduced blood pressure [86], exhibits mild CDI due to a 35% reduction in plasma AVP and, unlike observations in Brattleboro rats, normal plasma sodium and osmolality [87]. With regard to the renin-angiotensin system, low-renin hypertensive animal models (e.g., transgenic TGR(mREN2)27 rat carrying the murine Ren-2 gene) have also proven useful [88].

4. OT and low-sodium diets as complementary treatments of CDI

At the beginning of the twentieth century, patients and animals with CDI were successfully treated with pituitary extracts (which supposedly contained both AVP and OT) (see Qureshi et al. [89] for a review). However, the observation of another oxytocic effect associated with those treatments (stimulation of uterine muscle contraction) reduced the use of pituitary extracts and of OT itself. These data, alongside the discovery of Brattleboro rats, which apparently developed all DI symptoms, including blockage by nephrectomy, focused interest on a vasopressinergic approach to CDI [90]. Thus, it was considered that AVP deficit would be solely responsible for the excretion of large volumes of diluted urine (hypotonic polyuria) and would secondarily increase serum osmolality (hyperosmolality), serum sodium concentration (hypernatremia), and water intake (polydipsia). For this reason, the first-choice treatment for CDI patients is 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 hormone itself.

However, many studies reviewed in this chapter appear to suggest that other hormonal components besides AVP secretion are also interrupted, including OT in acquired CDI (the most frequent form). In this line, more recent studies [91] compared the effects of OT and desmopressin administration in CDI patients, finding that both treatments had positive effects on urine flow reduction, serum sodium concentration, and osmolality, and increased urine osmolality and urinary AQP2 excretion. Other authors also reported that the administration of minute amounts of pituitrin (containing AVP and OT) appears to control and improve fluid status with minimal adverse reactions [31]. This possible therapeutic option is consistent with the synergic natriuretic effect of low doses of OT and AVP observed in CDI animal models [40, 45]. It therefore seems plausible that the combined administration in humans of low-dose AVP and OT would enhance their effects while minimizing oxytocic side effects. Hence, besides its natriuretic and antidiuretic effects [24], OT administration in patients with CDI may exert a valuable hyponatremic effect [82].

In cases in which relatively large brain lesions are responsible for CDI (MBH model), the polydipsic response cannot be understood exclusively as a secondary effect of fluid excretion, because it continues to be observed in animals whose polyuria is interrupted by nephrectomy [61]. One of the factors that may explain this hyperdipsic response is diabetic hypernatremia, which would also not be solely a consequence of hypotonic excretion, in agreement with reports that lesions in the median eminence region may affect brain circuits that control body sodium levels [66].

Some more recent animal studies have suggested that food deprivation or a low-sodium diet may be potentially useful in CDI patients, always in combination with their habitual pharmacological treatment. In fact, low-sodium diets are frequently prescribed for patients with AVP-resistant or nephrogenic DI [5, 92]. These data also agree with classic studies that have indicated a relationship between diabetic polydipsia and dietary sodium. Thus, substances that increase body sodium levels were reported to exacerbate polydipsia [35, 59, 93], and, conversely, water intake was reduced in animals that were food deprived [59, 89] or on a low-sodium diet [59].

5. Concluding remarks

In summary, although Brattleboro rats are considered as the prototype model of CDI, the hydromineral characteristics of these animals do not seem to be fully comparable with an acquired CDI animal model. Thus, there is an AVP secretion deficit in Brattleboro rats, but OT remains available, whereas the CDI resulting from brain damage blocks the secretion of both hormones. Moreover, the symptoms and characteristics of humans and animals with aCDI indicate the involvement of other factors besides the habitual lack of AVP, which appear to be related to the neurobiological systems affected in each animal model. For instance, natriuresis and antidiuresis are increased after salt loading in hypox animals [48, 49] but not in MBH-lesioned animals [49] or humans with CDI [2].

Individualized therapies that take into account of the specific neurobiological system involved in each type of CDI are evidently desirable to improve the quality of life of these patients.

However, according to the research data reviewed in this chapter, all CDI patients might benefit from a low-sodium diet and from OT administration or, possibly, the combination of low doses of AVP and OT.

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Author details

Antonio Bernal*†, Javier Mahía† and Amadeo Puerto

*Address all correspondence to: antoniobernal@ugr.es

Department of Psychobiology and Mind, Brain and Behavior Research Center (CIMCYC), University of Granada, Spain

† These two authors contributed equally to the manuscript

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