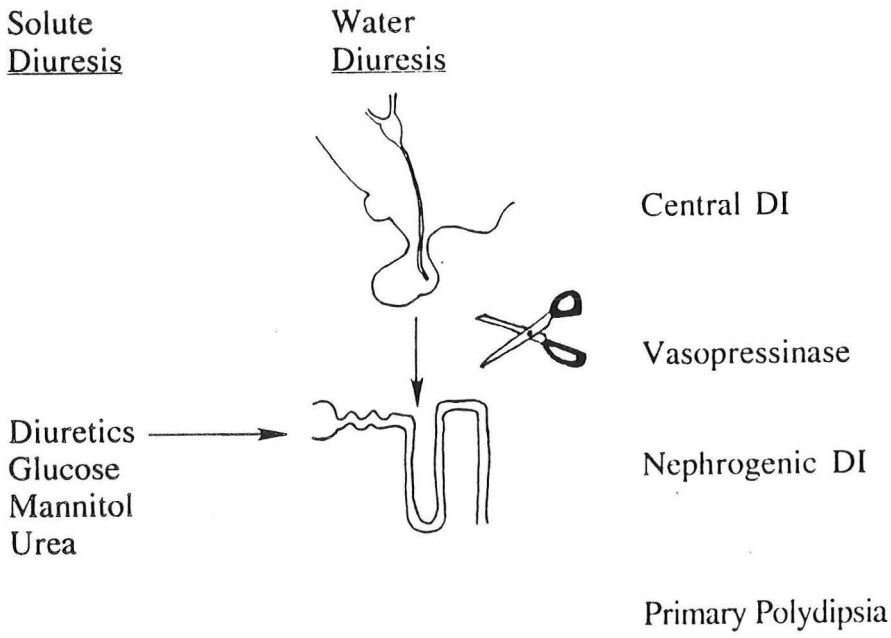
University of Texas
Southwestern Medical Center
at Dallas

Polyuria

Causes of Polyuria



Internal Medicine Grand Rounds
8 Aug 1991
Robert Alan Star, MD

Polyuria is a relatively common clinical complaint. True polyuria, i.e, urine volume of greater than 3 liters a day, is a disorder of water balance. Patients either drink too much water, or more typically, can not retain water. Plasma osmolality is typically near normal because of opposing feedback systems. The large urine volumes, sometimes associated with large losses of sodium make this a very dramatic syndrome. Fluid management in hospitalized polyuric patients is often very difficult, forcing us to appreciate the function of a normal kidney. In recent years, cell and molecular biology techniques have yielded insight into many aspects of polyuric disorders. The defects have shed light on the cellular processing of vasopressin, vasopressor signalling, and the urinary concentrating mechanism.

Physiology of normal water balance.

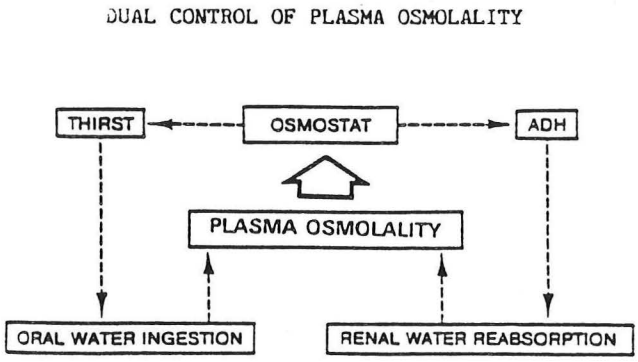


Figure 1

In healthy adults, plasma osmolality is maintained within a narrow range, deviating by only a few percent from 287 mOsm/kg, despite wide variations in water or solute intake. This consistence is achieved by the concerted action of two feedback control systems which modulate both water intake (thirst) and water loss (vasopressin) (Figure 1). The two systems are arranged so that a slight decrease in plasma osmolality suppress AVP and thirst, thereby increasing renal water loss which restores plasma osmolality. A slight increase in plasma osmolality simulates AVP release and thirst, thereby increasing water intake and minimizing renal water loss, again restoring plasma osmolality.

Figure 2 shows the extreme sensitivity of the system to changes in plasma osmolality, and how the overlapping ranges of the two systems prevent us from being thirsty all day. It is instructive to consider what happens after drinking several liters of water at bedtime, enough to decrease plasma osmolality to 275 mOsm/kg. At plasma osmolalities below 280 mOsm/kg, circulating AVP is not detectable. This causes a massive water diuresis, which increases plasma osmolality. Once plasma osmolality becomes greater than 280 mOsm/kg (the threshold for AVP release), AVP levels increase linearly with plasma osmolality. This causes urine concentration to increase, thus limiting renal water loss. At this point, the body still looses some water through sweat, respiration, and urine (total about 1 L/day. As plasma

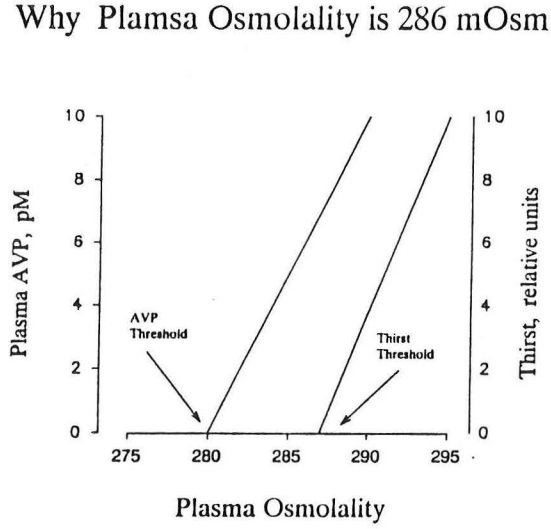


Figure 2

osmolalities increase above 290 mOsm/kg, the thirst mechanism finally becomes activated (Thirst threshold). This eventually leads to water ingestion which restores osmolality to normal. Thirst is completely suppressed, and AVP levels are slightly suppressed. This allows any excess water to be excreted. Therefore, normal plasma osmolality is maintained between these two extremes, and we are not thirsty most of the time. Instead, we drink water mainly for social reasons

Defects in either of these feedback control systems cause polyuria; the body must rely exclusively on the other system to stabilize body osmolality. These pathologic states are quite informative for understanding the true role of thirst and AVP in regulation of water balance. Abnormally increased thirst or pathologic water drinking will rapidly dilute plasma sodium, causing hyponatremia, unless the water is excreted. Since the low plasma sodium will suppress AVP release, the kidneys will excrete the ingested water. Therefore, the major role of AVP is to prevent water intoxication. On the other hand, an intact thirst mechanism is extremely important in patients with abnormal AVP release or ineffective AVP action. These patients have near normal plasma osmolalities as long as they are awake and alert. However, loss of consciousness (for example, during anesthesia) can cause rapid dehydration and hypernatremia unless water loss is prevented with AVP or replaced. Plasma osmolality can be successfully regulated without an effective renal concentrating mechanism as long as the thirst mechanism is intact and the access to water is unrestricted. Thus, the thirst mechanism is the major defense against dehydration. The only contribution of the AVP/concentrating mechanism is to lessen the dependence on the thirst mechanism and a nearby water supply and bathroom.

Causes of polyuria

True polyuria must be distinguished from a renal concentrating defect (400-500 mOsm/kg) which only slightly increases daily urine volumes (2 L/day). The latter can be caused by a multitude of diseases, while the differential diagnosis of polyuria is quite limited.

Polyuria can be caused either by a solute or water diuresis (Figure 3). A solute diuresis is usually obvious from the clinical setting or routine laboratory tests of urine. Typical causes are diuretics, massive glucosuria in uncontrolled diabetes mellitus, mannitol to control brain edema, or a urea diuresis. The latter is often not easily apparent. The most dramatic causes of pure water loss are caused by water diuresis; 43 L/d has been reported (1). Because of its overwhelming importance in control of urine volume, these disorders are classified according to AVP levels or effects. Water diuresis can be an appropriate response to water overloading, either iatrogenic or as occurs in primary polydipsia. The slight fall in osmolality suppresses AVP, thereby ensuing a water diuresis appropriate to the water overloading. On the other hand, inappropriate water loss occurs in diabetes insipidus (DI) due to lack of sufficient AVP release (central DI), destruction of plasma vasopressin by a circulating vasopressinase, or inability of the kidneys to respond to AVP (nephrogenic DI).

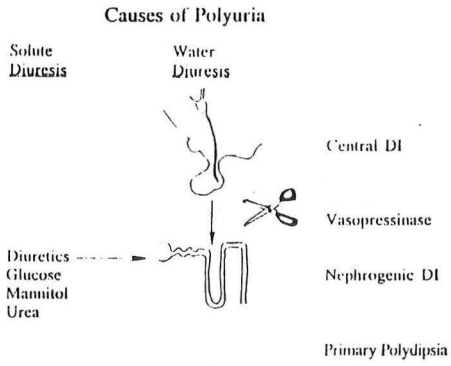


Figure 3

Normal Vasopressin Synthesis

Vasopressin is synthesized primarily in three portions of the anterior hypothalamus: the supraoptic, the paraventricular nucleus, and the suprachiasmic nucleus (Figure 4). There are two groups of cells: magnocellular (large cell bodies) and parvocellular (small cell bodies). Axons of the magnocellular neurons originating in the supraoptic nucleus and paraventricular nucleus traverse the pituitary stalk, and form axon terminals in the posterior pituitary. AVP from these axons is released in response to osmotic stimuli provided by osmoreceptors thought to reside in the organum vasculosum of the lamina terminalis region of the anterior hypothalamus (2). AVP is also release in response to baroreceptor information from receptors in the cardiac atria and carotid sinuses (2). The paraventricular nucleus also contains parvocellular neurons which release AVP into the portal capillaries in the median eminence; these neurons become important if the tract is damaged below the median eminence during surgery. Axons originating in the suprachiasmic nucleus terminate near the third ventricle, releasing AVP into the cerebrospinal fluid. These pathways are not regulated by osmolality, but may be important for establishing circadium rhythms.

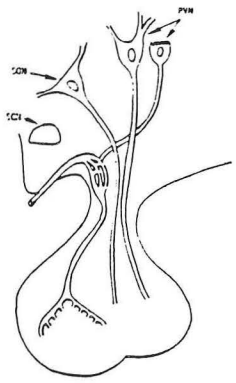
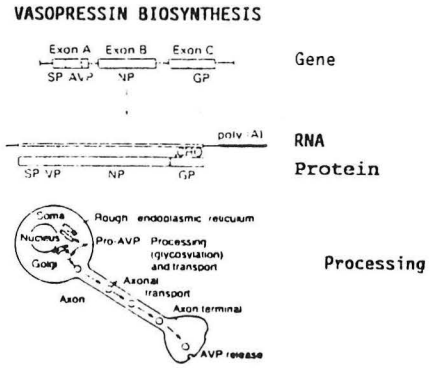


Figure 4

Vasopressin is a nonapeptide with a disulfide bond connecting cystines 1 and 6. Vasopressin biosynthesis occurs by cleavage from a larger precursor preprovasopressin, as occurs for other small peptide hormones (Figure 5). The hormone precursor contains three portions: a signal peptide to direct the peptide to an exocytic vesicle compartment, AVP, a neurophysin II, and a C-terminal glycopeptide of unknown function. After synthesis, the signal peptide is removed leaving the prohormone. Provasopressin is cleaved in to 3 peptides, and the C-terminal amino acid of AVP is amidated. The neurophysin acts as a carrier for AVP in the secretory granule. It tightly associates with vasopressin at the acidic pH of the secretory granule, and dissociates from AVP at the pH of extracellular fluid. The neurophysin may also serve to regulate proteolytic cleavage of AVP from its precursor by carboxypeptidase H (3). mRNA levels for both AVP and carboxypeptidase are coordinately regulated by osmolality (3).

The vasopressin gene is located on chromosome 20, near the oxytocin gene. Both genes were formed by gene duplication from a single ancestral gene. The AVP gene is 2000 base pairs in length, comprising three exons separated by two non-coding introns. The first exon codes for the single sequence, AVP itself, and a small portion of the neurophysin. The second exon and part of the third exon code for



From Schmale et al. Kidney Int 32:58, 1987;
Ganten et al. Hypertension 17:843, 1991

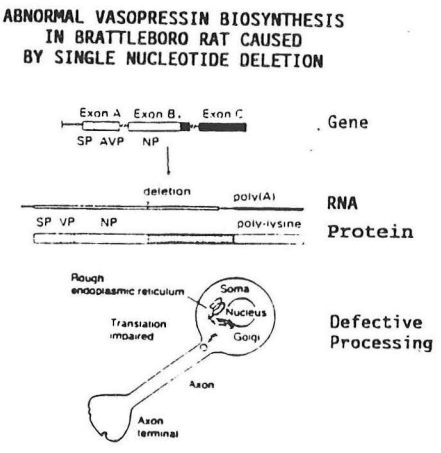
Figure 5

the remainder of the neurophysin. mRNA levels for the vasopressin gene increase during dehydration, but only in the supraoptic nucleus and paraventricular nucleus, the portions of the brain that receive osmoreceptor information.

Central Diabetes Insipidus

AVP secretion is impaired in a number of clinical disorders which disrupt the osmoreceptors, hypothalamic nuclei, or the neurohypophysis. The most common etiologies of central diabetes insipidus are head trauma from automobile accidents, following neurosurgery for pituitary tumors or craniopharyngiomas, following hypoxic-ischemic encephalopathy and an idiopathic form (4,5). MRI scans in patients with head trauma have shown rupture of the pituitary stalk. A significant fraction of cases (perhaps 33%) are idiopathic, presumably autoimmune in etiology (6). These patients do not become symptomatic until their mid-teens when urinary volumes become greater than 3-4 liters. Less common causes are from mass lesions or infiltrations. Central diabetes insipidus has been seen as a terminal event in healthy young women who develop symptomatic hyponatremia following elective procedures; brain edema causes pituitary and hypothalamic infarction (7). Central diabetes insipidus has also been reported to be transient (8), and limited to the recumbent position (9). Several drugs suppress AVP release: alcohol, vinblastine, dilantin (transiently), clonidine and narcotic agonists. However, these rarely cause sustained polyuria.

Familial Form. Central diabetes insipidus also occurs in an extremely rare familial form which accounts for 1-3% of the idiopathic group. It is transmitted as a autosomal dominant trait (10). Family members may regard their polydipsia as a family idiosyncrasy and refuse therapy. The disease is not present at birth, which distinguishes it from X-linked nephrogenic diabetes insipidus; rather, it begins in infancy or childhood. Post mortem studies in a few patients have shown loss of magnocellular neurons, with relative sparing of parvocellular neurons (11). This suggests that there is selective degeneration of AVP containing neurons which project to the posterior pituitary. Oxytocin production is normal.



From Schmale et al. Kidney Int 32:58, 1987; Ganten et al. Hypertension 17:843, 1991

Figure 6

In the early 1960's, an animal handler in Brattleboro Vermont noticed a cage of rats that were drinking tremendous quantities of water. Investigation by Valtin and colleagues found that homozygotes of this strain had hereditary diabetes insipidus caused by a deficiency of circulating AVP. Subsequent studies showed abnormal AVP biosynthesis, axonal transport, and lack of neurophysin II [reviewed in (12)]. The Brattleboro rat has served as a model for human hereditary diabetes insipidus, and has been invaluable for study of the renal concentrating and diluting mechanisms. Rat and human disease differ since the genetic defect is expressed at birth in rats, and is due to a biosynthetic failure rather than loss of neurosecretory neurons. In 1984, Schmale and Richter

showed that the genetic mutation is a single base deletion coding for the 64th amino acid residue in the neurophysin portion of the AVP gene (Figure 6) (13). The mutant gene is correctly transcribed and spliced, but the resulting mRNA is not efficiently translated. The resulting frame shift mutation extinguishes a stop codon and glycosylation site, producing an altered neurophysin with a C-terminus polylysine tail which is unable to leave the ribosome or becomes locked in the rough endoplasmic reticulum (12). Hypothalamic mRNA for vasopressin does not increase in response to fluid deprivation (14) unless rats are treated with vasopressin for two weeks (15).

In human autosomal dominant central diabetes insipidus, linkage studies in two pedigrees have suggested that the genetic locus is within or near the AVP-neurophysin gene (16). In a recent publication, the exons of the AVP-neurophysin gene were sequenced in two patients with familial diabetes insipidus (Figure 7). They were found to be heterozygous for a single base pair mutation (G1959A) resulting in a substitution of glycine for serine at position 57 in the neurophysin (17). This mutation was not found in 10 patients with idiopathic central diabetes insipidus or 5 normal patients, suggesting that it might be responsible for AVP deficiency in these patients. The mutation abolishes a MspI restriction site which facilitates screening for this mutation. The physiological significance of this mutation is unknown, but it is speculated to influence AVP binding or self-association of the neurophysin, which might allow proteolytic degradation of AVP or impair axonal transport.

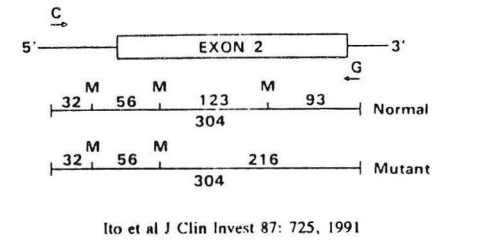


Figure 7

Stalk Section. Polyuria is frequent following neurosurgical operations, because of delayed excretion of peri-operative fluids, steroid induced hyperglycemia, or mannitol. Postoperative diabetes insipidus occurs in up to 75% of suprasellar operations for craniopharyngioma in children, and in 10-20% of transsphenoidal operations in adults (4). Interruption of vasopressin neurons at any level causes a retrograde degeneration of the hypothalamic nuclei. The extent of degeneration determines the extent of post-operative diabetes insipidus. In general, polyuria will not occur until greater than 90% of the AVP secretory capacity is lost. Polyuria usually starts within 24 hours after surgery; a very early onset is associated with major hypothalamic damage. There are three pattern of injury. In about 50% of cases, especially if

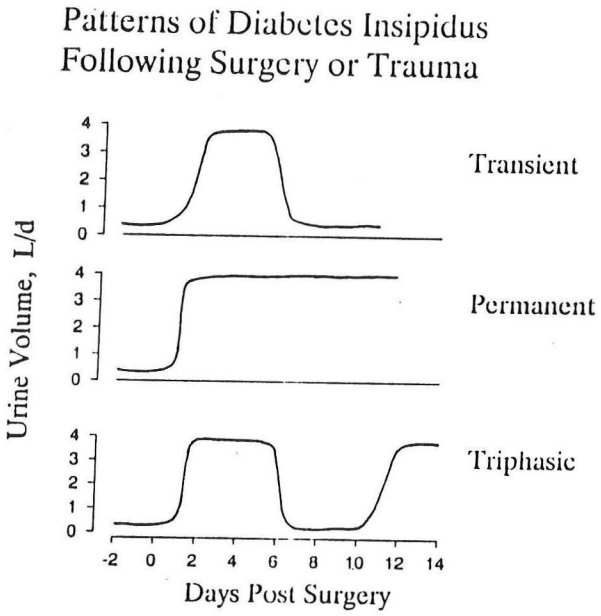
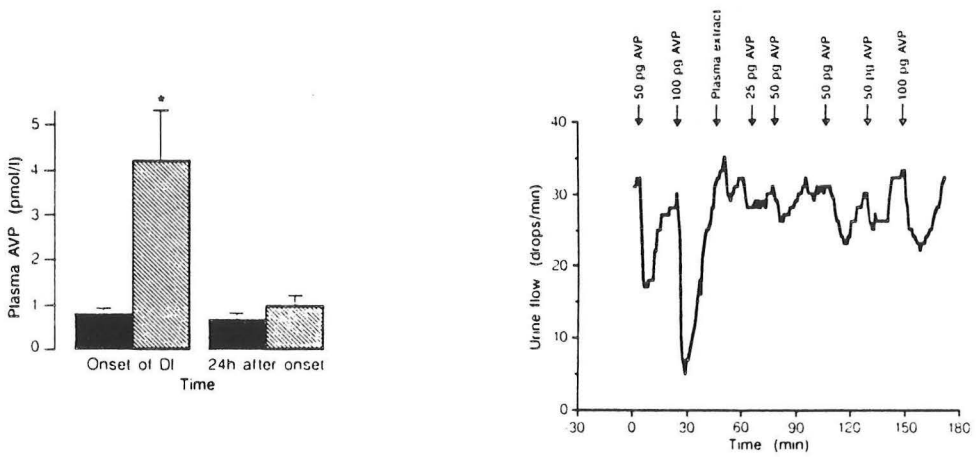


Figure 8

surgery is limited to the pituitary fossa, the diabetes insipidus is transient, resolving over 2-5 days (Figure 8). In 1/3 of cases, generally following high stalk section or suprasellar operations, diabetes insipidus is prolonged or permanent. In the remainder, urine flow follows a triphasic response; an initial transient polyuria for 4-8 days followed by an antidiuretic interphase for 1-14 days, then followed by permanent polyuria (18). The antidiuretic phase is thought to represent slow non-osmotically independent release of AVP from the degenerating neurons. This phase is important to recognize, because the resulting SIADH syndrome can lead to hyponatremia if water intake is excessive. Once stores are depleted, the diabetes insipidus becomes permanent. This phase must be differentiated from the impaired water excretion of glucocorticoid deficiency.

The initial polyuric stage was thought to represent inhibition of AVP release because of hypothalamic dysfunction. Indeed, vasopressin levels following trans-sphenoidal surgery are low



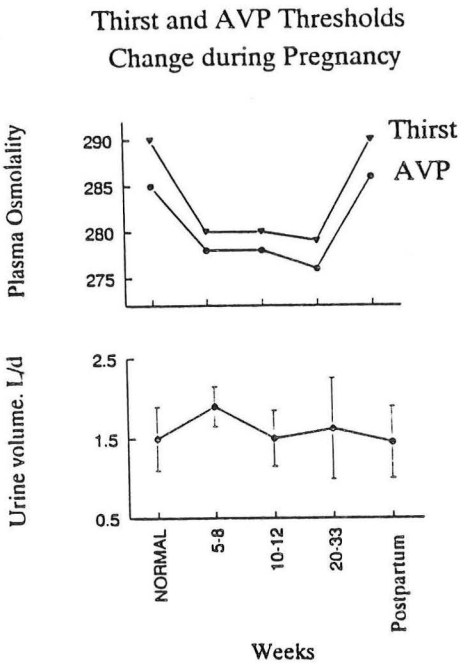
Seckl Lancet 355: 1353, 1990

Figure 9

(19). However, after trans-frontal surgery for craniopharyngiomas, plasma vasopressin levels are high, not low (Figure 9) (19). Furthermore, the plasma is not antidiuretic using a rat bioassay system, and the plasma greatly attenuates the antidiuretic response to standard AVP. These results suggest that hypothalamic surgery releases an AVP antagonist from the damaged hypothalamus or neurohypophyseal system. It is unknown if this substance binds authentic AVP, is a neurophysin breakdown product, a partially processed from of pro-AVP peptide, or a component of craniopharyngioma cyst fluid.

Vasopressinase

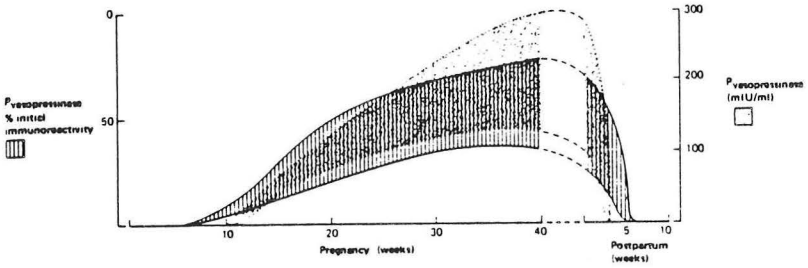
An unusual form of polyuria has been found in some women during and after pregnancy (20-24). The women develop severe thirst, polydipsia and polyuria during the third trimester of pregnancy and/or the post partum period. Glucosuria is absent. Pregnancy decreases the threshold for both AVP release and thirst (Figure 10). These changes occur during the first weeks of gestation, and remain low until the post partum period (25). It is postulated that human chorionic gonadotrophin is responsible, since similar changes occurred in a patient with a



Davidson et al J Clin Invest 81: 798, 1988

Figure 10

Plasma Vasopressinase During Pregnancy



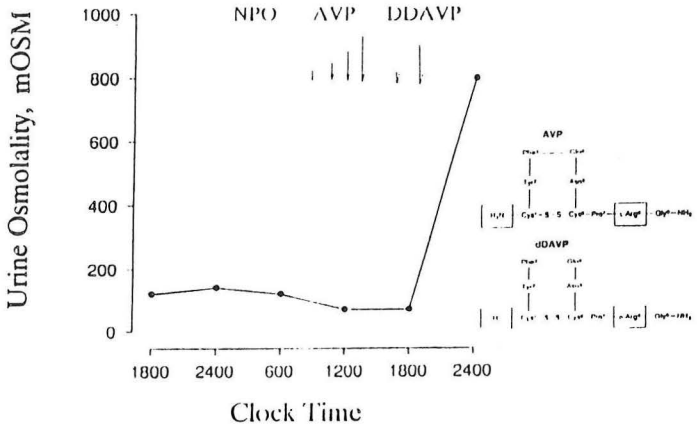
Davidson et al J Clin Invest 83:1313, 1989

Figure 11

hydatiform mole, and in normal subjects given hCG. Since both thirst and AVP thresholds change, these changes by themselves would decrease plasma osmolality by 10 mOsm/kg below normal, without affecting urine volume.

The most unusual aspect of this syndrome is its transient nature. A likely explanation of the transient polyuria is the presence of vasopressinase, a cystine aminopeptidase that is made by the placenta (Figure 11). Vasopressinase circulates in pregnant women during pregnancy, and decreases by about 25%/day during the post partum period (22,23). In some women, vasopressinase is present in extraordinary high levels (20,21), causing extreme polyuria even in the presence of normal AVP release and normal kidneys. In women with partial central or partial nephrogenic diabetes insipidus, only slight reductions in plasma AVP level can cause decompensation in previously asymptomatic patients (24). This disorder can be treated with DDAVP, a V_2 selective AVP

DDAVP Casuse Prompt Antidiuresis
in Transient Diabetes Insipidus of Pregnancy



data from Durr et al. NEJM 316:1070, 1987

Figure 12

analogue which resists degradation by vasopressinase (26) because the terminal cystine is blocked (Figure 12). In summary, these patients have diabetes, but insipidus rather than mellitus.

Control of renal water excretion by AVP

Vasopressin exerts its effects at the cell surface by activation of two classes of vasopressin receptors [reviewed in 773]. The V_1 receptors are found on smooth muscle cells and cause vasoconstriction by activation of phospholipase C, which releases inositol triphosphate and diacylglycerol. These mediators raise cell calcium and activate protein kinase C. A second vasopressin receptor, V_2 is more important for water balance. V_2 receptors activate adenylyl cyclase through a G-protein mechanism, generating cAMP. This mediates the antidiuretic response, causes release of renin, factor VIIIc, and von Willebrand factor high molecular weight multimers, and paradoxically causes vasodilation. This release of vWF and factor VIII has been used clinically to improve coagulation in several hemostatic disorders. V_2 agonists increase in forearm blood flow while V_1 agonists increase digital blood flow (27,28).

VASOPRESSIN RESPONSIVE SITES

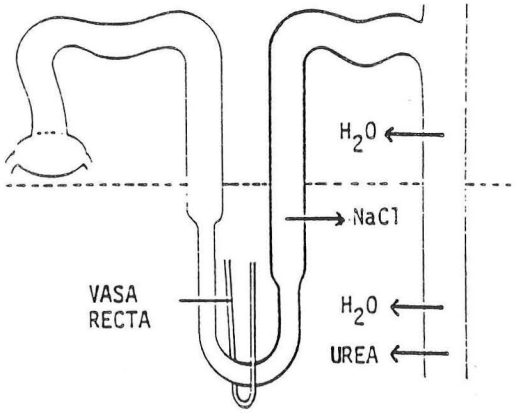


Figure 13

AVP INCREASES APICAL MEMBRANE WATER PERMEABILITY IN COLLECTING DUCT

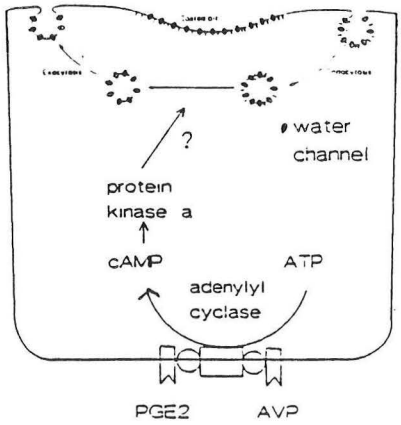


Figure 14

Figure 13 shows the AVP-responsive sites of the nephron that are important for renal water conservation. Approximately 66% of the water filtered at the glomerulus is absorbed by the proximal tubule and loop of Henle by mechanisms which are largely independent of AVP. The thick ascending limb absorbs sodium chloride but is impermeable to water, resulting in dilution of the lumen to about 100 mOsm/kg. In the absence of AVP, much of the collecting duct system is impermeable to water. The major exception is the terminal portion of the inner medullary collecting duct, which is water-permeable even in the absence of AVP (29). The resulting water absorption dilutes the medullary interstitium, removing the driving force for water absorption. Therefore, most these 20-30 liters would be excreted by the kidney. This number is important to remember when we discuss Primary Polydipsia, where patients do drink this amount or more a day. If they have a normal kidney, and AVP is suppressed, they can excrete 20-30 liters a day without becoming hyponatremic.

Water is absorbed by passive transport across the collecting duct, driven by a transepithelial osmotic gradient. Vasopressin acts at four sites in the kidney to promote the

formation of a concentrated urine (Figure 13). AVP increases interstitial osmolality by its actions to increase salt transport in the medullary thick ascending limb of Henle and in the cortical collecting duct (30,31). It increases water permeability in the cortical, outer medullary, and inner medullary collecting duct (29,32,33). Thus, AVP acts by two mechanisms to increase renal water absorption: it both increases the osmotic driving force for water absorption, and increases the water permeability. Urea is very important in the concentrating mechanism (34,35). AVP increases the urea permeability of the inner medullary collecting duct, preventing urea which has been concentrated in the lumen by water abstraction, from acting as a osmotic diuretic (34-36).

The mechanism by which AVP increases the water permeability of the collecting duct principle cell is shown in Figure 14. In the absence of AVP, the apical membrane is the barrier to water absorption across the cell (37). AVP increases the water permeability by binding to a V_2 receptor in the basolateral membrane. Through a series of intermediate steps which are poorly understood, the apical membranes are made water permeable by insertion of vesicles containing water channels (38). Recently, several groups have shown that vasopressin acts on both the luminal and basolateral membrane. Luminal vasopressin inhibits the water permeability by about 50%. The physiologic significance of this effect is unknown, but it could serve as a negative feedback to limit urine concentration.

Nephrogenic Diabetes Insipidus

Vasopressin resistant diabetes insipidus may be caused by two classes of defects: 1) the renal tubule is unresponsive to vasopressin, or 2) the renal counter-current multiplication system fails to generate an appropriately hypertonic medullary interstitium. Figure 15 gives a list of the usual causes of nephrogenic diabetes insipidus. The non-familial forms are either from electrolyte disorders (hypokalemia, hypercalcemia) or drug-induced (lithium, demeclocycline, methoxyflurane). The mechanisms are not well understood; some also cause an increase in thirst (especially hypokalemia). Sickle cell trait and anemia cause destruction of the normal renal medullary architecture because the hypoxic medulla predisposes to sickling. This causes destruction of the thick ascending limbs and infarction of the medulla.

Causes of Nephrogenic DI

Congenital

Drugs: Lithium
Demeclocycline
Methoxyflurane

Electrolyte disorders:
Hypercalcemia
Hypokalemia

Amyloidosis, Sjögren's syndrome
Sickle cell anemia
Urinary tract obstruction

Figure 15

Familial. A rare but extremely interesting form of diabetes insipidus occurs in families. Many of the North American cases can be traced to the descendants of a Scotsman who arrived from Nova Scotia in 1767 on the ship Hopewell (39). McIlraith, in 1892, was the first to describe three generations of a family with extreme polyuria; males had 'extreme thirst and passed large quantities of watery urine'. Females were slightly affected (40). The transmission was 'heredity occurring chiefly in the males on the female side of the house', i.e., X-linked

recessive. In 1947, Williams and Henry named the disease nephrogenic diabetes insipidus, stressing that the underlying defect was renal tubule insensitivity to AVP (41). The clinical and pathophysiological features of the disease are succinctly described by Waring et al. (reordered for clarity): "The syndrome is characterized by onset shortly after birth, .. polydypsia and polyuria which do not respond to pitressin, high serum values for sodium and chloride, .. rapid dehydration if fluids are reduced or withheld, inability to excrete urine of a high specific gravity, familial incidence and occupance in boys only (?), persistent constipation, and vomiting (during the first three months of life)" (42).

Afflicted males usually present in infancy with polyuria, polydipsia, dehydration, hypernatremia, hyperthermia, vomiting, constipation, and failure to thrive, all caused by the inability of the kidneys to excrete a concentrated urine. If 20% of the renal water load is excreted, this can amount to 50-85% of total body water per day. Small wonder that infants are so susceptible to dehydration, since they do not have access to free water. The vomiting is a consequence of insufficient gastric capacity or energy to consume the necessary amounts of fluid. During intercurrent infections and illnesses (especially diarrhea, vomiting, or fever), the increased water needs are especially difficult to meet. The growth retardation and mental deficiency are probably from chronic dehydration (43), but may be prevented by superlative care (44).

Female carriers usually show some impairment in maximal urine concentrating ability, but the defect can be quite variable. As will be discussed below, detection of carrier state had been difficult because of variable expression of concentrating defects; the recent discovery that DDAVP-stimulated renin release is abnormal in carriers should help in this regard (45). The gene involved have not been identified, and the molecular pathogenesis of X-linked nephrogenic diabetes insipidus is unknown. However, a mutation in the V2 vasopressin receptor or receptor complex is strongly suggested by two lines of evidence:

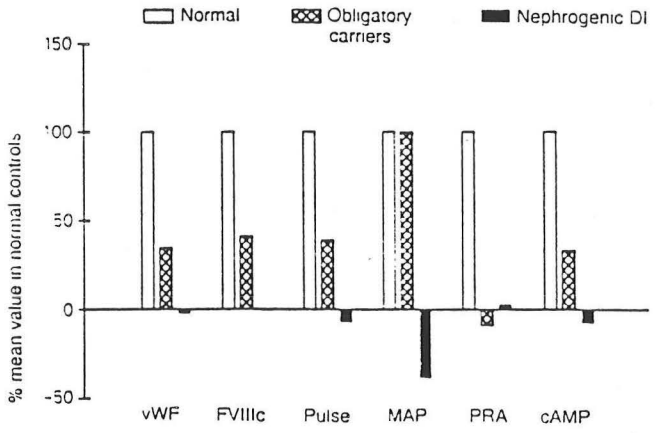


Figure 16

First, DDAVP, a strong V_2 receptor agonist, fails to elicit increases in urinary concentration, factor VIIIc release, von Willebrand Factor multimer release, renin release, and large blood vessel vasodilation (Figure 16) (46-50). Storage pools are normal (49). V1 responses are normal (49,51). Patients with central diabetes insipidus have normal responses to V2 (47). Taken together, these results indicate that patients with nephrogenic DI have a specific renal and extra-renal V2 receptor/receptor complex defect. Second, the X-lined nephrogenic diabetes insipidus gene has been mapped to the subtelomeric region of the X chromosome (52). Introduction of this region from a normal X chromosome into somatic cell hybrid lacking AVP receptors induces vasopressin binding and vasopressin stimulated cAMP

accumulation (53). The simplest interpretation is that this portion of the chromosome contains a V_2 vasopressin receptor; whether it contains a small regulatory protein or some component of a signalling system which activates latent inactive receptors awaits future studies.

Hereditary Nephrogenic Diabetes Insipidus in Mice Caused By Overactivity of Phosphodiesterase

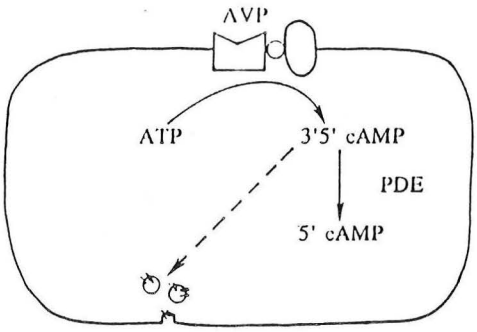


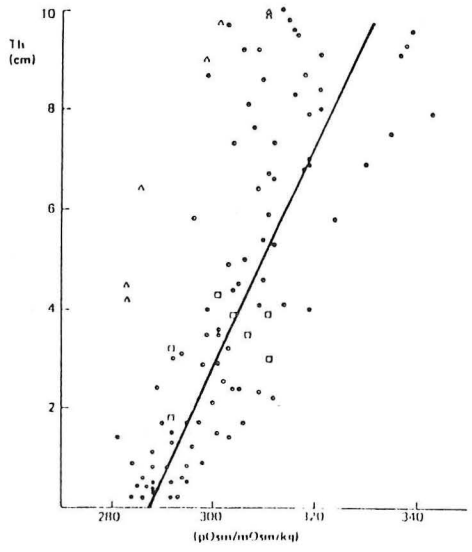
Figure 17

Hereditary vasopressin-unresponsive diabetes insipidus also occurs in the diabetes insipidus +/+ severe strain of mice. This mouse model has increased activity of cAMP phosphodiesterase, the enzyme which destroys cAMP (Figure 17) (54). Addition of rolipram and cilostamide, specific inhibitors of phosphodiesterase type III, restores normal vasopressin-stimulated cAMP accumulation to normal in tubules from all portions of the collecting duct (55,56). The mice may also have a defect in the coupling of the vasopressin receptor to the catalytic subunit of the adenylyl cyclase. How this model relates to human disease is unknown since Rolipram does not cause an antidiuresis in patients with X-lined nephrogenic diabetes insipidus (57).

Thirst in Central and Nephrogenic Diabetes Insipidus

Most patients with diabetes insipidus have normal thirst mechanisms, although thirst abnormalities may co-exist with vasopressin deficiency (Figure 18) (58). As noted above, a normal thirst mechanism allows urinary losses to be properly replaced, so that dehydration is seldom detectable. However, if the patient is hospitalized, bedridden or becomes unconscious, they may rapidly become dehydrated and severely hypernatremic.

Thirst in Diabetes Insipidus



Thompson and Baylis, Quart. J. Med. 65: 853, 1987

Figure 18

Primary Polydipsia

Inappropriate activation of drinking, or pathologic thirst, occurs when a patient continues to drink water despite normal or supra-normal hydration. Primary polydipsia can occur because of direct stimulation by hypokalemia, hypercalcemia or angiotensin II, irritation due to mass or inflammation, or in psychogenic polydipsia. The latter is found in patients with a history of psychosis, hysteria or depression who often have an irrational faith in the therapeutic value of water to rid themself of hiccups, worms, poisons, or cancer. This syndrome was first described by Sleeper and Jellinek in 1936, who

noted that many schizophrenic patients excrete large volumes of urine (59). In their 1959 classic paper, Barlow and de Wardener called this compulsive water-drinking (60). Most of the patients had a previous psychological disorder ranging from hysteria, delusions, depression; only one patient was normal. The water consumption, 5-20 L/day, fluctuated irregularly from hour to hour and day to day; relapses seemed to correlated with clinical remission. Mean plasma osmolality was lower than normal, in contrast to patients with diabetes insipidus (type unspecified) who had osmolalities higher than normal (Figure 19). Only one of 9 patients was hyponatremic.

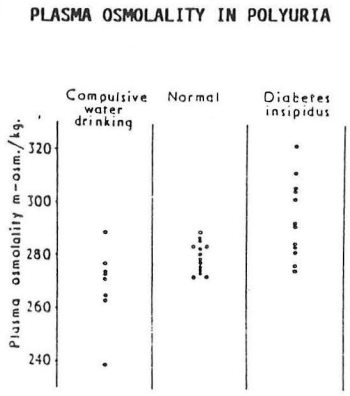


Figure 19

However, other studies have shown that some patients with psychogenic polydipsia are hyponatremic (1,61-64). Dr. Robert Cronin recently described 11 patients who were hospitalized a total of 70 times for hyponatremia (64). Unlike previous reports, these patients were not hospitalized schizophrenics, but there was a high incidence of chronic alcoholism, intractable hiccups, self-induced vomiting, and laboratory evidence of rhabdomyolysis. This hyponatremia is surprising, because the amount of water ingested should not be sufficient to cause hyponatremia in otherwise normal patients (i.e., normal kidneys and AVP levels suppressed). A SIADH-like syndrome has also been proposed, especially in patients with vomiting and nausea. Hariprasid in 1980 found 20 psychotic patients with hyponatremia (98-124 mEq/L) and psychogenic polydipsia; none were on lithium (1). Three patients were not on any psychotic drugs, and intensified treatment caused the psychosis to improve and polydipsia to decrease, indicating that polydipsia is a result of the psychosis and not of drug therapy. Urine became dilute during a water load, and exceeded plasma osmolality during fluid depravation. However, since the latter occurred at a plasma osmolality between 242-272 mOsm/kg, he suggested that the patients had a reset osmostat, which sustained the hyponatremia.

Formal AVP/thirst axis testing by Robertson et al. on 8 psychotic patients with polydipsia and hyponatremia and 7 psychotic patients with normal water intake revealed 1) downward resetting of the AVP-stat to 131 mM, 2) downward resetting of the thirst-stat, and 3) a small diluting defect (63). The observed changes in osmoregulation of vasopressin and thirst can easily explain the mild basal hyponatremia. A maximal water diuresis can occur only when vasopressin is suppressed, at sodium levels below 131 mM. The patients are still thirsty at this plasma sodium, so they will have a basal sodium of 131 mM, while excreting the extra water as dilute urine. Episodes of more profound hyponatremia are more difficult to explain unless one or more of these defects in AVP secretion or AVP action become more severe; there is some evidence to support more severe defects that coincide with

Mechanisms of Hyponatremia in Psychogenic Polydipsia

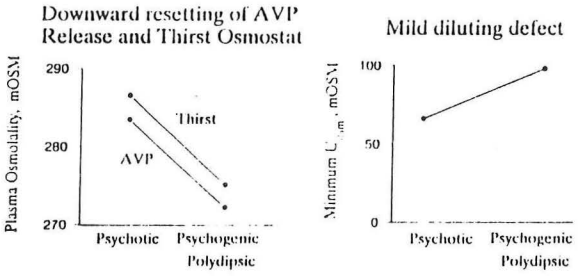


Figure 20

exacerbation of psychosis [reviewed in (1)]. While the diluting defect (Minimum Uosm 98 vs 66) is only mild, it is sufficient to prevent the patients from excreting more than 15 L of water a day; a normal kidney can excrete about 25-27 L of water a day.

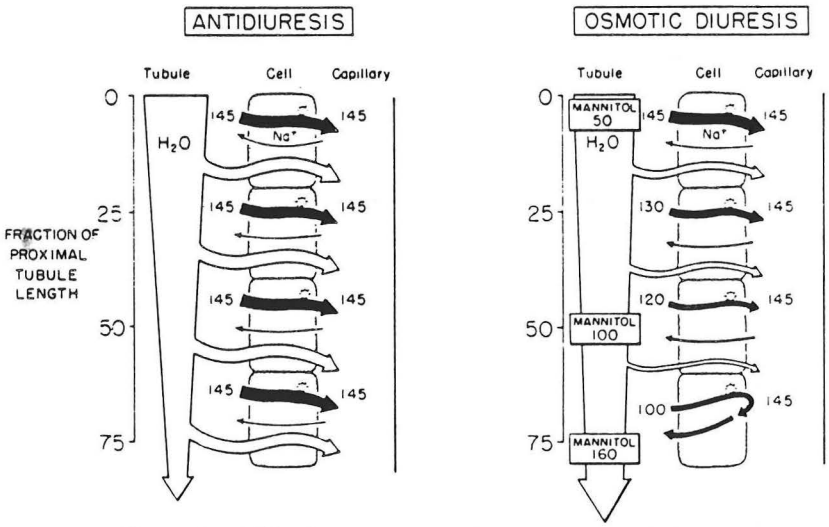
In summary, patients with compulsive water intake usually have slightly low plasma sodium concentrations. Some patients, particularly those with profound psychosis, become hyponatremic because of a downward resetting of the AVP and thirst osmoreceptors.

Robertson has also described a rare syndrome called dipsogenic polydipsia in 8 patients (65). These patients are not psychotic. These patients have inappropriate thirst, but their basal plasma sodium is not low as expected in psychogenic polydipsia. If anything, there plasma sodiums are in the upper range of normal. Formal AVP and thirst testing disclosed reversal of the normal thirst and AVP thresholds such that thirst occurred at levels of plasma osmolality below that required to secrete vasopressin. 'The patients drink themselves into a water diuresis' (65). These patients are essentially untreatable; DDAVP can lower plasma sodium and diminish thirst, but only at levels that induce signs and symptoms of water intoxication.

Osmotic Diuresis.

Osmotic diuresis are most commonly caused by glucose, mannitol, sodium chloride, and or urea. An osmotic diuresis causes large urinary losses of sodium and water, leading to volume depletion and hypernatremia unless urinary losses are replaced. The mechanism of the diuresis depends on the solute involved. Loop diuretics such as furosemide and bumetanide inhibit NaCl absorption in the thick ascending limb, thus impairing the urinary concentrating mechanism.

Na and H_2O Reabsorption in Proximal Tubule During Antidiuresis and Water Diuresis



Gennari and Kassirer, N Engl J Med 291: 714, 1974

Figure 21

Mannitol and glucose are low molecular weight substances which are freely filtered at the glomerulus. Because they are impermeable or relatively impermeable, their concentration in the

tubule lumen increases as water is reabsorbed. The presence of a non-resorbable molecule reduces reabsorptive water flux, reduces convective sodium reabsorption, and increases diffusive backflux of sodium across the tight junction (Figure 21) (66,67). The net result is decreased proximal tubule water and salt absorption. The effect of this increased load to the loop segment is incompletely understood. It is generally assumed that the high distal delivery of salt and water to the collecting duct system overwhelms the capacity of the collecting duct. The high flow rates wash urea out of the inner medulla, thus inhibiting the urinary concentrating mechanism. The results is polyuria with isosthenuria. Urine sodium is 50-75 mOsm, equivalent to the loss of 1/2 normal saline. The loss of fluid that is hypotonic to extracellular fluid results in volume depletion, and dehydration with increasing plasma sodium (68,69). It is important to remember that the osmotic agent obligates sodium excretion even in during severe volume depletion.

Urea diuresis occurs in the clinical setting of high-protein tube feedings or iv hyperalimentation (70-73). Urea is formed from hepatic protein metabolism. Unlike mannitol or glucose diuresis, urea diuresis is associated with a concentrated urine (700-900 mOsm/kg) (69,74). Urea commands less water for its excretion than other urinary solutes because the terminal portion of the inner medullary collecting duct is permeable to urea (29,34,75). This allows urea to be reabsorbed in to the interstitium, enhancing rather than detracting from the ability of the kidney to form a concentrated urine. Seldin and Tarail found that urea diuresis also increases salt excretion, but the effect is less than seen during mannitol infusion (69). Furthermore, volume depletion can suppress urine sodium excretion (71). This can result in hypernatremia if urinary losses are not replaced. This leads to the seemingly contradictory clinical situation of hypernatremia with a maximally concentrated urine. However, urea is not an effective osmole because it permeates cells (36,76). Only urinary sodium and potassium are effective osmoles. Therefore, the urine is <u>hypotonic</u> to plasma (similar to D1/5W). Loss of a hypotonic fluid will cause hypernatremia. Patients become hypernatremic if they are unable to drink water to satisfy their thirst. Renal water loss obligated by urea (or other unmeasured solute) is called "electrolyte free water" or EFW (73,77,78). It can be calculated from equation 1,

where V is the urine flow rate in L/d, P_{Na} is plasma sodium, and $U_{Na\ is}$ urine sodium, and U_K is urine potassium.

$$V_{EFW} = V \left(1 - \frac{U_{Na}+U_K}{P_{Na}} \right) \qquad (1)$$

Evaluation of Polyuria

Correct diagnosis of the specific cause of polyuria is critical. For example, incorrect diagnosis and treatment of a patient with primary polyuria with AVP or DDAVP could cause life-threatening hyponatremia. The diagnostic approach is outlined in Figure 22. The first question is: Is the diuresis caused by solute or water diuresis? While often this is obvious from the clinical setting, at times the differentiation may be difficult. In addition, hospitalized patients may present with simultaneous water and solute diureses (73). The second question is: Is the diuresis appropriate on inappropriate? Appropriate water diuresis are seen in patients with water overloading (either patient induced or iatrogenic), while appropriate solute diureses occurs in patients recovering from any form of volume expansion. Central or nephrogenic diabetes causes an inappropriate water diuresis which causes a secondary polydipsia. Inappropriate solute diuresis are very common; either as a result of glycosuria from uncontrolled diabetes, or less

Differential Diagnosis: Important Questions

1. Is the diuresis a solute or water diuresis?

2. Is the diuresis appropriate or inappropriate?

Major causes of polyuria

	Appropriate	Inappropriate
Water Diuresis	Primary Polydipsia D5W loading	Central DI Vasopressinase Nephrogenic DI
Solute Diuresis	Volume Expansion	Hyperglycemia High-protein feedings Mannitol

Figure 22

commonly, due to mannitol or high-protein enteral feedings. They should be suspected in patients with hypotension, doughy skin turgor, hypernatremia, and renal insufficiency.

Correct differentiation between solute and water diuresis is quite easy (Figure 23). In outpatients, a simple dip-stick test can exclude glucosuria. In inpatients, the cause is usually obvious from the clinical setting: mannitol in neurosurgical patients, urea in patients on high-protein feedings or hyperalimentation, or salt diuresis in patients following relief of urinary obstruction or given large volumes of normal saline. However sometimes the distinction is difficult. A spot urine osmolality is often helpful. A U_{osm} greater than 400 mOsm/kg indicates a solute diuresis. Measuring urine Na, glucose, urea concentrations can identify the major solute which is causing the diuresis. When sodium is the major solute, the diuresis is almost always appropriate as discussed above, whereas other solute diureses are always inappropriate to the patient's state of hydration. A U_{osm} below 150 mOsm/kg generally indicates a water diuresis; these patients need further study outlined below to determine its cause.

Is the diuresis a solute diuresis or water diuresis?

1. Urine osmolality from spot urine:

   < 150 mOsm/kg ——→ Water Diuresis

   300 mOsm/kg

   > 400 mOsm/kg ——→ Solute Diuresis

2. Calculate solute excretion rate ($V \cdot U_{osm}$) from timed urine collection:

   < 1000 mOsm/d ——→ Water diuresis

   > 1000 mOsm/d ——→ Solute Diuresis

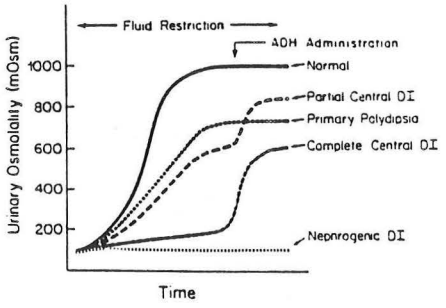
Figure 23

A U_{osm} close to 300 mOsm/kg is usually indicative of a solute diuresis, although partial defects in AVP secretion or action can also cause this picture. However, in the latter case, the

patients are unlikely to be polyuric since a normal solute excretion rate will obligate only 2-3 liters a day of urine. If there is any doubt, the solute excretion rate can be measured on a timed urine collection. The body normally excretes about 900 mOsm/day (400 mOsm inorganic ions and 500 mOsm/day urea) (79), so values in excess of this represent a solute diuresis. Occasionally, both water and solute diuresis coexist (73). These are detected by measuring both solute clearance and electrolyte-free water clearance (73).

Diagnosis of the cause of a water diuresis. Differentiation among the various causes of water diuresis while the patient is in a normal steady state (i.e., drinking water) is often very difficult. However, there are several clues that are helpful: 1) A desire for ice water is common in patients with central diabetes insipidus (80). These patients are indeed very thirsty and ice water quenches thirst rapidly through stimulation of oropharyngeal receptors. 2) A abrupt onset also suggests central diabetes insipidus; nephrogenic diabetes insipidus usually begins more slowly. 3) Moderate polyuria (4-5 L/d) indicates acquired nephrogenic diabetes insipidus from drugs or electrolyte disorder. 4) Plasma sodium is usually said to help distinguish appropriate polyuria (low Na) from inappropriate polyuria (high Na), but there is considerable overlap (Figure 21) (60).

Effect of Fluid Restriction and AVP Administration on Urine Osmolality



Alpern et al in **Fluids and Electrolytes**, p. 17, 1990

Figure 24

More definitive diagnosis is possible by a watching if and how the patient shifts from a steady state water diuresis to a steady state antidiuresis (Figure 24). This provocative test is accomplished by interrupting the thirst feedback loop with water restriction. Once the patient to becomes hypernatremic, normal central mechanisms should release endogenous AVP and raise urine osmolality. The urine volume, urine osmolality, and body weight are measured hourly until either plasma sodium reaches 145-150 mM (to ensure significant stimulus for AVP release) or urine concentration reaches a plateau ($<$ 30 mOsm/kg increase in two consecutive hourly specimens) (81). It is essential that AVP not be given before endogenous AVP levels are maximal, to avoid incorrect interpretation of the test. The second stage of the test is to give AVP (5 units iv or DDAVP 10 μg by nasal insufflation), and repeat the measurements for up to 3 hours.

Patients must be observed carefully during this test. Patients with high urine flows ($>$ 700 ml/hr) can become volume depleted very rapidly. Patients with primary polyuria have been known to find bizarre sources of water. Hypernatremic patients do not need the dehydration portion of the test since their AVP levels should be already elevated.

Figure 24 shows the 5 different patterns of response. In normals, the urine becomes maximally concentrated, and exogenous AVP has no additional effect because endogenous AVP levels are already elevated. Patients with nephrogenic diabetes show no response to dehydration or administration of AVP. Patients with complete central diabetes insipidus will not respond to

water restriction alone since endogenous vasopressin is lacking, but they will respond to exogenous vasopressin. Patients will primary polydipsia will show urinary concentration in response to endogenous AVP released during dehydration, but no response to exogenous AVP since AVP levels are already maximal. Finally, patients with partial central diabetes insipidus will partially respond to dehydration, and will show a further increase in urine osmolality with exogenous AVP. In summary, a response during the dehydration phase indicates that AVP is being released, while a response to AVP infusion indicates that AVP release is absent or sub-maximal.

Patients with chronic polyuria of any cause will not be able to maximally concentrate their urine for several reasons: 1) chronic polyuria washes out the medulla (82); reestablishment of medullary gradients takes several hours to days, 2) suppressed AVP (from primary polyuria or central diabetes insipidus) prevents urea accumulation in the inner medulla via entry through the AVP-responsive terminal inner medullary collecting duct (75). 3) Patients with no circulating vasopressin may have diminished numbers of vasopressin receptors.

Effect of Fluid Restriction on AVP Levels

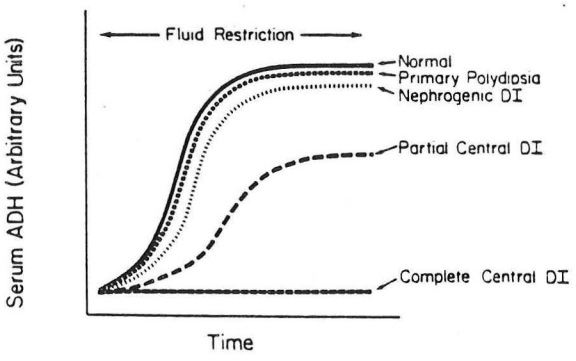


Figure 25

When properly performed, this standard dehydration/AVP test has a very high diagnostic accuracy. However, in one study which measured concomitant AVP levels, about 25% of patients were misdiagnosed (82). The most common mistake was failure to properly differentiate between psychogenic polydipsia and partial central diabetes insipidus. Figure 25 shows AVP levels in 24 patients studied during a dehydration test. Patients with nephrogenic diabetes insipidus and primary polydipsia had normal AVP levels, while patients with central diabetes insipidus had abnormally low levels of AVP. Unfortunately, the AVP assay is technically demanding, requires careful sample preparation, and is not readily available. Also, isolated AVP levels can confusing (83). In general, making sure that the patient has reached steady state during the dehydration phase should avoid many mistakes.

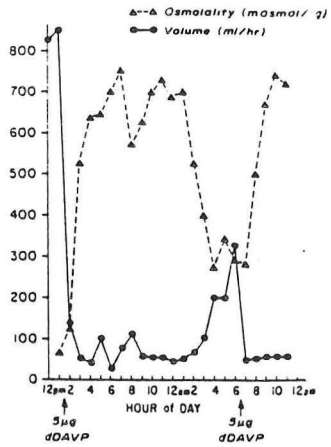
Treatment.

Longstanding diabetes insipidus may cause hydronephrosis and very large bladders. In addition, patients are at risk of dehydration if unconscious or unable to get to water. Therefore, polyuria must be controlled. Osmotic diuresis is the easiest form of polyuria to treat. Treatment is to stop the solute diuresis, and replace fluid and electrolyte deficits. The major problem is recognizing the disorder. In theory, patients with Psychogenic Polydipsia should be easy to treat by simply limiting the amount of water ingested. However, these patients can find and will drink water out of almost any container. In a hyponatremic patient, the problem is more complex. Hyponatremia can cause seizures, coma and death; at least 15 deaths have been reported in the past 20 years (62). If the patient is not symptomatic, often difficult to tell, a slow correction can

be achieved by gradual water restriction alone. In symptomatic patients, correction to 120-130 mM within about 12 hours should be achieved using fluid restriction, sometimes in association with saline infusion (62). In water-loaded patients, fluid restriction alone can lead to a rapid fluid excretion, and rapid uncontrolled correction of the serum sodium.

Central Diabetes Insipidus. Treatment of central diabetes insipidus has been greatly simplified by use of DDAVP, a long acting V_2 receptor agonist which can be given by intranasal spray or i.m. injection (84-86). The starting dose is 5 μg, given twice a day. Antidiuresis occurs within one hour (Figure 26). The dose is adjusted until the antidiuresis lasts 12 hours. Adverse side effects are minimal; DDAVP is the least vasoconstrictive of the vasopressin analogues. The major problem is water intoxication. This usually results from failure to adequately reduce water intake in patients with damaged thirst centers. DDAVP can improve attention, mental concentration, and memory. Unlike AVP, DDAVP does not increase renal prostaglandin synthesis, which would oppose its action in the collecting duct (87).

Effect of DDAVP on Urine Volume and Osmolaltity



Cobb Ann Int Med 88: 186, 1978

Figure 26

Aqueous vasopressin, with a short duration of action of 4-6 hours, is ideal for the acute management of central diabetes insipidus in hospitalized patients. The constantly changing fluid status can be reappraised frequently, and dosage of AVP changed. Doses of 5-10 U are given just as the polyuria reappears, thus minimizing the risk of water intoxication. Vasopressin tannate in oil must be given as an i.m. injection. It has a long duration of action (24-72 hours), which increases the risk of water intoxication.

Antibodies to vasopressin occasionally develop during treatment with AVP or Pitressin tannate in oil, resulting in secondary resistance to the antidiuretic effect (88,89). The antibodies do not cross react with DDAVP, so DDAVP can be substituted AVP. The antibodies only rarely interfere with the diagnosis of diabetes insipidus, mimicking a partial nephrogenic pattern. So far, no cases of diabetes insipidus have been seen with spontaneously occurring anti-AVP antibodies.

Chlorpropamide and clofibrate can be used in patients with some AVP release, since they potentiate AVP action. Their mechanism of action is uncertain. Because of their associated side effects, they are not used very frequently.

Paradoxically, hydrochlorothiazides can decrease urine output by 50%. This occurs by induction of a mild volume depletion which enhances proximal tubule salt and water absorption, delivering less to the collecting ducts, and less to the final urine (90,91). Sodium must be restricted otherwise the polyuria will return.

Nephrogenic Diabetes Insipidus. Treatment of nephrogenic diabetes insipidus is difficult unless the concentrating defect can be reversed by removing drugs, treating electrolyte disorders (hypokalemia, hypercalcemia). Specific therapy is not indicated unless the polyuria is severe or symptomatic. In congenital nephrogenic diabetes, several interventions can be made. First, it

is possible that female carriers can be detected by their abnormal response of plasma renin activity to DDAVP (45), but this needs to be evaluated in more patients. Second, affected newborn males must be recognized early to prevent brain damage from dehydration. Polyuria can be reduced by limiting solute load. HCTZ can be used as described above. Some female carriers respond to large doses of DDAVP.

Lithium-induced diabetes insipidus occurs in 19% of patients on chronic lithium therapy (92). The polyuria usually improves when the drug is stopped, but may persist for months to years. However, cessation may not be a viable alternative. Treatment is very difficult. Sodium depletion with diuretics may cause hypokalemia and variable blood levels of lithium by altering the renal clearance of lithium. Amiloride has been used in one study to decrease urine volumes by about 30% (93). Amiloride blocks the apical sodium channel in the collecting duct principal cell; the blockage may serve to prevent lithium entry thus limiting toxicity. Several groups have had success with a combination of DDAVP and indomethacin despite neither working alone (94-97). Indomethacin inhibits renal prostaglandin production, which opposes AVP action in the collecting duct (87). Presumably, the combination of supraphysiologic concentrations of DDAVP and blockage of renal prostaglandin synthesis overcomes the resistance to hormone action.

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