Journal of Diabetes and Metabolism
ISSN: 2155-6156
Shapiro and Weiss, J Diabetes Metab 2012, S6
DOI: 10.4172/2155-6156.S6-009
Review Article
Open Access

Diabetes Insipidus: A Review

Moshe Shapiro and Jeffrey P. Weiss*

Department of Urology, SUNY Downstate College of Medicine, USA

Introduction

Inappropriate secretion or action of serum antidiuretic hormone (ADH) is termed Diabetes Insipidus (DI), characterized by polyuria (defined as 24 hour urine output in excess of 40 ml/kg) and polydipsia [1]. As opposed to Diabetes Mellitus, where the urine is hypertonic and sweet (mellitus means honey in Greek), DI is defined as having urine that is hypotonic and bland, in the setting of polyuria. There are various mechanisms of pathogenesis of DI, all leading to the same clinical manifestation. In cases where the disorder is due to inadequate secretion of ADH, the disorder is termed Central DI, whereas when the disease is a result of renal insensitivity to ADH, the disease is termed Nephrogenic DI [1]. In cases where polyuria is due to vast amounts of ingested fluids driven primarily by behavioral or thirst disorders, it is called Primary Polydipsia (PP). Pregnant women can metabolize ADH in an accelerated manner leading to Gestational DI [2]. Overall, there are 3 cases of DI per 100,000 in the general population [3]. With regard to some familial forms of nephrogenic DI, incidence varies and some regions with common ancestry have higher incidence than other in the general population [4].

ADH, also known as arginine vasopressin (AVP), is produced in the hypothalamic nuclei. It is a highly evolutionarily conserved nonapeptide, with a 6 amino acid ring and a 3 amino acid tail with L-arginine in the 8th position. Oxytocin is also produced in the hypothalamic nuclei, with a structure similar to ADH, but with leucine in the 8th position. Both ADH and oxytocin are produced in the magnocellular neurosecretory cells (MNC) of the hypothalamus, mainly in the supraoptic (SON) and paraventricular (PVN) nuclei. While each MNC was initially thought to produce either ADH or oxytocin alone, more recent evidence indicates that there can be some overlap of production [5]. ADH is created as a composite precursor molecule composed of ADH, neurophysin-II (NPII), which is ADH's carrier protein, and copeptin- a glycopeptides [5,6]. Both NPII and ADH are produced from the same precursor mRNA. After passage through the golgi apparatus the prepropeptide complex is packaged into large dense core vesicles (LDCV) which exit from the trans golgi network. Inside the LDCV enzymatic processing of the precursor molecules takes place. This is facilitated by the LDCV's mildly acidic (pH 5-6) internal environment. Additionally the acidic environment keeps the fully processed ADH nonapeptide bound to the NPII. After their production, the LDCVs are transported in an anterograde fashion, down the neuronal axon along microtubules at a rate near 140 mm/day. LDCV's containing ADH is stored in the nerve terminals of the posterior pituitary, awaiting neurosecretion. When an action potential causes an influx of Ca^{2+}, the LDCVs fuse to the nerve terminal, releasing their contents via exocytosis. At normal plasma pH, NPII dissociates from ADH [7]. The LDCVs are then recovered via endocytosis and undergo retrograde transport to the cell body, where they are either reused, or degraded by lysosomes [5]. MNC's have an intrinsic capability to detect hyperosmolality [8,9]. Experimental studies have shown that this is a mechanically mediated capability. This is demonstrated by mechanical cell volume reduction of isolated MNCs *in vitro*, leading to increased depolarization of the cells [9,10]. This response to mechanical stretch is mediated via channels called transient receptor potential vanilloid 1 (TRPV1) channels. These TRPV1 channels, in response to MNC shrinkage due to hyperosmolality, allow activation of a cation current (Ca^{2+} and nonspecific monovalent cations), leading to increased action potential firing, resulting in ADH release [8-10]. Actin filaments are also required for the regulation of the TRPV1 channel activity, though the exact function is unknown [8,11,12]. Regulation of ADH secretion is both pre and post transcriptional. Pre transcriptionally, hyperosmolal conditions lead to ADH mRNA transcription, increased ADH mRNA quantity, with following ADH secretion [5]. Chronic osmotic stimulation leads to increased co expression of oxcytocin and ADH in MNC's [5]. When hyposmolal conditions prevail however, ADH secretion and transcription shut down. This is thought to be via a negative feedback under steroid control. During hyposmolal conditions, ADH secreting MNC's express a glucocorticoid receptor which has experimentally indicated that ADH release is suppressed under the influence of glucocorticoids. Post-transcriptionally there are two means of gene control. First, under hyperosmotic conditions there is an increase in the length of the poly (A) tail of the ADH mRNA transcripts, probably increasing the life of the mRNA. The means by which the polyadenylation is regulated is unclear, however poly(A) length and mRNA abundance are not linked, and thus are separately regulated. *In vitro* studies have shown that different stimuli can increase the poly(A) tail length without increasing mRNA abundance and vice versa. The second means of post-transcriptional regulation of the ADH gene product is through axonal transport. During hyperosmolal states, ADH mRNA has been detected in the neurohypophysis. Interestingly, the mRNA found in the neurohypophysis has regular length poly(A) tails. This has led to disagreement about the origin of the neurohypophyseal mRNA. One theory about the origin of the mRNA is that it is transported down the axon, originating in the cell body. This theory itself leads to 2 possibilities regarding the purpose of this transport. 1. ADH mRNA acts as a signaling molecule, carrying a message up and down the axons and possibly even beyond. 2. mRNA transport is actually a waste disposal mechanism, disposing of the older, shorter poly(A) mRNAs away from the perikaryon, leaving fresher, more efficient mRNAs in their stead. The second theory regarding the origin of the neurohypophyseal ADH mRNA, is local synthesis. This is hypothesized because of the finding of ADH mRNA in a subset of pituicytes. If this is the case it would explain why the poly(A) tail are

Corresponding author: Jeffrey P. Weiss, MD, FACS, Department of Urology, SUNY Downstate College of Medicine, 450 Clarkson Avenue, Box 79, Brooklyn, NY, 11203, USA, Fax: 212-838-3213; E-mail: urojock@aol.com

Received December 04, 2011; **Accepted** January 21, 2012; **Published** January 25, 2012

Citation: Shapiro M, Weiss JP (2012) Diabetes Insipidus: A Review. J Diabetes Metab S6: 009. doi:10.4172/2155-6156.S6-009

of a different length than the ADH mRNA poly(A) tails found in the cell body.

ADH acts on V_2 receptors in the kidney leading to increased water retention. This will be addressed in detail in later paragraphs. In addition to its effect on the kidneys, ADH acts on receptors found throughout the body called V_1 receptors, also known as V_{1a} receptors. The V_1 receptor, when activated by ADH activates a $G_{q/11}$ protein, leading to stimulation of phospholipases C, D, and A_2 and ultimately to increased intracellular [Ca^{2+}]. The V_1 receptor is found in the brain, liver, and smooth muscle of blood vessels. In smooth muscle, the increased [Ca^{2+}] leads to vasoconstriction, hence the alternate name of Vasopressin. V_{1b} or V_3 receptors are found in multiple tissues including the brain, thymus, heart, lung, spleen, uterus breasts, and anterior pituitary corticotroph cells. The V_3 receptor, when activated also acts via phospholipase stimulation, leading to increased intracellular Ca^{2+} concentrations. V_2 receptors can also cause vascular endothelial cell secretion of von Willebrand factor and factor VIII, at concentrations far above those necessary to induce changes at the level of the nephron [13].

Blood pressure and intravascular volume stimulation of ADH release are controlled by baroreceptors in the carotid sinus and the aortic arch. These receptors send afferent signals through cranial nerves IX and X to the brainstems' nucleus of the solitary tract. From the solitary nucleus, inhibitory signals are sent to the magnocellular neurons of the hypothalamic nuclei. Only in instances of extreme hypovolemia do baroreceptors increase ADH secretion, allowing for principally osmotic control of ADH secretion [5,14]. In cases of both severe hypovolemia and hyponatremia, the usual inhibition of ADH by osmoreceptors is overridden by the baroreceptor input and ADH is released despite the hyponatremia [14].

ADH's role in osmolality control is exerted though its influence on the kidney. ADH causes the kidney to reabsorb water in the collecting ducts and connecting tubules, and decreases plasma osmolality. In the principal cells of the collecting ducts, there are AVP V_2 receptors on the basolateral membrane. When AVP/ADH binds to the AVPR2 receptor, a signal cascade is initiated [1]. The AVPR2 receptor is linked to a G_s protein which activates adenylyl cyclase, raising cAMP levels. Increased cAMP stimulates protein kinase A (PKA) to phosphorylate vesicles containing aquaporin-2. This phosphorylation allows for transport of the vesicle to the apical surface of the cell. These vesicles then insert into the membrane and allow for water's passage from urine into the tubular cell and thence back into the blood through aquaporins (3 and 4) fixed in the cell membrane. This phosphorylation of vesicles is limited by phosphodiesterases. When AVP is not present, AQP-2 channels are retrieved via endocytosis. In the basolateral membrane of the cell, AQP-3 and AQP-4 channels allow for waters' passage though the cell and into circulation [15-17]. Aquaporins are a family of water channels. Aquaporins 1, 3 and 4 are all expressed without any hormonal regulation, whereas AQP-2 is expressed in response to ADH. AQP-1, the first aquaporin to be discovered, is widely expressed not just in the kidneys, but also in red blood cells and in cellular vesicles and vacuoles. Its main function in the kidney is passive water reabsorbtion in the thin descending limb of the loop of Henle and proximal tubule, and is a major component of the countercurrent multiplier [18]. Prostoglandins also play a role. Centrally, PGE-2 infusion causes increased ADH secretion [19,20]. In the kidneys though, prostaglandin's role is somewhat unclear. There is evidence showing that prostaglandin E_2 activates a G_i protein, which prevents cAMP accumulation (the reverse of the action on cAMP occasioned by G_s protein), decreasing AQP-2 insertion into the apical membrane and promoting dieresis [21,22]. This is a potential mechanism by which prostaglandin inhibitors such as nonsteroidal anti-inflammatory agents may cause fluid retention. Recent studies done in Madin-Darby canine kidney cells show that AQP-2 phosphorylation and apical insertion are increased by prostaglandin EP2 and EP4 receptors activation [23]. It has also been shown in rats that butaprost, a EP2 agonist can increase urinary concentration in rats with the V2R blocked. Further research is required to determine the exact nature of the role of prostaglandins in water balance.

Osmolal Regulation

ADH secretion is largely determined by plasma osmolality. Further, blood pressure (BP) and intravascular volume (IVV) can also influence secretion of ADH. However, the changes in BP and IVV need to decrease by 10-20% for ADH secretion to be affected, whereas ADH secretion is affected by osmolality changes of 1-2%; hence, osmolality as a stimulus for ADH secretion is 10-fold more effective than either BP or IVV. When plasma osmolality increases, there are two responses - an increase in ADH secretion and stimulation of thirst. Some studies have claimed that in healthy individuals, the ADH-osmolality system is sensitive enough to allow incidental fluid ingestion to be adequate to conserve euosmolality, without physiological "thirst" playing a role [24]. However others experiments have shown that the threshold for both thirst and ADH secretion are near the same [25]. These differences can be explained by inter-individual genetic variability among people [26]. In instances where ADH secretion is maximal and fluid intake does not suffice to maintain plasma osmolality, physiological thirst kicks in at the higher levels of plasma osmolality. Hence depending on the individual, thirst and ADH secretion have varying thresholds, where thirst acts as a backup to ADH osmolality control, with ADH having a 1-2% change in osmolality sensitivity while thirst only becomes apparent after a 2-3% change in osmolality. In fact, even without thirst in the normal individual, fluid is usually consumed in excess, allowing ADH alone to determine plasma osmolality. Osmolality induced ADH secretion is centrally controlled by signaling from the organum vasculosum of the lamina terminalis (OVLT), via glutaminergic and GABAergic afferents to the MNCs of the SON and PVN [5,27]. The OVLT is a circumventricular organ of the brain, outside of the blood-brain-barrier (BBB) which contains neurons capable of detecting osmolality [5,9,19]. While the MNCs are intrinsically osmosensitive, the OVLT, positioned outside the BBB can sense osmolites such as urea and mannitol, that do not penetrate the BBB [9,28,29]. Additionally the OVLT integrates signals from various hormones including angiotensin II, relaxin, and atrial natriuretic peptide. These signals influence OVLT to act on the MNCs in either an inhibitory or excitatory fashion, in addition to the OVLT's osmosensing regulation. Similar to MNC osmosensing, the neurons of the OVLT are mechanically regulated, with hypertonic cell shrinkage leading to increased firing [30]. This osmomechanical regulation is mediated via TRPV1 channels which are non selective cation channels. The TRPV channels are mechanically activated due to cell shrinkage [30]. Other influences on ADH secretion include sleep cycle, and thermal regulation. Normally during sleep, ADH secretion rises, to prevent water loss at a time when water not accessible. This is due to the suprachiasmatic nucleus' (SCN) influence on the MNCs. During waking hours, the SCN sends inhibitory signals

to the MNCs of the SON and PVN, blunting their response to changes in osmolality. However during late phase sleep these inhibitory signals decrease, leading to heightened MNC sensitivity to changes in osmolality, and hence increased MNC firing and ADH secretion. ADH has been implicated as a contributing inhibitory signaler, released from the SCN to act at the MNCs. Thermal regulation also seems to play a part in ADH release. When core body temperature rises by even 1degree Celsius, due to non febrile causes, ADH secretion is boosted. This increase in ADH output is anticipatory of future water losses due to panting, sweating and the like, and occurs before any changes in osmolality occur. This thermally regulated ADH output is also assumed to be mediated via a heat sensitive variant of the TRPV1 channel [30].

Osmolality is also is detected and influenced peripherally [31,32]. Signals from oropharynx, small intestine and liver all contribute to osmostasis [31,32]. In the liver, in contrast to central osmosensing, signaling is stimulated by hyposmolality, as opposed to the hyperosmolal stimulated increase in neuron firing found in the OVLT and MNCs. This is mediated by the osmosensitive TRPV4 channels which are activated hyposmotically, increasing cell electrical activity under hypotonic conditions. These signals are transmitted to the thoracic dorsal root ganglia and possibly the nodose ganglia and are then carried further to the nucleus of the solitary tract of the brain to modulate osmostasis. It has also been demonstrated in humans that ADH secretion is suppressed by non osmotic influences such as oropharyngeal stimulation caused by drinking. In rats distension of the stomach, and [Na^+] in the small intestine also influence [ADH], anticipatory of imminent osmolal change [32].

Destruction of the osmosensitive areas in humans, leads to the inability to secrete ADH in response to increased osmolality as well as absent thirst mechanisms. However, in cases where only the magnocellular neurons that produce ADH are damaged, patients do not secrete ADH appropriately in response to dehydration, but still have intact thirst mechanisms. While amongst different people the plasma osmolality ranges from 280-295 mOsm/kg, in any one individual, the osmolality is very tightly controlled, with changes of even 1% osmolality causing immediate adjustment of the rate of ADH secretion from the posterior pituitary [33]. The relationship between plasma osmolality and ADH concentration is linear, even beyond normal physiological levels of osmolality, such as that seen with hypertonic saline infusion or with the dehydration of patients with nephrogenic diabetes insipidus (NDI) [33]. There is a linear relationship between ADH concentration and urine osmolality as well. However, urine osmolality plateaus once it reaches maximum concentration regardless of ADH levels, which can be elevated far beyond what is needed to maximally concentrate the urine. Normally BP and IVV are controlled by the renin–angiotensin-aldosterone system. While arterial baroreceptors which are located in the walls of the aortic arch and carotid sinuses also influence ADH secretion, a much greater deviation from baseline is needed for this to occur. To re-emphasize, a 1% deviation from plasma osmolality alters the rate of ADH secretion, while a deviation of 10-15% of BP or IVV is needed to change the rate of ADH secretion [14,33]. Angiotensin II (Ang II) has been shown to increase the osmosensory neuron's sensitivity to changes in osmolality. Meaning, under Ang II's influence osmosensory neurons will have a greater response per increase in osmolality than the same osmotic stimulus without Ang II present. This effect is due to Ang II increasing the mechanosensitivity in the osmosensory neurons. When Ang II signals an osmosensitive neuron, protein kinase C is activated via $G_{q/11}$ protein activation of phospholipase C, which hydrolyzes PIP_2 into inositol triphosphate and diacylglycerol [34]. Protein kinase C is then activated by diacylglycerol. This ultimately leads to increased F-actin density. As mentioned above, actin plays a definite, yet as of now an unclearly defined role, in osmosensitive response to hyperosmotic stimuli [11,34].

Central Diabetes Insipidus (CDI)

Inadequate secretion of ADH leading to polyuria and secondary polydipsia is termed CDI. The dose response curve of ADH is sigmoidal in nature and is due to the kidneys inability to concentrate urine much beyond 1200mOsm/kg on one end of the curve, and the high sensitivity of the kidney to low concentrations of ADH on the other [35,36]. Therefore under dehydrated conditions the posterior pituitary is able to secrete more ADH than can effectively increase urine osmolality. Hence, a large decrease (80-90%) in ADH output is necessary for symptomatic polyuria to occur. Once this decrease takes place, urine osmolality drops to below 300 mOsm/kg, and polyuria becomes clinically evident, with urine production rising above 50ml/kg BW/day [37]. As the patient increases his or her urine output, plasma osmolality rises until the thirst threshold is reached. At this threshold, plasma osmolality is higher than normal and is maintained at the thirst threshold. ADH deficiency does not need to be complete for CDI to occur, only that the maximal ADH plasma level at the thirst threshold is insufficient to concentrate urine [38]. Symptomatically, though, the onset is abrupt once the threshold is reached. On MRI imaging in a normal person, the posterior pituitary has a high intensity T1-weighted signal, appearing as a bright spot in the sella turcica, best seen in sagittal views [3,39]. This bright spot represents stored ADH [40]. The absence of a bright spot is not necessarily diagnostic of CDI, since, in many cases, patients with NDI are lacking a bright spot as well. However, the presence of a bright spot on MRI can rule out CDI with 95% sensitivity [40]. In the few cases of CDI with a bright spot present, it is thought that this spot is due to oxytocin stored rather than ADH [41]. MRI is also useful in detecting infundibular thickening. When infundibular stalk thickening is detected, in the absence of a pituitary bright spot, there are a number of disorders that should be considered in the differential diagnosis: granulomatous disease, craniopharyngioma, metastases to the hypothalamus, TB and, rarely, lymphocytic infiltration of the infundibulum of the posterior pituitary. Hence when DI is present along with infundibular stalk thickening and an absent bright spot, it is necessary to rule out a systemic cause for DI [41].

There is a wide range of lesions, as well as inherited defects, which can cause CDI. Despite this, in the majority of cases, such diseases present without CDI [42]. In adults, CDI is mainly caused by primary brain tumors, head trauma or is of autoimmune/idiopathic/familial origin. In children, however, a larger percent of CDI (50%, as opposed to 30% in adults) is due to brain tumors (or their treatment), with 29-54% resulting from familial/idiopathic/autoimmune causes [3,43,44]. Histocytosis X is a significant cause of CDI in children (16%), however it is not a significant cause of new onset cases in adults [3]. Children are also more likely to have an infectious etiology than adults. Granulomatosis, sarcoidosis, alcohol, phenytoin and clonidine cause 5% of adult cases, as opposed to essentially none in children [3].

Familial CDI is usually of autosomal dominant (AD) inheritance. It is caused by mutations of prepro-AVP_2, also known as vasopressin-neurophysin II. Onset occurs in children older than one year of

age and develops as late as young adulthood [43,45,46]. There are over 40 known mutations of this gene. Most of the mutations are in the neurophysin portion of the prepro-$AVP_{2,}$ leading to impaired trafficking and formation of disulfide bonds [3,47]. In the autosomal dominant form, there is still one normal copy of the gene producing ADH. However, with time, the accumulation of the misfolded proteins in the magnocellular neuron becomes toxic, leading to neural demise and CDI. However, magnocellular neurons need not die for CDI to occur. Rather, in some cases, due to the buildup and entrapment of the misfolded proteins, normal selective degradation of proteins can be overwhelmed. In its place, a non-selective degradation takes place, destroying both ADH proper and misfolded protein alike [48,49]. Autosomal recessive (AR) CDI is caused by a missense mutation, changing the position-7 proline to leucine. This creates a mutated product that has 30 times less binding activity of normal ADH [50,51]. Alternatively, autosomal recessive CDI can also be part of a constellation of disorders known as Wolfram syndrome. Wolfram syndrome or DIDMOAD (diabetes insipidus diabetes mellitus optic atrophy and deafness) is an autosomal recessive disorder caused by mutation of the WFS1 gene. The WFS1 gene encodes for a transmembrane protein localized in the endoplasmic reticulum(ER) [52]. The WFS1 protein has been shown to play a key role in mouse pancreas beta cell response to stimulus, with eventual loss of beta cell mass, likely due to ER stress [53]. It is very possible that the CDI component of Wolfram syndrome is from impaired ER functioning that can either lead to ER stress and eventual cell neuronal death, or cause impaired response of the MNC's to stimulus, or both. Both these forms of autosomal recessive CDI are rarer than the AD form. The AR form presents earlier than the AD type, usually within in the first year of life. CDI in Wolfram syndrome usually appears in the mid adolescent years [54]. Other etiologies of CDI are due to interruptions of secretion and/or destruction of the posterior pituitary and hypothalamic nuclei. Granulomatous disease, post-infectious processes, trauma, neoplasms, drugs (ethanol, phenytoin and others) and vascular injury all can disrupt ADH secretion, leading to CDI. Idiopathic CDI, which constitutes a sizable percentage of CDI, is now thought to be of autoimmune origin [43,44,55]. In some patients with CDI, a lymphocytic infiltration of the posterior pituitary has been suspected, and then confirmed by autopsy. The manner of infiltration was similar to previously documented anterior pituitary lymphocytic infiltration. As alluded to above, MRI can now help diagnose lymphocytic infundibuloneurohypophysitis through detection of a thickened stalk, or through enlargement of the posterior pituitary [56]. In some cases, both hypophysitis and infundibuloneurohypophysitis can coexist and present simultaneously. Additionally, evidence for an autoimmune origin of CDI is that in as many as 1/3 of patients with idiopathic CDI and 2/3 of patients with Langerhans histiocytosis, anti-ADH antibodies are detected, while patients with CDI caused by tumors have no anti-ADH antibodies. Further, patients with detected anti-ADH antibodies but no symptoms of CDI were either found to have partial CDI or had a high likelihood of developing CDI in the future: 3 of 5 such patients followed for 4 years developed CDI [56].

In patients with osmoreceptor dysfunction, a state similar to CDI can be present without polydipsia, and instead presents with severe dehydration and hypernatremia due to lack of thirst and decreased water intake [57,58]. Thirst is both regulated directly via the osmoreceptor mechanism discussed above, as well as a result of angiotensin II's effect on the thirst center [59]. Many of the same etiologies of CDI can cause osmoreceptor dysfunction, but these lesions are located more anteriorly in the hypothalamus. One cause of osmoreceptor dysfunction is anterior communicating cerebral artery aneurism repair, causing infarction of the osmoreceptor cells [60]. Regardless of the cause of the damage, when these cells are injured, there is a lack of thirst and usually, inadequate ADH secretion stimulated by hyperosmolality. With osmoreceptor dysfunction, absent thirst leads to moderate hyperosmolality, typically ranging from 300-340 mOsm/kg H_2O. Even in normal humans there appears to be a somewhat blunted thirst response in relation to levels of dehydration. This leads to the eventual elevated secretion of angiotensin II and has been implicated as a possible source of hypertension [59].

While patients with CDI usually have little if any hyperosmolality, patients with osmoreceptor dysfunction can present with severe even life threatening hyperosmolality [61]. ADH secretion due to hypovolemia or decreased BP however, can still be intact [62]. Since baroreceptor pathways are still intact, the ADH and subsequent renal response are still elicited when hypovolemia occurs. Therefore it is important to recognize osmoreceptor dysfunction, with absent thirst and hyperosmolality, despite seemingly normal urine concentrating capability [62].

In cases of surgical or traumatic origin there are several distinct patterns in which CDI can manifest. There may be abrupt onset of polyuria followed by spontaneous resolution within several days [63,64]. Occasionally the damage is severe enough to cause permanent CDI immediately past the injurious event. There is also a distinct triphasic presentation that can occur, characterized by an initial phase of polyuria, due to axonal shock and inhibited secretion of ADH, lasting from hours to days. The second phase, lasting 2-14 days, is the antidiuretic phase, caused by uncontrolled release of ADH from the damaged neurons. The third phase is again, polyuria. During the second phase it is important to not overhydrate patients, in order to prevent hyponatremia from the uncontrolled ADH release. Frequently, there can be isolated transient hyponatremia (phase 2) following transphenoidal surgery, with spontaneous resolution [64-66]. Regardless of the pattern of presentation, in post-surgical patients with serum sodium ≤145 mEq/l spontaneous resolution is the rule [67]. In post-surgical patients with serum sodium >145 mEq/l, permanent CDI is likely [67]. In cases of post-traumatic CDI as opposed to post-surgical CDI, once polyuria has persisted for a few weeks, CDI is likely to be permanent [68].

While CDI, or any type of DI for that matter, is usually not life threatening, there are certain circumstances where CDI can be lethal. Children, especially infants, do not have free access to fluid. This can cause severe hypernatremia, dehydration, and death. It is especially important to have a high index of suspicion because the symptoms of CDI in young children are non-specific [3]. Usually, CDI presents with poor feeding and failure to thrive. Because breast milk has such a low solute load, polyuria is often not noticed until later in life when solid food is introduced and solute delivery to the kidneys is increased [3]. When polyuria becomes evident, it is usually accompanied by hypernatremia, dehydration and fever. CDI can also present with constipation and small hard stools [3]. In the past, frequent dehydration and subsequent hypernatremia led to seizures and almost invariably caused mental retardation. However, with better and earlier recognition of the disease and more effective treatment, this is no longer the case [3,69]. Children with CDI, however, have hyperactivity

disorder as well as short-term memory problems, most probably due to frequent voiding and drinking [3]. CDI is also reported in 50-90% of patients with brain death [65].

Clinical presentation

CDI is characterized by polyuria, polydipsia, urinary frequency and nocturia. Polyuria is defined as 24 hour urine production in excess of 40ml/kg [70]. Nocturia in CDI is caused by increased urine production overall while bladder capacity remains normal-high normal. CDI usually has a sudden onset, due to the fact that urine can be concentrated up until 80-90% of ADH secreting cell are destroyed, after which urine can no longer be effectively concentrated and CDI becomes apparent [35,36]. Patients with CDI usually present with high-normal plasma osmolality, though in pediatric patients or in patients with absent thirst or no access to water, CDI can present with life threatening hypernatremia and severe dehydration. For unknown reasons, patients with CDI also report craving for ice water, and that ice water quenches their thirst better [3,71]. Patients with CDI, for unidentified reasons, also have decreased bone density. It is postulated that diminished ADH, and hence a decreased effect on prostaglandins and bone production, is a possible reason for the osteopenia associated with CDI [72].

Nephrogenic Diabetes Insipidus (NDI)

Congenital NDI, characterized by insensitivity of the kidneys to ADH, occurs rarely in the general population. For example, X linked NDI with some observational studies showing incidence of 8.8 cases per million live male births [4]. In more specific areas with residents of common ancestry, rates of NDI are even higher [4]. The vast majority of inherited cases of NDI are X-linked recessive, but there are both autosomal dominant and autosomal recessive variants as well. However, most NDI is not inherited, but rather results from either exogenous causes (e.g. lithium, demeclocycline) or renal disease [73,74]. In pediatric patients, NDI be a concomitant of obstructive uropathy [3,75]. Normally, ADH-induced signaling leads to the insertion of AQP2 into the apical membrane of the principal cells of the collecting duct. In X-linked disease, NDI is caused by mutations of the $AVPR_2$ gene, leading to absent signaling for AQP2 insertion into the apical membrane. It is possible to clinically possible to detect mutations in the V2R and the AQP2 genes with genetic sequencing [76]. There are 5 classes of V_2 receptor mutations leading to NDI [1,77]: (I) Abnormal mRNA that is untranslated or leads to aborted proteins (II) Translated proteins that are trapped in the endoplasmic reticulum (III) Proteins that are in the correct location but do not signal in response to ADH (IV) Proteins that are in the correct location but do not bind ADH (V) Proteins that are transported to improper organelles [77]. Close to half of X-linked NDI is due to class II mutations [77,78]. These class II mutations are resultant of a missense mutation. This mutation prevents the export of the functional V_2 receptor to the basolateral membrane of the cell, and leaves the functional protein trapped in the endoplasmic reticulum. This prevents the receptor's interaction with circulating ADH and subsequent insertion of AQP2 into the apical membrane. Female carriers are usually unaffected but can occasionally be symptomatic. Normally in females, inactivation of one of the X chromosomes occurs randomly in every cell, leading to a roughly equal amount of each of the chromosomes remaining active [79-81]. In symptomatic carriers, there usually is a correlation between a skewed X chromosome inactivation detected in leukocytes and symptomatic disease. In cases where the female patient is symptomatic but skewed X inactivation is not detected in leukocytes, it is possible that the disease is due to different X inactivation rations between different tissues. Carriers can also have decreased urine concentration capability though asymptomatic, with no polyuria [79]. Autosomal NDI, both recessive and dominant, is caused by a variety of AQP2 mutations, similar to the case with X-linked CDI.

Lithium, widely used in therapy of bipolar disorder, is the commonest cause of acquired NDI. While lithium usually causes impaired urine concentration, only about 15% of patients taking lithium for >15 years develop full-blown NDI [74,82]. Lithium's mechanism in causing NDI is unknown and a variety of mechanisms have been proposed - one of which is by decreasing cellular cAMP, causing decreased insertion of AQP2 into the apical membrane [83,84]. Other research shows that lithium's action is likely not due to cAMP, but rather, to AQP2 transcription reduction and AQP2 mRNA degradation [85]. Another proposed method of decreased aquaporin 2 insertion is via lithium's inhibition of glycogen synthase kinase 3 (GSK-3), one of the regulatory enzymes of AQP2 and epithelial sodium channels (ENaC's). When GSK-3 is inhibited, there is decreased cellular sensitivity to ADH, leading to decreased AQP2 insertion [86,87]. While lithium-induced impaired urine concentration is initially reversible, with time, the defect becomes permanent.

Hypokalemia and hypercalcemia are 2 metabolic etiologies of NDI, associated with decreased sensitivity to ADH. Hypercalcemia is another common cause of NDI [88]. The etiology of NDI with hypokalemia (plasma potassium <3.0 mEq/l) is incompletely understood, though it is postulated that, in addition to a decreased sensitivity to ADH, there is also decreased production of the countercurrent gradient via the Na-K-2Cl co-transporter in the thick ascending limb of Henle (TAL) [89]. Hypokalemia also can induce thirst leading to associated polyuria and polydipsia [90]. Hypercalcemia (plasma calcium >11 mg/dL) causes impaired countercurrent multiplier function in the nephron associated with decreased NaCl reabsorption in the TAL, in part, due to increased PGE-2 production [91]. Hypercalcemia also may decrease AQP2 expression [92]. Both hypercalcemia and hypokalemia are reversible with correction of the imbalance; however, effects of chronic hypercalcemia are unknown [88].

Bilateral urinary tract obstruction is also another source of NDI. There are manifold etiologies leading to obstruction, including congenital origin, resulting from neoplastic processes, inflammatory reactions and others, all affecting the upper and lower urinary tract. These will not be discussed here and are beyond the scope of this paper. In bilateral ureteral obstruction, in addition to retained solutes, there is also significant volume expansion due to retained fluid. This increased fluid leads to increased BP and resulting secretion of atrial natriuretic peptide (ANP) [93]. Once obstruction occurs, there is an acute decrease in urine concentration capability. This is thought to be due to a variety of factors including decreased AQP expression, ischemic renal tubular damage and impaired ENaCs [94]. Increased PGE2 may play a role in the decreased AQP2 expression [95,96]. These defects, combined with decreased urinary concentrating capability, increased ANP, and the supernormal volume of fluid and solute, leads to dieresis [95]. In patients with significant obstruction, this impaired concentrating capability may remain long after the obstruction is removed [94-97]. It is postulated that defects in AQP1 expression are the cause of continued urinary obstruction-associated polyuria [94].

Since the osmoregulatory center of the brain is intact, such polyuria causes secondary polydipsia [98].

Broadly included in NDI are polycystic kidney disease, renal manifestations of Sjogren's syndrome, and renal amyloidosis [99,100]. Bardet-Biedl syndrome, another cause of NDI, is a rare autosomal recessive disorder with obesity, mental retardation, retinopathy, polydactyly, male hypogonadism as well as polydipsia and polyuria [101]. In this syndrome there is an absent ADH receptor not on the basolateral side of the cells, but rather on the luminal side [101]. Bartter syndrome, an AR disease, is also characterized by polyuria and polydipsia; however, the impaired urinary concentration and resulting polydipsia come from impaired Na^+ reabsorption in the TAL of Henle [102]. Bartter syndrome also leads to hypokalemia, which also leads to NDI, as described above.

Clinical presentation

In adults, NDI, as opposed to CDI, tends to present more gradually than CDI; as sensitivity to ADH decreases, polyuria increases [3]. Nocturia may be a presenting sign of NDI. During the night, there is normally maximally increased urine, due to lack of fluid intake. However, with NDI, this concentration does not happen and nocturia results. In contrast to the case for CDI, there has been no reported link between NDI, decreased bone density or craving for ice water [3]. Hereditary NDI usually presents in the first week of life [3,103]. One of the first signs of NDI in children is fever, accompanied by irritability, and constant crying [3,82]. Neonates will have vigorous sucking but will vomit soon after feeding, unless feeding is preceded by water [103]. These patients will also have signs of dehydration, such as constipation, hypernatremia, hyperchloremia, and prerenal azotemia [3]. Hypertonic dehydration can lead to seizures and death [103]. Classically, mental retardation was considered a feature of hereditary NDI, but is now recognized to result from the frequent dehydration and subsequent seizures [3,103]. With better recognition, mental retardation is rarely a complication of the disease. However, children with NDI frequently have short term memory and hyperactivity disorders, possibly related to frequent urination and fluid seeking, which interferes with normal ability to focus, cognitively [3]. Pediatric NDI often is accompanied by growth retardation due to decreased caloric intake, as well as lower urinary tract dilatation and obstruction, caused by increased urinary volume [3,104].

Gestational Diabetes Insipidus (GDI)

During pregnancy, the placenta produces cysteine aminopeptidase (vasopressinase), which metabolizes both oxytocin and ADH [2]. When cysteine aminopeptidase levels are greatly elevated, ADH is degraded beyond the capacity of the hypothalamic/pituitary axis to secrete it sufficiently to maintain proper urinary concentration [2]. This results in GDI, also known as "transient DI of pregnancy". Patients with GDI have decreased hepatic function, leading to decreased hepatic clearance of cysteine aminopeptidase [2]. In light of this, GDI is often associated with preeclampsia and the HELLP syndrome (hemolysis, elevated liver enzymes; low platelet count) [2]. In subsequent pregnancies, GDI is unlikely to return [2,105]. While increased urinary frequency and nocturia are normal during pregnancy, true polyuria is abnormal and deserves investigation.

Primary Polydipsia

Opposite in origin from the other forms of DI is primary polydipsia. Rather than having voluminous amount of dilute urine causing thirst and then ingestion of fluid as in DI, PP is characterized by the ingestion of vast amounts of fluid, most frequently water, causing hypotonic polyuria [106]. The patient ingests massive amounts of fluid, plasma osmolality decreases, and decreased secretion of ADH follows. Less circulating ADH results in reduced AQP2 expression and insertion. This causes a dilute polyuria. Eventually, the body sets this new, lower plasma osmolality as the threshold for ADH [107]. Frequent voluminous urination also causes medullary "washout," (loss of the concentration gradient in the medulla), further impairing urine concentration capability [107]. Many cases of PP are manifestations of psychiatric disorders such as schizophrenia or obsessive compulsive disorder [108]. In extreme cases of PP the kidneys' excretory capacity of around 20L/day can be surpassed, leading to a phenomenon called PIP syndrome (psychosis, intermittent hyponatremia, polydipsia) [109]. It is characterized by transient hyponatremia that corrects itself when the patient sleeps and fluid ingestion ceases. Polydipsia is extremely common in patients with chronic mental illness with around 25% of patients being affected. In schizophrenics < 50 years of age hyponatremia is a significant cause of mortality. Dipsogenic polydipsia is a PP subvariety caused by a defect in the patient's thirst center [106]. This can either be idiopathic, or, as a result of a structural lesion, similar in origin to the causes of CDI. PP may caused by drugs that cause dry mouth, a common side effect of many psychiatric medications. Primary polydipsia can be behavioral as well, due to recommendations to drink copious amounts, both for good reasons, such as recurrent nephrolithiasis, and for reasons based upon erroneous assumptions of the salubrious benefits of "hydration" [110,111].

Differential Diagnosis of Diabetes Insipidus

By definition, DI is characterized by polyuria with hypotonic urine. Therefore, before determining the variant of DI, it is prudent to verify that there is polyuria, and it is indeed hypotonic. For polyuria to be present, urine output needs to be in excess of 40ml/kg/24 hours [37,70,112]. In order to diagnose DI, urine osmolality should measure < 300 mOsm/kg. If urine is not hypotonic, then other etiologies of the polyuria should be investigated, e.g. diabetes mellitus (solute diuresis). Once the diagnosis of hypotonic polyuria is established, a history should be taken to characterize the polyuria. Onset of polyuria should be delineated as gradual or abrupt. The patient should be asked about craving for ice water [3,71]. While most cases of hereditary DI manifest at young ages, hereditary DI occasionally develops in adolescence; hence, family history can aid in diagnosis [3]. Generally speaking, DI is diagnosed by osmotically stimulating ADH secretion (e.g. by overnight fasting), and then measuring the response by either urine osmolality testing or direct measurement of plasma ADH levels. The gold standard is a dehydration test followed by plasma ADH levels, but ADH levels are difficult to measure commercially, and the indirect measurement of urine concentration is usually used first [3,113]. The relationship between plasma osmolality and urine osmolality is also helpful in establishing a diagnosis. Patients who are hyperosmolar do not have PP, so they can be tested for a response to DDAVP, a synthetic analogue of ADH. If the patient responds to DDAVP by concentrating their urine more than 800 mOsm/kg then CDI is the diagnosis. If DDAVP is administered and their urine osmolality remains below 2-300 mOsm/kg, NDI is present [3,112]. Patients with normal range plasma sodium and hypotonic polyuria should be worked up as follows: Serum and urine osmolality as well as serum ADH should be taken at baseline. Water should be restricted. Measure urine osmolality

and volume with each voiding, stopping either when body weight decreases by 3%, urine osmolality levels off for 2 consecutive voids, or plasma Na^+ reaches 145 mmol/L. Once plasma becomes hyperosmolar, treat with DDAVP and monitor urine osmolality for another 2 hours. If urine concentration increases by 50% or more, then CDI is the diagnosis. If DDAVP causes urine osmolality to increases by <10%, the patient has NDI. If urine osmolality reaches more than 750 mOsm, either CDI or PP is the diagnosis; the latter two may be distinguished by urine concentrating ability in response to dehydration which is normal in patients with PP [3,38]. MRI can aid in the diagnosis of DI; patients with the characteristic bright spot in the sella turcica are unlikely to have CDI (see above) [3,39,114]. Some difficulties may arise differentiating between NDI, CDI and PP, in that the latter may present with lower than expected concentration capacity, due to medullary washout caused by the massive amount of flow, leading to lack of a concentration gradient. NDI may present with residual sensitivity to ADH, or with secretion of ADH occurring at higher levels of plasma osmolality in patients with partial CDI. ADH assay, while helpful to differentiate between the two, is often inaccurate due to ADH's instability in the blood. Radioimmunoassays which detect copeptin, a stable molecule secreted with ADH may be helpful in quantification of serum ADH levels [113,115].

Treatment of DI

In general, the mainstay of treatment of DI is to correct current deficits and reduce future fluid loss. In most patients with intact thirst and mobility, there are only minor fluid deficits that may be immediately correctable. In patients who are unable to respond to thirst, such as infants, unconscious patients and patients with absent thirst, fluid deficits can be severe and need to be corrected slowly [116]. Correcting hypernatremia too quickly leads to water osmotically entering the brain, causing edema, seizures, and even death [116]. Hypernatremia should be corrected at a rate of no more than 0.5 mEq per hour [117].

CDI

The preferred replacement therapy for treating CDI is 1-desamino-8-D-arginine vasopressin, also known as DDAVP. It is similar to ADH but with the 8-position arginine a D-isomer (instead of L) and the terminal cysteine is deaminated. It is preferred to pitressin, a synthetic peptide identical to ADH, because DDAVP lacks the pressor effects of ADH, unlike pitressin [3,118]. DDAVP is useful in GDI, since DDAVP is resistant to placental vasopressinase [2,119]. DDAVP can be given as an intranasal spray, oral tablet or lyophilisate (melt) form [120]. A possible side effect is hyponatremia, brought on by continued ingestion of fluids despite the resolution of the polyuria, which can be avoided by allowing effects of the DDAVP to wear off before re-administering [121,122]. This is especially important while monitoring patients with post surgical CDI. By allowing the effects of DDAVP to dissipate before the next dose, the diuretic phase will not be missed and severe hyponatremia can be avoided [122]. Treatment of CDI in brain-dead organ donors has shown to improve both quality and quantity of organs harvested [65,123]. Continuous infusion of pitressin has been used in these donors [3,65,123]. Chlorpropamide also reduces polyuria by up to 75% by acting on the renal tubule to respond more effectively to residual ADH and is also thought to act by causing release of ADH [3,112,124,125]. Chlorpropamide is mainly used in patients with mild DI who need only modest reduction in urine output [124].

NDI

Patients with NDI respond to neither ADH nor DDAVP; hence, treatment of NDI differs from that of CDI. First and foremost, in cases of acquired NDI, it is essential to remove the offending agent i.e. lithium, whenever possible (which is not often). Additionally, adequate water must be given, especially in infants who cannot access water on their own [3]. A low sodium diet, combined with a thiazide diuretic, paradoxically aids in reducing polyuria by producing volume contraction [126,127]. This approach is thought to work by causing sodium loss, leading to reduced extracellular volume, decreased glomerular filtration rate, and increased proximal tubular sodium and water reabsorption [126]. Thiazides may also act on the inner medullary collecting duct to reabsorb water [126]. Thiazides may also increase AQP2 expression, in the setting of Li^+ induced NDI [126,127]. Amiloride is used, as well, to cause volume contraction; it is especially helpful with Li^+ induced NDI, because it prevents lithium entry into distal tubule cells [1,86]. Despite the contradictory evidence regarding prostoglandin's effects on the kidney, prostaglandin synthase inhibitors, such as indomethacin, can limit diuresis. Hence while the precise mechanism for their action is unclear, prostolandin synthase inhibitors increase cellular concentration of cAMP, leading to increased AQP-2 insertion into the apical membrane of the collecting duct and resulting higher urine concentration [128,129]. However, since these drugs can actually cause kidney injury and gastric problems with long-term use, they were classically used after other treatments have been tried [3,130,131]. Recent evidence shows a link between long-term thiazide therapy and renal cell carcinoma, especially in women. This may lead to increased treatment with prostaglandin synthase inhibitors and other therapies [131]. Thiazides and prostaglandin synthase inhibitors can also be used in CDI [132]. In contrast to CDI, treatment of NDI can only raise urine osmolality to plasma osmolality and no further [133]. DDAVP usually has no effect on patients with NDI but may be effective in patients with partial resistance to ADH; therefore, it is worthwhile to try a high dose of DDAVP [134]. Other potential treatments for NDI include possible rescue of trapped V_2 receptors stuck in the endoplasmic reticulum, as seen with class II mutations [78,135]. Rescue of these receptors via chemical compounds known as nonpeptide chaperones looks to be promising [78]. These nonpeptide chaperones stabilize the V_2 receptor trapped in the endoplasmic reticulum of the collecting duct cells. This stabilization allows the V_2 receptor to be exported to the golgi apparatus. There the receptors are glycosylated and inserted properly into the basolateral membrane. Another potential treatment of hereditary NDI being investigated is the use of phosphodiesterase (PDE) inhibitors, used to increase intracellular cAMP levels in the renal cells. Animal studies have showed that the PDE4 inhibitor rolipram and the PDE5 inhibitor sildenafil increase urine concentration [136,137].

PP

Fluid restriction is the preferred treatment of PP, however in patients with psychogenic polydipsia, adherence is suboptimal [138]. Clozapine has been shown to be effective in reducing water intake in schizophrenic patients. Despite this many clinicians will not use clozapine to treat PP unless there is significant hyponatremia, as clozapine has a significant side effect profile. However in cases of PIP clozapine is the standard treatment [138]. In fact clozapine is likely to be the reason for the apparent decrease in incidence of hyponatremia and polydipsia among psychiatric patients in recent years. Using

desmopressin or thiazides in PP can be lead to hyponatremia, and must be avoided. In patients with dipsogenic polydipsia, alternatives to fluid intake, such as sour candies, gum or ice chips, may be useful.

Summary

DI is a disease of polydipsia and hypotonic polyuria caused by one of 4 etiologies: 1) Inadequate ADH secretion such as in CDI 2) Lack of response to ADH, as seen in NDI 3) Increased metabolism of ADH as occurs in GDI 4) Massive fluid ingestion as in psychogenic or dipsogenic polydipsia. Both CDI and NDI can be inherited or acquired. CDI is usually acquired as a result of an idiopathic/autoimmune process, and inherited mostly as an autosomal dominant disease. NDI is usually acquired as a result of lithium toxicity and occasionally inherited as an X-linked recessive trait. GDI is thought to be related to decreased hepatic clearance of vasopressinase, with increased metabolism of ADH. PP is usually caused as a result of psychiatric illness but can also be caused by a damaged thirst center, leading to the polydipsia. Treatment of DI consists of correcting deficits and preventing further polyuria. CDI is treated effectively with DDAVP; milder cases benefit from therapy with chlorpropamide. Caution should be used with DDAVP so as not to induce hyponatremia, while titrating the initial dosage. NDI is treated with less satisfactory results through volume contraction via sodium restriction and thiazide diuretics. Prostaglandin synthase inhibitors are effective as well, but should be used with caution, as they may cause renal disease on a long-term basis. PP is treated with fluid restriction, which is rarely successful although patients do not suffer from serious complications as they are able to maintain homeostasis at the expense of increased urine output and fluid intake. While DI is usually a benign disease, in patients with impaired lack of access to water such as infants and trauma victims, DI can be a life threatening illness.

References

1. Karet FE (2011) Disorders of water and acid-base homeostasis. Nephron Physiol 118: p28-34.
2. Aleksandrov N, Audibert F, Bedard MJ, Mahone M, Goffinet F, et al. (2010) Gestational diabetes insipidus: a review of an underdiagnosed condition. J Obstet Gynaecol Can 32: 225-231.
3. Saborio P, Tipton GA, Chan JC (2000) Diabetes Insipidus. Pediatr Rev 21: 122-129.
4. Arthus MF, Lonergan M, Crumley MJ, Naumova AK, Morin D, et al. (2000) Report of 33 novel AVPR2 mutations and analysis of 117 families with X-linked nephrogenic diabetes insipidus. J Am Soc Nephrol 11: 1044-1054.
5. Burbach JP, Luckman SM, Murphy D, Gainer H (2001) Gene regulation in the magnocellular hypothalamo-neurohypophysial system. Physiol Rev 81: 1197-1267.
6. Acher R, Chauvet J, Rouille Y (2002) Dynamic processing of neuropeptides: sequential conformation shaping of neurohypophysial preprohormones during intraneuronal secretory transport. J Mol Neurosci 18: 223-228.
7. Chen LQ, Rose JP, Breslow E, Yang D, Chang WR, et al. (1991) Crystal structure of a bovine neurophysin II dipeptide complex at 2.8 A determined from the single-wavelength anomalous scattering signal of an incorporated iodine atom. Proc Natl Acad Sci U S A 88: 4240-4244.
8. Sudbury JR, Ciura S, Sharif-Naeini R, Bourque CW (2010) Osmotic and thermal control of magnocellular neurosecretory neurons--role of an N-terminal variant of trpv1. Eur J Neurosci 32: 2022-2030.
9. Bourque CW (2008) Central mechanisms of osmosensation and systemic osmoregulation. Nat Rev Neurosci 9: 519-531.
10. Sharif Naeini R, Witty MF, Séguéla P, Bourque CW (2006) An N-terminal variant of Trpv1 channel is required for osmosensory transduction. Nat Neurosci 9: 93-98.
11. Prager-Khoutorsky M, Bourque CW (2010) Osmosensation in vasopressin neurons: changing actin density to optimize function. Trends Neurosci 33: 76-83.
12. Zhang Z, Kindrat AN, Sharif-Naeini R, Bourque CW (2007) Actin filaments mediate mechanical gating during osmosensory transduction in rat supraoptic nucleus neurons. J Neurosci 27: 4008-4013.
13. Kaufmann JE, Iezzi M, Vischer UM (2003) Desmopressin (DDAVP) induces NO production in human endothelial cells via V2 receptor- and cAMP-mediated signaling. J Thromb Haemost 1: 821-828.
14. Thrasher TN (1994) Baroreceptor regulation of vasopressin and renin secretion: low-pressure versus high-pressure receptors. Front Neuroendocrinol 15: 157-196.
15. Knoers NV (2005) Hyperactive vasopressin receptors and disturbed water homeostasis. N Engl J Med 352: 1847-1850.
16. Klussmann E, Maric K, Rosenthal W (2000) The mechanisms of aquaporin control in the renal collecting duct. Rev Physiol Biochem Pharmacol 141: 33-95.
17. Fujiwara TM, Bichet DG (2005) Molecular biology of hereditary diabetes insipidus. J Am Soc Nephrol 16: 2836-2846.
18. King LS, Choi M, Fernandez PC, Cartron JP, Agre P (2001) Defective urinary concentrating ability due to a complete deficiency of aquaporin-1. N Engl J Med 345: 175-179.
19. Johnson AK, Thunhorst RL (1997) The neuroendocrinology of thirst and salt appetite: visceral sensory signals and mechanisms of central integration. Front Neuroendocrinol 18: 292-353.
20. Sklar AH, Schrier RW (1983) Central nervous system mediators of vasopressin release. Physiol Rev 63: 1243-1280.
21. Nadler SP, Hebert SC, Brenner BM (1986) PGE2, forskolin, and cholera toxin interactions in rabbit cortical collecting tubule. Am J Physiol 250: F127-135.
22. Zelenina M, Christensen BM, Palmér J, Nairn AC, Nielsen S, et al. (2000) Prostaglandin E2 interaction with AVP: effects on AQP2 phosphorylation and distribution. Am J Physiol Renal Physiol 278: F388-394.
23. Olesen ET, Rützler MR, Moeller HB, Praetorius HA, Fenton RA (2011) Vasopressin-independent targeting of aquaporin-2 by selective E-prostanoid receptor agonists alleviates nephrogenic diabetes insipidus. Proc Natl Acad Sci U S A 108: 12949-12954.
24. Thrasher TN, Keil LC, Ramsay DJ (1982) Hemodynamic, hormonal, and drinking responses to reduced venous return in the dog. Am J Physiol 243: R354-362.
25. Thompson CJ, Bland J, Burd J, Baylis PH (1986) The osmotic thresholds for thirst and vasopressin release are similar in healthy man. Clin Sci 71: 651-656.
26. Bouby N, Fernandes S (2003) Mild dehydration, vasopressin and the kidney: animal and human studies. Eur J Clin Nutr 2: S39-46.
27. Trudel E, Bourque CW (2010) Central clock excites vasopressin neurons by waking osmosensory afferents during late sleep. Nat Neurosci 13: 467-474.
28. Thrasher TN, Brown CJ, Keil LC, Ramsay DJ (1980) Thirst and vasopressin release in the dog: an osmoreceptor or sodium receptor mechanism? Am J Physiol 238: R333-339.
29. Zerbe RL, Robertson GL (1983) Osmoregulation of thirst and vasopressin secretion in human subjects: effects of various solutes. Am J Physiol 244: E607-614.
30. Ciura S, Liedtke W, Bourque CW (2011) Hypertonicity sensing in organum vasculosum lamina terminalis neurons: a mechanical process involving TRPV1 but not TRPV4. J Neurosci 31: 14669-14676.
31. Lechner SG, Markworth S, Poole K, Smith ES, Lapatsina L, et al. (2011) The molecular and cellular identity of peripheral osmoreceptors. Neuron 69: 332-344.
32. Smith CA, Curtis KS, Smith JC, Stricker EM (2007) Presystemic influences on thirst, salt appetite, and vasopressin secretion in the hypovolemic rat. Am J Physiol Regul Integr Comp Physiol 292: R2089-2099.

33. Robertson GL (1976) The regulation of vasopressin function in health and disease. Recent Proq Horm Res 33: 333-385.

34. Zhang Z, Bourque CW (2008) Amplification of transducer gain by angiotensin II-mediated enhancement of cortical actin density in osmosensory neurons. J Neurosci 28: 9536-9544.

35. Maccubbin DA, Van Buren JM (1963) A quantitative evaluation of hypothalamic degeneration and its relation to diabetes insipidus following interruption of the human hypophyseal stalk. Brain 86: 443-464.

36. Atmaca H, Tanriverdi F, Gokce C, Unluhizarci K, Kelestimur F (2007) Posterior pituitary function in Sheehan's syndrome. Eur J Endocrinol 156: 563-567.

37. Weiss JP, Blaivas JG (2000) Nocturia. J Urol 163: 5-12.

38. Zerbe RL, Robertson GL (1981) A comparison of plasma vasopressin measurements with a standard indirect test in the differential diagnosis of polyuria. N Engl J Med 305: 1539-1546.

39. Arslan A, Karaarslan E, Dincer A (1999) High intensity signal of the posterior pituitary. A study with horizontal direction of frequency-encoding and fat suppression MR techniques. Acta Radiol 40: 142-145.

40. Moses AM, Clayton B, Hochhauser L (1992) Use of T1-weighted MR imaging to differentiate between primary polydipsia and central diabetes insipidus. AJNR Am J Neuroradiol 13: 1273-1277.

41. Robinson AG, Verbalis JG (2011) Posterior pituitary. In: Melmed S, Williams Textbook of Endocrinology, 12th ed Philadelphia: Saunders Elsevier: 298.

42. Verbalis JG (2011) Disorders of water imbalance. In: Taal MW, Brenner and Rector: The Kidney, 9th ed Philadelphia: Saunders Elsevier: 553.

43. Batista SL, Moreira AC, Antunes-Rodrigues J, Castro M, Elias LL, et al. (2010) Clinical features and molecular analysis of arginine-vasopressin neurophysin II gene in long-term follow-up patients with idiopathiccentral diabetes insipidus. Arq Bras Endocrinol Metabol 54: 269-273.

44. Maghnie M, Cosi G, Genovese E, Manca-Bitti ML, Cohen A, et al. (2000) Central diabetes insipidus in children and young adults. N Engl J Med 343: 998-1007.

45. Christensen JH, Rittig S (2006) Familial neurohypophyseal diabetes insipidus--an update. Semin Nephrol 26: 209-223.

46. Nieboer P, Vellenga E, Adriaanse R, van de Loosdrecht AA (2000) Central diabetes insipidus preceding acute myeloid leukemia with t(3;12)(q26;p12). Neth J Med 56: 45-47.

47. Rittig S, Siggaard C, Ozata M, Yetkin I, Gregersen N, et al. (2002) Autosomal dominant neurohypophyseal diabetes insipidus due to substitution of histidine for tyrosine(2) in the vasopressin moiety of the hormone precursor. J Clin Endocrinol Metab 87: 3351-3355.

48. Si-Hoe SL, De Bree FM, Nijenhuis M, Davies JE, Howell LM, et al. (2000) Endoplasmic reticulum derangement in hypothalamic neurons of rats expressing a familial neurohypophyseal diabetes insipidus mutant vasopressin transgene. FASEB J 14: 1680-1684.

49. Davies J, Murphy D (2002) Autophagy in hypothalamic neurones of rats expressing a familial neurohypophysial diabetes insipidus transgene. J Neuroendocrinol 14: 629-637.

50. Willcutts MD, Felner E, White PC (1999) Autosomal recessive familial neurohypophyseal diabetes insipidus with continued secretion of mutant weakly active vasopressin. Hum Mol Genet 8: 1303-1307.

51. Abu Libdeh A, Levy-Khademi F, Abdulhadi-Atwan M, Bosin E, Korner M, et al. (2010) Autosomal recessive familial neurohypophyseal diabetes insipidus: onset in early infancy. Eur J Endocrinol 162: 221-226.

52. Takeda K, Inoue H, Tanizawa Y, Matsuzaki Y, Oba J, et al. (2001) WFS1 (Wolfram syndrome 1) gene product: predominant subcellular localization to endoplasmic reticulum in cultured cells and neuronal expression in rat brain. Hum Mol Genet 10: 477-484.

53. Ishihara H, Takeda S, Tamura A, Takahashi R, Yamaguchi S, et al. (2004) Disruption of the WFS1 gene in mice causes progressive beta-cell loss and impaired stimulus-secretion coupling in insulin secretion. Hum Mol Genet 13: 1159-1170.

54. Chaussenot A, Bannwarth S, Rouzier C, Vialettes B, Mkadem SA, et al. (2011) Neurologic features and genotype-phenotype correlation in Wolfram syndrome. Ann Neurol 69: 501-508.

55. Imura H, Nakao K, Shimatsu A, Ogawa Y, Sando T, et al. (1993) Lymphocytic infundibuloneurohypophysitis as a cause of central diabetes insipidus. N Engl J Med 329: 683-689.

56. De Bellis A, Colao A, Di Salle F, Muccitelli VI, Iorio S, et al. (1999) A longitudinal study of vasopressin cell antibodies, posterior pituitary function, and magnetic resonance imaging evaluations in subclinical autoimmune central diabetes insipidus. J Clin Endocrinol Metab 84: 3047-3051.

57. Crowley R, Sherlock M, Agha A, Smith D, Thompson CJ (2007) Clinical insights into adipsic diabetes insipidus: a large case series. Clin Endocrinol 66: 475-482.

58. Baylis PH, Thompson CJ (1988) Osmoregulation of vasopressin secretion and thirst in health and disease. Clin Endocrinol 29: 549-576.

59. Thornton SN (2010) Thirst and hydration: physiology and consequences of dysfunction. Physiol Behav 100: 15-21.

60. McIver B, Connacher A, Whittle I, Baylis P, Thompson C (1991) Adipsic hypothalamic diabetes insipidus after clipping of anterior communicating artery aneurysm. BMJ 303: 1465-1467.

61. Alshayeb HM, Showkat A, Babar F, Mangold T, Wall BM (2011) Severe hypernatremia correction rate and mortality in hospitalized patients. Am J Med Sci 341: 356-360.

62. Smith D, McKenna K, Moore K, Tormey W, Finucane J, et al. (2002) Baroregulation of vasopressin release in adipsic diabetes insipidus. J Clin Endocrinol Metab 87: 4564-4568.

63. Olson BR, Gumowski J, Rubino D, Oldfield EH (1997) Pathophysiology of hyponatremia after transsphenoidal pituitary surgery. J Neurosurg 87: 499-507.

64. Kristof RA, Rother M, Neuloh G, Klingmuller D (2009) Incidence, clinical manifestations, and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: a prospective observational study Clinical article. J Neurosurg 111: 555-562

65. Domínguez-Roldan JM, Garcia-Alfaro C, Díaz-Parejo P, Murillo-Cabezas F, Barrera-Chacon JM, et al. (2002) Risk factors associated with diabetes insipidus in brain dead patients. Transplant Proc 34: 13-14.

66. Olson BR, Rubino D, Gumowski J, Oldfield EH (1995) Isolated hyponatremia after transsphenoidal pituitary surgery. J Clin Endocrinol Metab 80: 85-91.

67. Sigounas DG, Sharpless JL, Cheng DM, Johnson TG, Senior BA, et al. (2008) Predictors and incidence of central diabetes insipidus after endoscopic pituitary surgery. Neurosurgery 62: 71-78.

68. Verbalis JG (2011) Disorders of water imbalance. In: Taal MW, Brenner and Rector: The Kidney, 9th ed. Philadelphia: Saunders Elsevier: 555.

69. Ranadive SA, Rosenthal SM (2009) Pediatric disorders of water balance. Endocrinol Metab Clin North Am 38: 663-672.

70. van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D (2002) The Standardisation of Terminology in Nocturia: report from the Standardisation Sub-Committee of the International Continence Society. Neurourol Urodyn 21: 179-183.

71. Salata RA, Verbalis JG, Robinson AG (1987) Cold water stimulation of oropharyngeal receptors in man inhibits release of vasopressin. J Clin Endocrinol Metab 65: 561-567.

72. Pivonello R, Colao A, Di Somma C, Facciolli G, Klain M, et al. (1998) Impairment of bone status in patients with central diabetes insipidus. J Clin Endocrinol Metab 83: 2275-2280.

73. Garofeanu CG, Weir M, Rosas-Arellano MP, Henson G, Garg AX, et al. (2005) Causes of reversible nephrogenic diabetes insipidus: a systematic review. Am J Kidney Dis 45: 626-637.

74. Bendz H, Aurell M (1999) Drug-induced diabetes insipidus: incidence, prevention and management. Drug Saf 21: 449-456.

75. Shapiro SR, Werner S, Adelman RD, Palmer JM (1978) Diabetes insipidus and hydronephrosis. J Urol 119: 715-719.

76. Bichet DG (2011) The posterior pituitary. In: The Pituitary, 3rd Ed Melmed S (ed) Elsevier Press Inc: 261-299.

77. Robben JH, Knoers NV, Deen PM (2006) Cell biological aspects of the vasopressin type-2 receptor and aquaporin 2 water channel in nephrogenic diabetes insipidus. Am J Physiol Renal Physiol 291: F257-270.

78. Los EL, Deen PM, Robben JH (2010) Potential of nonpeptide (ant)agonists to rescue vasopressin V2 receptor mutants for the treatment of X-linked nephrogenic diabetes insipidus. J Neuroendocrinol 22: 393-399.

79. Satoh M, Ogikubo S, Yoshizawa-Ogasawara A (2008) Correlation between clinical phenotypes and X-inactivation patterns in six female carriers with heterozygote vasopressin type 2 receptor gene mutations. Endocr J 55: 277-284.

80. Chan Seem CP, Dossetor JF, Penney MD (1999) Nephrogenic diabetes insipidus due to a new mutation of the arginine vasopressin V2 receptor gene in a girl presenting with non-accidental injury. Ann Clin Biochem 36: 779-782.

81. Faerch M, Corydon TJ, Rittig S, Christensen JH, Hertz JM, et al. (2010) Skewed X-chromosome inactivation causing diagnostic misinterpretation in congenital nephrogenic diabetes insipidus. Scand J Urol Nephrol 44: 324-330.

82. Boton R, Gaviria M, Batlle DC (1987) Prevalence, pathogenesis and treatment of renal dysfunction associated with chronic lithium therapy. Am J Kidney Dis 10: 329-345.

83. Bichet DG (2006) Lithium, Cyclic AMP Signaling, A-Kinase Anchoring Proteins, and Aquaporin-2. J Am Soc Nephrol 17: 920-922.

84. Christensen S, Kusano E, Yusufi AN, Murayama N, Dousa TP (1985) Pathogenesis of nephrogenic diabetes insipidus due to chronic administration of lithium in rats. J Clin Invest 75: 1869-1879.

85. Li Y, Shaw S, Kamsteeg EJ, Vandewalle A, Deen PM (2006) Development of lithium-induced nephrogenic diabetes insipidus is dissociated from adenyl cyclase activity. J Am Soc Nephrol 17: 1063-1072.

86. Oliveira JL, Silva Júnior GB, Abreu KL, Rocha Nde A, Franco LF, et al. (2010) Lithium Nephrotoxicity. Rev Assoc Med Bras 56: 600-606.

87. Grünfeld JP, Rossier BC (2009) Lithium nephrotoxicity revisited. Nat Rev Nephrol 5: 270-276.

88. Garofeanu CG, Weir M, Rosas-Arellano MP, Henson G, Garg AX, et al. (2005) Causes of reversible nephrogenic diabetes insipidus: a systematic review. Am J Kidney Dis 45: 626-637.

89. Luke RG, Booker BB, Galla JH (1985) Effect of potassium depletion on chloride transport in the loop of Henle in the rat. Am J Physiol 248: F682-687.

90. Berl T, Linas SL, Aisenbrey GA, Anderson RJ (1977) On the mechanism of polyuria in potassium depletion. The role of polydipsia. J Clin Invest 60: 620-625.

91. Mangat H, Peterson LN, Burns KD (1997) Hypercalcemia stimulates expression of intrarenal phospholipase A2 and prostaglandin H synthase-2 in rats. Role of angiotensin II AT1 receptors. J Clin Invest 100: 1941-1950.

92. Earm JH, Christensen BM, Frøkiaer J, Marples D, Han JS, et al. (1998) Decreased aquaporin-2 expression and apical plasma membrane delivery in kidney collecting ducts of polyuric hypercalcemic rats. J Am Soc Nephrol 9: 2181-2193.

93. Ryndin I, Gulmi FA, Chou SY, Mooppan UM, Kim H (2005) Renal responses to atrial natriuretic peptide are preserved in bilateral ureteral obstruction and augmented by neural endopeptidase inhibition. J Urol 173: 651-656.

94. Li C, Wang W, Kwon TH, Isikay L, Wen JG, et al. (2001) Downregulation of AQP1, -2, and -3 after ureteral obstruction is associated with a long-term urine-concentrating defect. Am J Physiol Renal Physiol 281: F163-F171.

95. Murer L, Addabbo F, Carmosino M, Procino G, Tamma G, et al. (2004) Selective decrease in urinary aquaporin 2 and increase in prostaglandin E2 excretion is associated with postobstructive polyuria in human congenital hydronephrosis. J Am Soc Nephrol 15: 2705-2712.

96. Nørregaard R, Jensen BL, Topcu SO, Nielsen SS, Walter S, et al. (2006) Cyclooxygenase type 2 is increased in obstructed rat and human ureter and contributes to pelvic pressure increase after obstruction. Kidney Int 70: 872-881.

97. Li C, Wang W, Norregaard R, Knepper MA, Nielsen S, et al. (2007) Altered expression of epithelial sodium channel in rats with bilateral or unilateral ureteral obstruction. Am J Physiol Renal Physiol 293: F333-F341.

98. Frøkiaer J, Marples D, Knepper MA, Nielsen S (1996) Bilateral ureteral obstruction downregulates expression of vasopressin-sensitive AQP-2 water channel in rat kidney. Am J Physiol 270: F657-668.

99. Carone FA, Epstein FH (1960) Nephrogenic diabetes insipidus caused by amyloid disease. Evidence in man of the role of the collecting ducts in concentrating urine. Am J Med 29: 539-544.

100. Shearn MA, TU WH (1965) Nephrogenic Diabetic Insipidus and other Defects of Renal Tubular Function in Sjoerrgren's Syndrome. Am J Med 39: 312-318.

101. Marion V, Schlicht D, Mockel A, Caillard S, Imhoff O, et al. (2011) Bardet-Biedl syndrome highlights the major role of the primary cilium in efficient water reabsorption. Kidney Int 79: 1013-1025.

102. Peters M, Jeck N, Reinalter S, Leonhardt A, Tönshoff B, et al. (2002) Clinical presentation of genetically defined patients with hypokalemic salt-losing tubulopathies. Am J Med 112: 183-190.

103. Niaudet P, Dechaux M, Trivin C, Loirat C, Broyer M (1984) Nephrogenic diabetes insipidus: Clinical and pathophysiological aspects. Adv Nephrol Necker Hosp 13: 247-260.

104. Shalev H, Romanovsky I, Knoers NV, Lupa S, Landau D (2004) Bladder function impairment in aquaporin-2 defective nephrogenic diabetes insipidus. Nephrol Dial Transplant 19: 608-613.

105. Iwasaki Y, Oiso Y, Kondo K, Takagi S, Takatsuki K, et al. (1991) Aggravation of subclinical diabetes insipidus during pregnancy. N Engl J Med 324: 522-526.

106. Robertson GL (1998) Differential diagnosis of polyuria. Annu Rev Med 39: 425-442.

107. Goldman MB, Robertson GL, Luchins DJ, Hedeker D (1996) The infuence of polydipsia on water excretion in hyponatremic, polydipsic, schizophrenic patients. J Clin Endocrinol Metab 81: 1465-1470.

108. Goldman MB, Luchins DJ, Robertson GL (1988) Mechanisms of altered water metabolism in psychotic patients with polydipsia and hyponatremia. N Engl J Med 318: 397-403.

109. Vieweg WV, Carey RM, Godleski LS, Tisdelle DA, Pruzinsky T, et al. (1990) The syndrome of psychosis, intermittent hyponatremia, and polydipsia: Evidence for diurnal volume expansion. Psychol Med 8: 135-144.

110. Valtin H (2002) "Drink at least eight glasses of water a day." Really? Is there scientific evidence for "8×8"? Am J Physiol Regul Integr Comp Physiol 283: R993-R1004.

111. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, et al. (1996) Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol 155: 839-843.

112. Robertson GL (1995) Diabetes insipidus. Endocrinol Metab Clin North Am 24: 549-572.

113. Diederich S, Eckmanns T, Exner P, Al-Saadi N, Bähr V, et al. (2001) Differential diagnosis of polyuric/polydipsic syndromes with the aid of urinary vasopressin measurement in adults. Clin Endocrinol (Oxf) 54: 665-671.

114. Kurokawa H, Fujisawa I, Nakano Y, Kimura H, Akagi K, et al. (1998) Posterior lobe of the pituitary gland: Correlationbetween signal intensity on T1-weighted MR images and vasopressin concentration. Radiology 207: 79-83.

115. Nigro N, Muller B, Morgenthaler NG, Fluri F, Schütz P, et al. (2011) The use of copeptin, the stable peptide of the vasopressin precursor, in the differential diagnosis of sodium imbalance in patients with acute diseases. Swiss Med Wkly 141: w13270.

116. Pollock AS, Arieff AI (1980) Abnormalities of cell volume regulation and their functional consequences. Am J Physiol 239: F195-205.

117. Blum D, Brasseur D, Kahn A, Brachet E (1986) Safe oral rehydration of hypertonic dehydration. J Pediatr Gastroenterol Nutr 5: 232 -235.

118. Fjellestad-Paulsen A, Hoglund P, Lundin S, Paulsen O (1993) Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. Clin Endocrinol (Oxf) 38: 177-182.

119. Brewster UC, Hayslett JP (2005) Diabetes insipidus in the third trimester of pregnancy. Obstet Gynecol 105: 1173-1176.

120. Juul KV, Bichet DG, Nørgaard JP (2011) Desmopressin duration of antidiuretic action in patients with central diabetes insipidus. Endocrine 40: 67-74.

121. Dunn AL, Powers JR, Ribeiro MJ, Rickles FR, Abshire TC (2000) Adverse events during use of intranasal desmopressin acetate for haemophilia A and von Willebrand disease: A case report and review of 40 patients. Haemophilia 6: 11-14.

122. Schwab M, Wenzel D, Ruder H (1996) Hyponatraemia and cerebral convulsion due to short term DDAVP therapy for control of enuresis nocturna. Eur J Pediatr 155: 46-48.

123. Salim A, Martin M, Brown C, Belzberg H, Rhee P, et al. (2006) Complications of brain death: frequency and impact on organ retrieval. Am Surg 72: 377-381.

124. Pokracki FJ, Robinson AG, Seif SM, (1981) Chlorpropamide effect: measurement of neurophysin and vasopressin in humans and rats. Metabolism 30: 72-78.

125. Durr JA, Hensen J, Ehnis T, Blankenship MS (2000) Chlorpropamide upregulates antidiuretic hormone receptors and unmasks constitutive receptor signaling. Am J Physiol Renal Physiol 278: F799-808.

126. Loffing J (2004) Paradoxical antidiuretic effect of thiazides in diabetes insipi¬dus: another piece in the puzzle. J Am Soc Nephrol 15: 2948- 2950.

127. Kim GH, Lee JW, Oh YK, Chang HR, Joo KW, et al. (2004) Antidiuretic effect of hydrochlorothiazide in lithium-induced nephrogenic diabetes insipidus is associated with upregulation of aquaporin-2, Na-Cl co-transporter, and epithelial sodium channel. J Am Soc Nephrol 15: 2836-2843.

128. Delaney V, de Pertuz Y, Nixon D, Bourke E (1987) Indomethacin in streptozocin-induced nephrogenic diabetes insipidus. Am J Kidney Dis 9: 79-83.

129. Kim GH, Choi NW, Jung JY, Song JH, Lee CH, et al. (2008) Treating lithium-induced nephrogenic diabetes insipidus with a COX-2 inhibitor improves polyuria via upregulation of AQP2 and NKCC2. Am J Physiol Renal Physiol 294: F702-709.

130. Huerta C, Castellsague J, Varas-Lorenzo C, García Rodríguez LA (2005) Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. Am J Kidney Dis 45: 531-539.

131. Zaki M, Schöneberg T, Al Ajrawi T, Al Said AN, Sangkuhl K, et al. (2006) Nephrogenic diabetes insipidus, thiazide treatment and renal cell carcinoma. Nephrol Dial Transplant 21: 1082-1086.

132. Rivkees SA, Dunbar N, Wilson TA (1999) The management of central diabetes insipidus in infancy: desmopressin, low renal solute load formula, thiazide diuretics. J Pediatr Endocrinol Metab 20: 459-469.

133. Kirchlechner V, Koller DY, Seidl R, Waldhauser F (1999) Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. Arch Dis Child 80: 548-552.

134. Postina R, Ufer E, Pfeiffer R, Knoers NV, Fahrenholz F (2000) Misfolded vasopressin V2 receptors caused by extracellular point mutations entail congenital nephrogenic diabetes insipidus. Mol Cell Endocrinol 164: 31-39.

135. Morello JP, Bichet DG (2001) Nephrogenic diabetes insipidus. Annu Rev Physiol 63: 607-630.

136. Sohara E, Rai T, Yang SS, Uchida K, Nitta K, et al. (2006) Pathogenesis and treatment of autosomal-dominant nephrogenic diabetes insipidus caused by an aquaporin 2 mutation. Proc Natl Acad Sci 103: 14217-14222.

137. Sanches TR, Volpini RA, Massola Shimizu MH, Bragança AC, Oshiro-Monreal F, et al. (2012) Sildenafil Reduces Polyuria in Rats with Lithium-Induced NDI Am J Physiol Renal Physiol 302: F216-225.

138. Goldman MB (2010) The assessment and treatment of water imbalance in patients with psychosis. Clin Schizophr Relat Psychoses 4: 115-123.

This article was originally published in a special issue, **Metabolomics: Diabetics** handled by Editor(s). Dr. Ippei Kanazawa, Shimane University Faculty of Medicine, Japan