Neuroendocrine Factors Influencing Polydipsia in Psychiatric Patients: An Hypothesis

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Polydipsia and water intoxication cause considerable morbidity and mortality in chronic psychiatric patients. The pathophysiology of the disorder is unknown, and there is no effective treatment. Angiotensin II is an important dipsogen in animals; in humans, some conditions with abnormal thirst are associated with increased angiotensin function. Chronic D_2 dopamine receptor blockade increases angiotensin II–induced thirst in animals; in humans, increased peripheral response to angiotensin II is documented. Chronic D_2 blockade with typical neuroleptics may increase sensitivity to angiotensin II and induce thirst. Clozapine, which has negligible D_2 blocking action may improve polydipsia. Recent case reports demonstrate improvement of polydipsia during clozapine therapy. Angiotensin II releases vasopressin; this could explain water intoxication, which occurs later in the syndrome. This paper suggests an etiological model and a treatment modality for this disorder. ***[Neuropsychopharmacology 9:157–166, 1993]***

KEY WORDS: *Polydipsia; Hyponatremia; Angiotensins; Vasopressin; Atrial natriuretic peptide*

Polydipsia in psychiatric patients has been described since the 1930s prior to the use of neuroleptics, but systematic study of the disorder has been done mostly in the last two decades. There are many names for the disorder, which include psychogenic polydipsia (Bauer 1925), compulsive water drinking (Barlow and De Wardener 1959), psychosis, intermittent hyponatremia and polydipsia (PIP) syndrome (Vieweg et al. 1985) and self-induced water intoxication (Hobson and English 1963). The main purpose of this paper is to propose an hypothesis about the pathophysiology of the disorder and to reconceptualize some of the thinking about it. The existing data are reviewed to put the hypothesis in perspective.

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Clinical Features and Natural History

There are three stages of the disorder. In the first stage, about 5 to 15 years after the onset of the psychotic disorder, some patients start to consume excess quantities of fluids (Vieweg et al. 1984a). Polydipsia causes secondary polyuria. Polydipsia is the primary and enduring feature, and for many patients, the only symptom. It is not always recognized by care givers, and patients rarely complain about it. It often comes to attention with the onset of the second stage, water intoxication, which occurs 1 to 10 years from the onset of polydipsia (Vieweg et al. 1984b). Water intoxication occurs in 50% of polydipsic patients (Jos and Perez-Cruet 1979). The kidney is normally able to excrete large amounts of fluids, but these patients become unable to excrete all the ingested fluids, resulting in hemodilution and hyponatremia. Acute episodes of hyponatremia cause cerebral edema, the symptoms of which are called water intoxication. A wide range of symptoms

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is seen that include headache, blurred vision, anorexia, nausea, vomiting and diarrhea, muscle cramps, restlessness, confusion, exacerbation of psychosis, convulsions, coma, and death. Vieweg et al. (1985b) estimated that it accounts for 18% of deaths in schizophrenics under 53 years of age. The third stage develops 5 years after the onset of water intoxication, and it includes other physical complications (Vieweg et al. 1984a). The complications are bladder and bowel dilatation, renal and cardiac failure, hydronephrosis, osteopenia, and pathological fractures (Blum et al. 1983). The latter may be due to increased urinary calcium excretion in the polyuria that accompanies polydipsia (Delva et al. 1989). The time course is based on retrospective studies of small numbers of patients with particularly severe symptoms, so the time frames for the stages are approximations.

The symptoms are often episodic, which was seen in one third of the patients in a longitudinal study (Peh et al. 1990). There is also significant diurnal variation in severity. Patients consume large amounts of fluids over the day, resulting in diurnal weight gain. They excrete a very dilute urine and lose weight in the evening and night, often returning to their base weight by morning (Crammer 1991).

Epidemiologic Data

Most of the studies on polydipsia have been done on chronically ill patients, and prevalence rates of 6.6% (Jos and Perez-Cruet 1979) to 17.5% (Blum et al. 1983) have been reported. Studies have used differing strategies for case finding, usually chart review and staff reports, which results in significant underreporting. Vieweg and coworkers (1986) reported a rate as high as 39% using urine specific gravity as an estimate of polyuria. This method could cause some false positives, as other factors like lithium can cause polyuria.

Risk Factors

Some studies suggest that polydipsia without water intoxication and with water intoxication may have different antecedents. The former is associated with high intelligence quotients (Sleeper and Jellinek 1936), good premorbid functioning (Lawson et al. 1985), and positive symptoms (Kirch et al. 1985). Water intoxication is associated with tardive dyskinesia and ventricular dilatation (Lawson et al. 1985) and negative symptoms (Kirch et al. 1985). Sample sizes were small, which limits the generalizability of these data.

Chronicity of the illness is a strong association with polydipsia and water intoxication in most studies. In terms of diagnostic groups, 80% of patients have schizophrenia; other diagnoses include affective disorders, alcohol abuse, mental retardation, organic brain disorders, and personality disorders (Illowsky and Kirch 1988). Polydipsia has been reported to be more common in females and whites (Jos and Evenson 1980), although Shah and Greenberg (1992) found an overwhelming preponderance of males in their study. Both studies used staff reporting as the method to identify potential cases, and cases were included on the basis of differing levels of serum sodium. Staff reporting identifies only the more severe cases, and it varies according to the level of awareness and interest in different institutions. This is an episodic disorder, hence data on epidemiology and risk factors are limited by the cross-sectional nature of most of the studies quoted.

Diagnostic Criteria

There are no formal, generally agreed upon criteria for the syndrome. Studies have used differing criteria, which varied according to whether they were studying polydipsia or water intoxication. Older studies used staff reporting of excessive drinking or water intoxication to include patients, but this is an unreliable method. Later studies have started using more quantifiable measures. Most studies did not measure actual fluid intake; obtaining measurements can be very difficult because of patient noncompliance (Lawson et al. 1992). Polyuria has been used as an index of polydipsia even in the earlier studies (Sleeper 1935). Lawson and coworkers (1985) used 2.5 liters as the threshold for polyuria. Reliable urine collection is also difficult, and hence, Vieweg and coworkers (1988a) estimated urine output from urine creatinine concentration. However, this method assumes a number of factors such as muscle mass and diet and is also an approximation. These patients excrete large amounts of dilute urine, and hence, urine specific gravity less than 1.008 has been used to establish polyuria (Blum and Friedland 1983). Other causes of polyuria such as ingestion of lithium and diuretics can confound results.

Water retention is assessed using chart reviews and staff reports of abnormal behavior, especially in the afternoon (Koczapski et al. 1987). Diurnal weight changes have been used to assess drinking and water retention. Normalized diurnal weight gain (NDWG), expressed by the equation (evening weight − morning weight) × 100/morning weight, is now used in a number of studies as a measure (Vieweg et al. 1988b). Normalized diurnal weight gain greater than 7% is associated with a significant risk of water intoxication (Delva and Crammer 1988). Normalized diurnal weight gain is thus a composite measure of both polydipsia and water retention (Vieweg et al. 1988b). Studies using NDWG as the sole criterion would miss patients with only polydipsia. Serum sodium has been used as a measure, but there is considerable interindividual variation in resting sodium levels (Koczapski and Millson 1989), and

hence, it may not be very useful for screening. Water intoxication is more related to acute changes in sodium than to absolute levels.

The best approach to diagnosis is to use a combination of methods. We conducted a survey in a state hospital, using staff reporting, urine specific gravity, and diurnal weight gain and found a prevalence rate of 22%, much higher than was predicted by staff reporting alone (De Leon et al. unpublished data).

Classification

In the absence of conditions such as chronic renal failure, hypocalcemia, and lithium and diuretic therapy, polydipsia is classified with the diabetes insipidus (DI) group of disorders. Diabetes insipidus–like disorders are characterized by polyuria and polydipsia. The three types of DI are neurogenic and nephrogenic diabetes insipidus and primary polydipsia. Vasopressin-induced reabsorption of fluids in the kidney is one of the primary means of osmoregulation. Deficient secretion of vasopressin (neurogenic DI) and deficient response to secreted vasopressin (nephrogenic DI) are associated with loss of water in the kidney and polyuria, with compensatory polydipsia. Fluid loss is the primary problem, and hence, plasma osmolality is in the high normal range, often around 295 mosmol/kg. In primary polydipsia, excess water intake is followed by polyuria. Plasma osmolality is in the low normal range, less than 280 mosmol/kg, and vasopressin function is normal (Vokes and Robertson 1988; Robertson 1988). Primary polydipsia is divided into dipsogenic and psychogenic: the latter is mainly distinguished by its association with psychiatric disorders and is the subject of this paper. Dipsogenic polydipsia is seen in medical patients, most of whom do not have psychiatric symptoms. They also do not show features of water intoxication. The pathophysiology of the disorder is not known, although it is known to occur in association with damage to the hypothalamus (Mellinger and Zafar 1983). It is a rare disorder, and its incidence in the community is not known. It comprised 11% of polydipsics referred to a university center (Vokes et al. 1988). It is possible that some cases of dipsogenic polydipsia may share the pathophysiology of "psychogenic" polydipsia: both conditions may be related to disturbances in angiotensin II function, as described later.

Hyponatremia is seen with fluid loss (diarrhea, diuretic use, etc.), fluid overload (cardiac, renal, and hepatic failure), and in syndrome of inappropriate secretion on antidiuretic hormone (SIADH). The later section on antidiuretic hormone (ADH) has further discussion on ADH function in psychiatric patients with polydipsia. Disturbances of water balance are shown in Table 1.

Etiological theories on polydipsia in psychiatric patients, as discussed in reviews (Riggs et al. 1991; Illowsky and Kirch 1988), do not offer a comprehensive model to explain polydipsia and hyponatremia. Goldman (1991) commented that the etiology of polydipsia is unknown, and there is no definitive treatment for it (Crammer 1991). Studies so far have focused on vasopressin function, which can only account for hyponatremia, not polydipsia, the primary problem. In the next section, we examine data on angiotensin II (A-II). It is a known dipsogen in animals (Fitzsimons and Simons 1969), and in man, it is associated with disorders with abnormal thirst (Yamamoto et al., 1986; Phillips et al. 1985b). Dopamine-2 blockade by typical neuroleptics increases A-II–induced thirst in animals (Sumners et al. 1981) and enhances peripheral response to A-II in man (Missale et al. 1989). A-II releases vasopressin; thus, changes in A-II could also be responsible for hyponatremia. We propose that chronic D_2 blockade by typical neuroleptics could raise A-II levels and contribute to polydipsia in some patients. Clozapine, because of its unique pharmacology, may improve the condition.

THIRST PHYSIOLOGY AND ANGIOTENSINS

Much data have accumulated in the last two decades on the physiology of the control of thirst. In normal healthy humans and most mammals with free access to water, habitual, anticipatory, and prandial consumption of fluids prevents the development of fluid deficits; there are no significant changes in body fluid variables, including A-II (Phillips et al. 1984; Fitzsimons 1972).

Table 1. Disorders of Water Balance

Diagnosis	Clinical Features	ADH Secretion	ADH Action	Serum Osmolality
DI (neurogenic)	PU, PD	Decreased	Normal	Increased
DI (nephrogenic)	PU, PD	Normal	Decreased	Increased
Dipsogenic PD	PD, PU	Normal	Normal	Decreased
SIADH	Water intoxication	Increased	Normal or increased	Decreased
PD in psychiatric pts	PD, PU, water intoxication	Increased in some patients	Normal or may be sensitive to low levels of ADH	Decreased in many patients

PU = polyuria; PD = polydipsia.

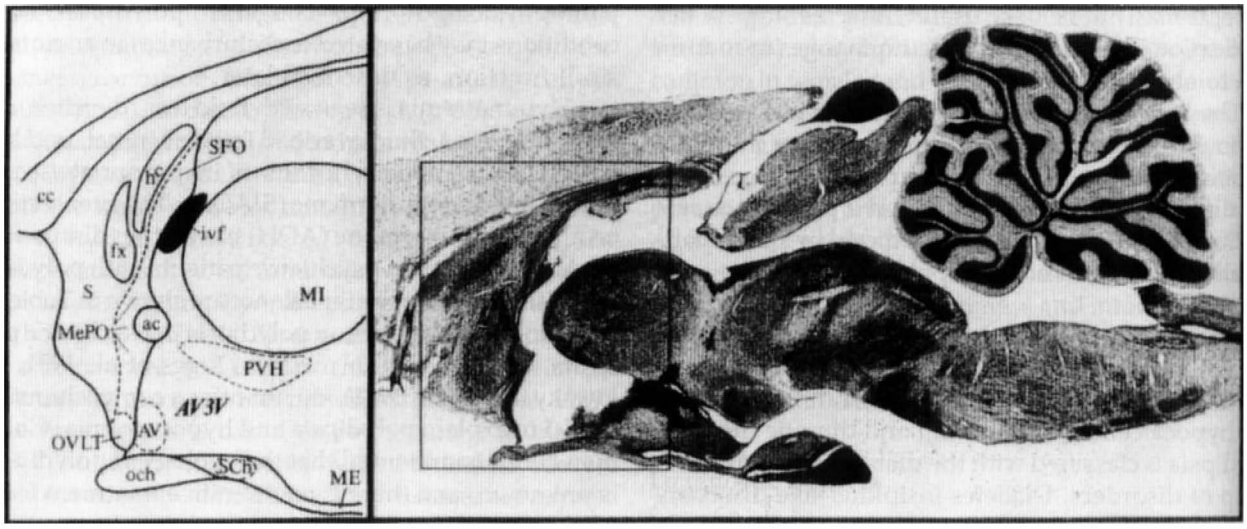

Figure 1. Midsagittal section of rat brain. Inset shows midline structures of the basal forebrain. Lamina terminalis consists of subfornical organ (SFO), median preoptic nucleus (MePO), and organ vasculosum lamina terminalis (OVLT). Anteroventral third ventricle (AV3V), corpus callosum (cc), fornix (fx). Reprinted from *Clinical and Experimental Hypertension*. Part A—Theory and Practice, A10 (Suppl.1):79–105 (1988), courtesy of Marcel Dekker Inc.

Fluid deficits result in plasma hyperosmolality, which is the principal determinant of thirst (Thompson and Baylis 1988). Most authors believe that rising osmolality initially causes vasopressin secretion and reabsorption of water in the kidney, and that further increases in osmolality cause thirst (Baylis and Robertson 1980). Thompson and coworkers (1986) believe that vasopressin secretion and thirst occur in parallel and have a similar threshold in healthy men.

The anatomic basis of fluid homeostasis is well studied in animals (Fig. 1). Plasma hyperosmolality is detected by the circumventricular organs in the anterior wall of the third ventricle (lamina terminalis). These are the subfornicial organ, and the organ vasculosum of the lamina terminalis, located in the area called anteroventral third ventricle. They are highly vascular and have specially fenestrated capillaries, which do not pose a blood-brain barrier, thus monitoring plasma content. The circumventricular organs send efferent fibers to the median preoptic nucleus, which lies between them, using A-II as the chemical messenger (Lind et al. 1984). The receptors governing thirst appreciation and vasopressin release are in proximity. However, they are not identical structures; some patients with brain damage show absence of thirst with intact vasopressin function (Hammond et al. 1986).

Angiotensin II was initially thought to be produced only in the kidneys but is now found to be widely distributed in the body. The enzymes and genetic message for its synthesis are found in the brain (Ganten et al. 1984). Angiotensin II has a profound effect on thirst and drinking in animals. Angiotensin II injected intravenously (Fitzsimons and Simons 1969) and intraventricularly (Epstein et al. 1970) causes a potent and immediate dipsogenic response. The subfornicial organ responds to blood borne A-II, whereas the anteroventral third ventricle and the median preoptic nucleus respond to central A-II. Lesions of the median preoptic nucleus eliminate drinking to both central and peripheral A-II (Lind and Johnson 1982). An extensive literature has accumulated on the subject and is well reviewed by Lind (1988). Ferrario et al. (1988) have shown that A-III is also dipsogenic.

Stimulation of central nervous system A-II receptors results in complex and reproducible responses which include drinking, pressor responses, release of vasopressin, oxytocin, adrenocorticotropic hormone, and leutinizing hormone-releasing hormone, and modulation of prolactin release (Lang et al. 1983). Tract tracing showed that the subfornicial organ sends fiber tracts to the magnocellular neurons in paraventricular and supraoptic regions, where vasopressin is synthesized (Hartle and Brody 1984).

In contrast to the facts presented above, some authors (Abraham et al. 1975) found that physiologic doses of A-II were not dipsogenic in sheep. Saralasin, an A-II antagonist, did not affect drinking in dogs (Ramsay and Reid 1975).

Under physiologic conditions, humans drink anticipatorily, and angiotensin does not play a big role in fluid balance. An experiment in which volunteers were given infusions of hypertonic saline showed that thirst was not associated with raised A-II (Phillips et al. 1985a). Nevertheless, a number of pathologic con-

ditions with increased thirst are associated with raised A-II and plasma renin activity. Peripherally, renin secreted by the kidneys acts on plasma angiotensinogen to form A-I, which is converted to A-II by an angiotensin-converting enzyme (ACE). Polydipsia and weight gain were associated with raised A-II levels in patients with chronic renal failure on dialysis (Heidbreder et al. 1990). This was confirmed by another group, who also found that polydipsia improved with an ACE inhibitor (Yamamoto et al. 1986). Kamoi and coworkers (1991) divided a sample of noninsulin-dependent diabetics into those with thirst and without thirst. The group with thirst had significantly higher levels of A-II and vasopressin, which returned to normal after treatment of the diabetes; the patients stopped feeling thirsty as well. Phillips et al. (1985b) administered intravenous A-II to young healthy males, using a single-blind design. Thirst and vasopressin secretion were stimulated in 4 of 10 subjects, albeit at supraphysiologic levels. A study on thirst and A-II in alcoholics, when compared to normal subjects, did not find a relationship between the two. The authors, however, commented that alcohol may have an effect of blunting A-II receptors (Collins et al. 1992).

There are few reports in which ACE inhibitors have been used in the treatment of polydipsia (Lawson et al. 1988; Sebastian and Bernadin 1990). These reports were based on the observation that A-II increased thirst in animals (Epstein et al. 1970). These authors reported varying degrees of success. These were more in the nature of case reports and open studies than formal studies. The negative results could have been due to low doses of drugs and differences in the drug's ability to penetrate into the blood-brain barrier. Later in this paper, we consider evidence of a possible link between the use of typical neuroleptics and polydipsia; the patients in these studies continued to be on their regular neuroleptic, and this could also have been an exacerbating factor. There is a need for well-designed studies in this area to examine the role of ACE inhibitors in the treatment of polydipsia.

A vital goal-directed behavior such as fluid intake cannot be governed by one transmitter system alone. Animal studies show that cholinergic stimulation results in drinking. This was related to atropinic fibers, and nicotinic fibers had only a weak effect. Atropine blocked drinking in a number of studies (Myers 1974). Other systems that influence drinking are opiates (Hoffmann and Phillips 1981), gamma-aminobutyric acid (Jones and Mogenson 1982), and norepinephrine (Bellin et al. 1987). There is much less data on these systems, and they are believed to play a less important role.

Thus, high A-II levels are associated with thirst in a number of pathologic conditions. "Psychogenic" polydipsia is certainly not a normal condition, and a very powerful drive to drink or defective satiety signals must exist to account for the fact that patients drink water until they are very ill or die. Although A-II does not appear to influence drinking under normal circumstances, it is a possible cause of polydipsia in psychogenic and dipsogenic polydipsia. The next section discusses how dopamine systems interact with A-II function, and how neuroleptics may contribute to polydipsia.

DOPAMINE SYSTEMS AND ANGIOTENSIN II

Animal studies have shown that catecholaminergic fibers are essential for A-II–mediated dipsogenic responses. Central dopaminergic depletion by 6-hydroxydopamine substantially reduced drinking, whereas noradrenergic depletion did not (Gordon et al. 1985). Unilateral lesions of the dopaminergic nigrostriatal pathway decreased, and bilateral lesion virtually abolished A-II–induced drinking (Sumners et al. 1981). These studies, however, did not clearly dissect out the role of these lesions on motor behavior.

Dopamine depletion and acute blockade resulted in reduced drinking, and dopamine agonists caused an increase in drinking (Fitzsimons and Setler 1975). Sumners and colleagues (1979) also reported that in the acute situation, typical neuroleptics blocked A-II–induced drinking proportional to the clinical potency of the drug; trans-flupenthixol, the inactive isomer of flupenthixol had no effect. Another study showed that clozapine had the least effect on A-II–induced drinking when compared to a number of typical neuroleptics (Munday et al. 1978). The results of chronic administration of haloperidol, a typical neuroleptic, were quite different. Sumners and coworkers (1981) administered haloperidol to a group of rats for three weeks, according to the method of Seeman and coworkers (1978). They then studied water drinking in response to intracerebroventricular injection of two dipsogens, A-II (doses of 10 pmol to 1000 pmol) and carbachol (1080 pmol). Rats with chronic D_2 blockade drank significantly more in response to A-II when compared to normal controls. This response was specific to A-II, and responses to carbachol were unaffected. The haloperidol-pretreated rats had significantly more stereotypies in response to apomorphine, suggesting a dopamine supersensitive state. Thus, in this experiment, chronic D_2 blockade was associated with dopamine supersensitivity and increased A-II–induced drinking.

We did not find any human studies examining the central effects of dopamine blockade on thirst and A-II. Most of the studies on the interaction of dopamine and the renin–angiotensin system were done in the field of cardiovascular pharmacology. Peripherally, there is strong evidence that dopamine selectively inhibits the action of A-II in the adrenal cortex, acting through D_2

receptors. Dopamine-2 blockers increased the response to A-II in normal volunteers (Gordon et al. 1983). This effect was seen in most of the studies reviewed by Missale and coworkers (1989). Many of these were acute studies in normal volunteers, and dietary sodium intake had an effect on the response in some studies. Dopaminergic control of A-II function was not confirmed in a study in which carbidopa-induced inhibition of dopamine synthesis had no effect on the renal response to A-II (Eadington et al. 1991). However, the subjects in this study were sodium replete, not sodium depleted, as in the studies mentioned earlier.

Thus, animal data suggest that chronic central D_2 blockade increases thirst via an A-II–related mechanism. In humans, D_2 blockade increases the response to A-II in the periphery. We did not find any human studies on the relation of dopamine and dopamine blockade to central A-II function and thirst. However, it is believed that osmoregulatory systems do not vary much between species and that the data support similar functioning in man (Bayliss and Thompson 1988). We hypothesize that chronic D_2 blockade induced by typical neuroleptics may increase A-II levels in some patients, resulting in the syndrome of polydipsia in psychiatric patients. This hypothesis does not seek to explain all cases of polydipsia; the reports of polydipsia before the use of neuroleptics and nonpsychiatric cases could be related to brain damage, which is not uncommon in psychiatric patients.

In these contexts, a special mention must be made of the unique place of clozapine, which differs from traditional neuroleptics in that it blocks D_1 receptors far more effectively than D_2 receptors, and it does not raise prolactin (Coward et al. 1989). In fact, Meltzer (1991) presented evidence that clozapine may actually increase dopamine release in certain brain areas such as the frontal cortex and striatum. In the animal studies on thirst mentioned earlier (Munday et al. 1978), clozapine had the least effect on drinking. Clozapine's properties may ensure that it would not have a possible dipsogenic action like that of typical neuroleptics, and it may even reduce thirst. Polydipsia improved on clozapine therapy (Lee et al. 1991) and the possible role of neuroendocrine factors has been commented on (Verghese et al. 1992). We have unpublished data on three cases in which longstanding polydipsia improved when the patients were started on clozapine therapy.

We are not aware of any studies or papers that have examined the relationship between neuroleptic administration, A-II function, and polydipsia.

ARGININE VASOPRESSIN OR ANTIDIURETIC HORMONE

Arginine vasopressin (AVP) is released primarily in response to plasma hyperosmolality, causing water retention in the kidney. It lowers plasma osmolality and concentrates the urine. It is also secreted in response to nonosmotic stimuli like hypotension, hypovolemia, stress, and nicotine. Angiotensin-II is a potent stimulus for AVP release in animals. In humans, this is seen under pharmacologic conditions (Phillips et al. 1985b); the physiological significance of the effect is not known.

The low plasma osmolality seen in psychiatric patients with polydipsia has prompted studies on their AVP function. In general, schizophrenia is not associated with raised AVP levels (Beckman et al. 1985). Neuroleptics do not directly raise AVP levels except through hypotension, a nonosmotic stimulus for AVP (Dorsa and Raskind 1985).

Most, if not all of the neuroendocrine studies on polydipsia/hyponatremia have examined ADH functioning, focusing on the possibility that these patients have SIADH. In a typical SIADH, as seen in medically ill patients, secretion of ADH does not shut off at low plasma osmolality values, resulting in continued water retention and dilutional hyponatremia. Water retention makes the urine hyperosmolar with reference to plasma. Hence, the ADH secretion at these osmolalities is "inappropriate." Type I SIADH shows no relation between plasma osmolality and ADH. In Type II, the osmoreceptor is reset to suppress ADH at lower osmolalities than normal.

Vieweg et al. (1987) reported that these patients have Type I SIADH. Hariprasad et al. (1980) described Type II SIADH. Goldman et al. (1988), in a well-controlled study, found that psychiatric patients with polydipsia had higher levels of vasopressin at any given level of osmolality. They noted that changes in AVP secretion and action were not sufficient to explain the altered sodium levels and osmolality.

Polydipsia/hyponatremia in psychiatric patients differs from classic SIADH on clinical, biochemical, and treatment response parameters. Polydipsia and polyuria are prominent features, but they are absent in SIADH. The symptoms of SIADH are those of water intoxication (Vokes and Robertson 1988). Biochemically, polydipsia/hyponatremia is associated with low urine specific gravity (<1.008), large urine volumes, and low urine osmolality less than 150 mosmol/kg (Goldman 1991). In SIADH, urine is hypertonic to plasma, usually greater than 300 mosmol/kg (Moses and Streeten 1991), which differs from the very dilute urine in polydipsia/hyponatremia.

The syndrome of inappropriate secretion of antidiuretic hormone has been treated with demeclocycline, an ADH antagonist (DeTroyer 1977). However, a well-designed study found that demeclocycline had no effect on plasma sodium in polydipsic patients (Alexander et al. 1991); polydipsia does not improve in these studies (Crammer 1991). The elevated vasopressin in some patients does not constitute a typical SIADH; the only common feature between the two syndromes is plasma

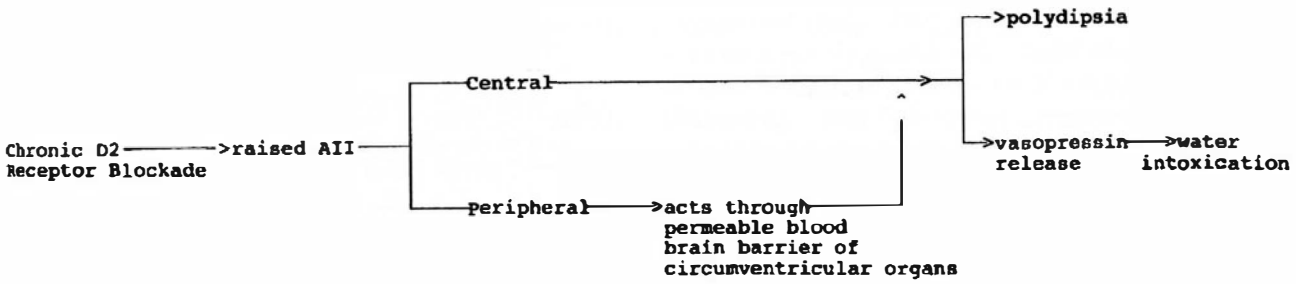

Figure 2. Proposed mechanism for the role of neuroleptics in a polydipsia/hyponatremia.

hypoosmolality. Nicotine elevates AVP, and psychiatric patients smoke heavily; this may be a confounding factor in some of the reports of raised AVP. These facts are reflected in the admonition in standard textbooks that to make a diagnosis of SIADH, one must exclude primary polydipsia, which is associated with dilute urine (Moses and Streeten 1991). Currently, it is believed by most researchers that vasopressin abnormalities in polydipsic patients are SIADH.

A point to be noted here is the interaction between A-II and vasopressin. It is known that A-II releases vasopressin in animals. In humans, A-II and vasopressin were elevated in parallel (Kamoi et al. 1991). Supraphysiologic doses of A-II elevated vasopressin levels in volunteers (Phillips et al. 1985b). The reverse does not hold true, because vasopressin inhibits the secretion of renin in animals and man, in both physiologic and pathologic conditions (Reid et al. 1983). It was earlier mentioned that renin initiates the formation of A-II. The possibility exists that long-term neuroleptic treatment stimulates A-II, which then releases vasopressin. This is corroborated clinically by the fact that patients are often polydipsic for many years before developing water retention, which remains an intermittent problem.

Thus, polydipsia is the primary and enduring problem in these patients. Arginine vasopressin does not cause thirst and drinking in human beings (Greenleaf 1992); it is normally released in parallel with stimuli that also
in the development of water intoxication by retaining water, but is unlikely to have a role in polydipsia. The studies in the field so far have focused on abnormalities of vasopressin function, which do not explain the primary problem. In fact, for the reasons discussed above, vasopressin disturbances may be secondary to changes in A-II. The proposed mechanism is outlined in Figure 2.

OTHER HORMONES

Other recently discovered peptides have been found to influence drinking and fluid balance. Atrial natriuretic peptide is secreted by the cardiac atria in response to fluid overload and causes diuresis and sodium loss (Kenyon and Jardine 1989). It is an A-II antagonist and reduces thirst and suppresses vasopressin (Johnston et al. 1989). Acute studies showed that dopamine blockade did not affect renal actions of atrial natriuretic peptide (Freestone et al. 1989). The question remains whether long-term D_2 blockade in some patients would inhibit the ability of atrial natriuretic peptide to inhibit A-II, thus contributing to water consumption. Endothelin-3 is another newly discovered peptide, which reduced water consumption in a number of situations, including A-II administration (Samson et al. 1991). The role of these compounds in the genesis of polydipsia in psychiatric patients is not clearly known, but they could be areas of future enquiry.

COMMENTS

This syndrome has been recognized since the 1920s and is associated with significant morbidity and mortality, probably more than tardive dyskinesia, which has received considerably more attention. Like the tardive movement disorders, it is related to changes in brain functioning, occurs spontaneously and in nonpsychiatric patients, but is much more common in psychiatric populations; it is exacerbated by typical neuroleptics, and there is evidence to suggest that clozapine may improve the condition.

Angiotensin II is an important central regulator of thirst in animals and in man in some pathologic conditions. Dopamine projections, acting through D_2 receptors, influence A-II function and drinking in animals. Chronic D_2 blockade increases A-II–induced thirst. In humans, D_2 blockade enhances peripheral A-II action. It is postulated that chronic D_2 blockade by typical neuroleptics increases A-II levels and may contribute to polydipsia. Angiotensin II releases vasopressin and thus could explain both the polydipsia and water retention.

Clozapine has negligible D_2 action and would not raise A-II. Case reports of improvement in polydipsia with clozapine treatment are already appearing in the literature. This would be the first definitive treatment for the disorder. Longitudinal studies, using strict

criteria for improvement, are particularly necessary in this episodic condition. Neuroendocrine and other biological studies are also necessary to establish the biological basis of what has been called "psychogenic polydipsia." Until then, the disorder will remain an enigma, as noted by Crammer (1991).

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