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The Physiology of Vasopressin Release and the Pathogenesis of Impaired Water Excretion in Adrenal, Thyroid, and Edematous Disorders

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Osmotic control for vasopressin release has been recognized for several years. Further understanding of factors affecting the sensitivity and threshold of ADH release has been advanced by the technological development of a sensitive radioimmunoassay.

Evidence suggesting that ADH secretion is also mediated by nonosmotic stimuli involving a separate anatomic pathway from the hypothalamic osmoreceptor has been well documented. Experimental results suggest that the parasympathetic afferent pathways from both "high" and "low" pressure receptors constitute the most important nonosmotic pathways for ADH release. Factors such as hypoxia, altered hemodynamic states, alpha- and beta-adrenergic stimuli, nicotine, adrenal insufficiency, and advanced hypothyroidism are likely examples which activate this nonosmotic pathway.

Clarification of the exact interrelationship between the osmotic and nonosmotic release of ADH needs further examination, particularly in the area of central neurotransmitters. However, available information allows for the proposal of a model of this interaction and its clinical implications which may explain many cases of "reset osmostat."

Recent available data also provide support for ADH playing a role in the maintenance of blood pressure under certain circumstances. Like other potent vasoconstrictors, preliminary evidence suggests that ADH requires transcellular calcium influx for its vascular effects.

Adrenal, thyroid, and edematous disorders have all been shown to be associated with abnormal water excretion. The results of recent studies indicate that these abnormal physiological states have impaired water excretion as a result of both nonosmolar factors stimulating ADH release and intrarenal factors, including diminished glomerular filtration rate or increased proximal tubule reabsorption which lead to decreased distal fluid delivery to the diluting segment of the nephron.

Verney's original studies demonstrating the osmoreceptor regulation of ADH release remain a milestone in renal physiology. In the past decade, considerable new information about nonosmotic regulation of ADH has led to further understanding of renal water regulation in health and disease; nevertheless, many of these answers have only stimulated the imagination to ponder even more questions.

INTRODUCTION

In the presence of large variations in water intake, the osmotic concentration of body fluids in a healthy man is maintained within a narrow range between 286 and 294 mOsm/kg H_2O. This ability to maintain the body fluids' osmotic concentration within a normal range is dependent on the operation of a functioning thirst-

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neurohypophyseal-renal feedback system. Osmotic control for vasopressin (ADH) release from the neurohypophyseal system has been recognized for several years [1]. With the technological advancement of a highly accurate radioimmunoassay for ADH measurement, further characterization of the sensitivity of this feedback system has recently been elucidated. Although some evidence existed many years ago that nonosmotic stimuli also could affect ADH release [1], recent experimentation has unequivocably demonstrated that ADH secretion is also mediated by nonosmotic stimuli which are modulated by a separate anatomic pathway from the hypothalamic osmoreceptor. Clinical studies, as well as sensitive electrophysiological studies, have been helpful in clarifying the relationship between the osmotic and nonosmotic pathways for ADH release. Recent experiments are also beginning to explore the central nervous system neurotransmitters which may mediate the release of ADH. Finally, the role of ADH in the maintenance of blood pressure and in the pathophysiology of impaired water excretion in various disease states is also beginning to be clarified. The purpose of this paper is to review the current state of the art regarding the control of ADH release and the role this hormone plays in various pathophysiological conditions.

OSMOTIC CONTROL OF ADH RELEASE

Verney's classical experiments on conscious dogs were the first to demonstrate the existence of an "osmoreceptor" regulating urine flow [1]. These studies were also the first to suggest that the "osmoreceptor" influences the release of ADH from the posterior pituitary gland. Subsequent experiemnts have localized the "osmoreceptor" to the anterior hypothalamus [2].

Other investigators have suggested a "sodium receptor" theory for the release of ADH [3,4]. Indirect evidence against this hypothesis is that comparable increments in plasma osmolality during hypertonic saline and hypertonic mannitol infusions provide the same degree of rise in plasma ADH levels, yet extracellular fluid (ECF) sodium concentration decreases with hypertonic mannitol [5,6]. More direct evidence against the "sodium receptor" theory is that with infusions of hypertonic saline, hypertonic sucrose, or hypertonic urea, sodium concentration increases in the cerebrospinal fluid, but, as will be discussed later, only hypertonic saline and sucrose cause an antidiuresis [4,7,8].

Until the recent technological advancement of the measurement of plasma ADH by radioimmunoassay, little additional knowledge was added to Verney's original views of secretion and control of ADH. Robertson and his colleagues, with the aide of a sensitive radioimmunoassay for ADH assay, have been able to support Verney's observation by showing a close interrelation between plasma osmolality and ADH levels [9]. The osmotic threshold for ADH release is defined using linear regression analysis as the point of intercept on the horizontal axis (280 mOsm/kg H_2O). The slope of the linear regression line characterizes the sensitivity of the osmoreceptor. This use of linear regression analysis to define the functional properties of the osmoreceptor has recently been challenged [10]. However, whether the mathematical model to define the relationship among the osmoreceptor, plasma ADH, and plasma osmolality is linear or exponential makes little functional difference within the physiological range of plasma osmolality [11].

Robertson and his associates have also demonstrated a significant correlation between plasma ADH levels and urinary osmolality [12]. Patients with nephrogenic diabetes insipidus are, of course, the exception to this relationship. Use of the radioimmunoassay of plasma ADH has confirmed the remarkable sensitivity of the

osmoreceptor-ADH-renal reflex. A mere 1 percent increase in total body water can decrease plasma ADH levels and urine osmolality while a 2 percent increase in total body water causes maximum suppression of ADH and dilution of urine. In the opposite direction, maximum urinary concentration and increased ADH secretion occurs with just a 2 percent decrease in total body water [13].

Several potential factors may affect the initial release of ADH during a rise in plasma osmolality (Table 1). The osmotic threshold for ADH release may be influenced by genetic or environmental factors [12,15,16] as well as species variation [6,9,14,16–18]. Soem evidence suggests that the intracellular solute concentration may influence the osmotic threshold for ADH release [12,17]. Nonosmotic stimuli such as hypovolemia or hypotension appear to lower the osmotic threshold of the system [6,17,19].

Several potential factors affect the sensitivity of the release of ADH (Table 2). Recent evidence has shown that there is a greater rise in plasma ADH for the same degree of increase in plasma osmolality in older rather than younger individuals [20]. No detectable differences in osmotic threshold, however, were observed between the different age groups. Evidence also suggests that the faster the rate of change of plasma osmolality, the sensitivity of ADH release appears to increase also [6,12]. As there are individual variations in osmotic threshold, individual variations in the sensitivity of the osmoreceptor mechanism are also seen [12]. Verney originally demonstrated, and others have confirmed, that the type of solute utilized to provide an osmotic stimulus for ADH release must be considered [1,5,6]. Hypertonic saline and hypertonic mannitol infusions provide the same degree of rise in ADH levels. Hypertonic urea, however, is a poor osmotic stimulus for ADH secretion. Since osmoreceptor cells appear to sense cell volume and urea easily penetrates into cells, it is unable to provide an "effective" osmotic stimulus [13]. Pertinent to this area of discussion is the hypothesis that the blood-brain barrier is the semipermeable membrane for osmoregulation [3]. If this were the case, urea, which does not readily penetrate the blood-brain barrier, would be a potent stimulus for ADH secretion. This datum suggests, therefore, that the location of the osmoreceptor is in a portion of the brain that is anatomically exterior to the blood-brain barrier. The subfornical organ and the organum vasculosum of the lamina terminalis meet these anatomical requirements [3,13].

Results from Athar and Robertson [5,6] show, in contrast to studies from Verney [1], that in man suppression of ADH release results from the infusion of hypertonic glucose. This information leads one to speculate that the polyuria associated with poorly controlled diabetes mellitus may not just be the result of an osmotic diuresis with glucosuria but also is due to ADH suppression [13]. The mechanism and confirmation of this proposed suppression of ADH by hyperglycemia remains to be studied.

TABLE 1
Potential Factors Affecting the Initial Release of ADH During a Rise in Plasma Osmolality

1. Genetic versus environmental versus methodology
2. Species variation
3. Intracellular solute concentration
   a. Decreased potassium
   b. Starvation
4. Nonosmotic stimuli
   a. Hypovolemia
   b. Hypotension

TABLE 2
Potential Factors Affecting the Sensitivity (Slope) of the Osmotic Release of ADH

1. Age
2. The rate of change of the osmotic stimulus
3. Individual variation in osmotic threshold for release
4. Nature of the solute providing the osmotic stimulus
   a. Hypertonic saline
   b. Mannitol
   c. Urea
   d. Glucose
5. Angiotensin II (?)
6. Nonosmotic stimuli
   a. Hypovolemia

In the scientific literature, controversy exists as to the role of angiotensin II stimulating ADH release [21–24]. A clear dissociation between plasma ADH levels and renin activity has been demonstrated in man [25]. The reason for the discordant results may be due to differences in experimental design and methodology [13]. Further experiments are indicated to clarify the controversy in this specific area.

Finally, there is the question of whether nonosmotic stimuli can affect the sensitivity of the osmoreceptor. Studies from the same laboratory and in the same species have shown different results concerning this subject [17,19]. More data, therefore, are needed to examine the role of changes in volume status and other nonosmotic stimuli on the sensitivity of the osmoreceptor [13].

NONOSMOTIC CONTROL OF ADH RELEASE

Verney's original studies were primarily concerned with the role of osmotic control of ADH release [1]. These early experiments, however, also revealed that the production of "emotional stress" by electrical stimulation of the flanks of the dogs resulted in a small and transient antidiuresis. These investigators also noted that, with the electrical stimulation, simultaneous elevations in blood pressure accompanied the antidiuresis. Denervation of the adrenals and kidneys bilaterally and sectioning of the splanchnic nerves were undertaken to eliminate the possibility that sympathetic stimulation during the "emotional stress" was obscuring an even greater antidiuresis. They postulated an inhibitory effect on ADH release or a diminished end-organ response by stimulation of the sympathetic nervous system. Indeed, when electrical stimulation was performed after interruption of these neural pathways, a larger and more sustained antidiuresis resulted. Further support for a role of the sympathetic nervous system was obtained since electrical stimulation also failed to produce a significant antidiuresis when these animals were infused with either norepinephrine or tyramine. The question still remained as to whether the sympathetic discharge inhibited ADH release or diminished the end-organ response to ADH. Experiments performed in water diuresing animals being infused with tyramine and then given posterior pituitary extract demonstrated an antidiuresis which was comparable to that observed in control animals not receiving tyramine. This finding suggested a central, rather than a renal, interaction between ADH and the sympathetic nervous system. Verney and his associates reasoned that the suppression of ADH release via the sympathetic nervous system was not secondary to the pressor effects since bilateral occlusion of the common carotid arteries increased systemic pressure to the same degree as infusions of catecholamines yet did not interfere with ADH release [1].

Several years later, however, studies performed by Share and Levy demonstrated that common carotid artery occlusion by itself without elevation in blood pressure could produce an antidiuresis [26]. Later, Schrier and Berl performed bilateral cervical vagotomy and also produced an ADH-dependent antidiuresis, thereby further stimulating interest about the role of the autonomic nervous system in the control of renal water excretion [27] (Fig. 1). These investigators also used atropine to block the efferent limb of the parasympathetic nervous system and this maneuver did not alter the effect of cervical vagotomy on renal water excretion. These results therefore implicated afferent vagal pathways in the nonosmotic release of ADH.

The next development in the area of nonosmotic release of ADH involved studies of the mechanism by which norepinephrine causes a water diuresis. Some *in vitro* results had suggested a direct antagonism of norepinephrine on the effect of ADH at the level of the renal tubule epithelium [28,29]. However, *in vivo* studies performed in our laboratory on ADH-free animals receiving a simultaneous constant infusion of exogenous vasopressin demonstrated that norepinephrine failed to cause a water diuresis [30–32], thus not supporting the *in vitro* results [28,29]. These experiments indicated that intravenous norepinephrine caused a water diuresis by inhibition of endogenous ADH secretion [33]. Further experiments from our laboratory demonstrated that norepinephrine did not directly suppress the central release of ADH secretion but worked through a baroreceptor-mediated mechanism [30] (Fig. 2). In these experiments a more significant free water diuresis was achieved during intravenous as compared to intracarotid infusion of norepinephrine. The diuresis with intravenous norepinephrine could be abolished by baroreceptor denervation (bilateral cervical vagotomy and carotid sinus denervation). Since norepinephrine was shown to inhibit ADH release through a baroreceptor-mediated mechanism and this inhibitory phenomenon was blocked with an alpha-adrenergic antagonist [34], it seemed reasonable to examine whether beta-adreneregic agonists stimulate ADH

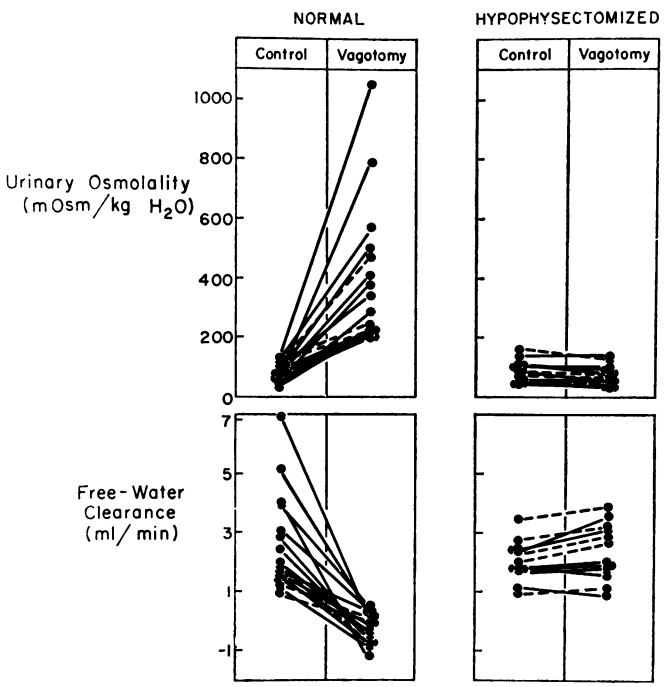

FIG. 1. Comparison of effect of bilateral cervical vagotomy on urinary osmolality and free water clearance in the normal (*left*) and hypophysectomized (*right*) dog. The broken lines denote the denervated kidneys. (With permission from [32].)

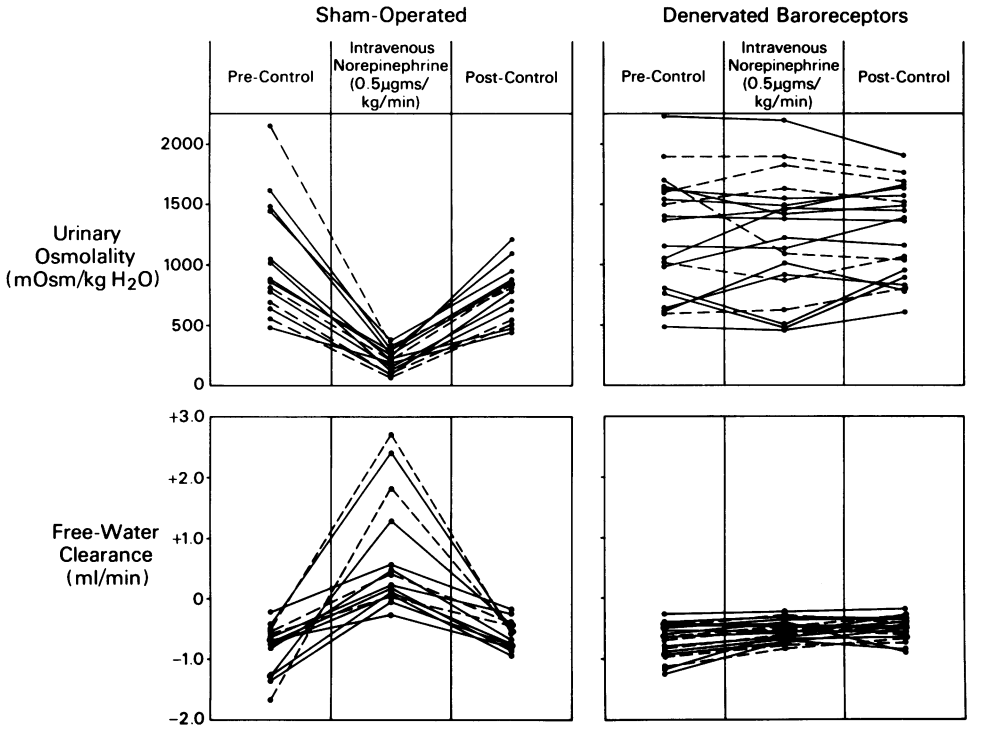

FIG. 2. Effect of intravenous norepinephrine on Uosm (*above*) and $^{C}H_2O$ (*below*) in animals with cervical sham operation (*left*) and denervation of baroreceptors (*right*). Denervation of baroreceptors abolished the diuretic effect of intravenous norepinephrine. (With permission from [30].)

release. Isoproterenol infusion caused a potent antidiuresis which was ADH-mediated and, like alpha-adrenergic stimulation, was dependent on the integrity of baroreceptor pathways [31,35–37].

There is evidence accumulating which suggests that the primary nonosmotic pathway for regulation of ADH release involves baroreceptor pathways [38,39]. Entirely different stimuli such as exogenous catecholamines [30–37], acute constriction of the thoracic vena cava [40] (Fig. 3), acute hemorrhage [41], hypoxia [42], left atrial distension [43], atrial tachycardia [44], and nicotine [45] are all dependent on the integrity of the baroreceptors for their effect on ADH release. The nicotine and hypoxia stimuli are interesting in that both of these stimulate ADH secretion via a baroreceptor-mediated mechanism without producing hypotension [42,45]. Hence, it appears that increased sympathetic stimulation, even in the absence of a fall in arterial pressure, will activate the baroreceptor pathway for the nonosmotic release of ADH.

Some controversy has arisen concerning the role of low pressure (left atrial) baroreceptors in modulating the nonosmotic release of ADH [41,46]. Utilizing bioassay measurements of plasma ADH, the results of some studies suggest that suppression of ADH does not mediate the diuresis associated with left atrial distension while other experiments provide contrary results [47,48]. de Torrente et al. have recently found, in animals without an endogenous source of ADH release, that with infusion of exogenous ADH left atrial distension did not cause a diuresis [43]. Left atrial distension in intact animals also was associated with a reversible decrease

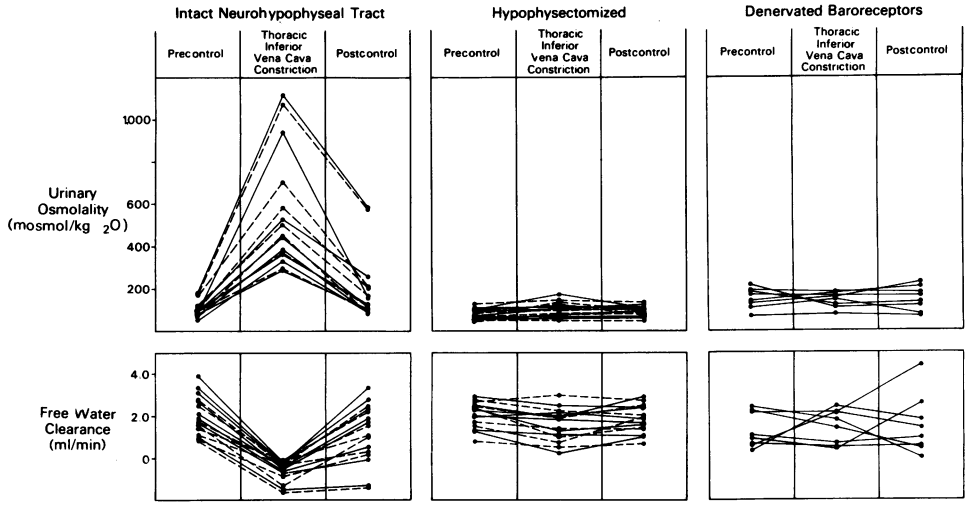

FIG. 3. Effect of TIVC constriction on Uosm (*above*) and $^{C}H_2O$ (*below*) in intact (*left*), hypophysectomized (*middle*), and baroreceptor-denervated animals (*right*). The denervated and innervated kidneys are denoted by dashed and solid lines, respectively. (With permission from [40].)

in radioimmunoassayable titers of ADH (Fig. 4). Suppression of ADH via vagal pathways has also been shown to be important in pacemaker-induced atrial tachycardia associated with elevated left atrium pressure [44]. Recently, Bennett and Yaron have produced an antidiuresis associated with an elevated plasma ADH titer measured by radioimmunoassay in a model of pulmonary hypertension which decreases left atrial pressures [49]. Taken together, these experimental results indicate that low, as well as high, pressure baroreceptors are important in modulating the nonosmotic release of ADH.

Other pathways for stimulation of ADH release have been suggested. These include a cerebral pain center [50], chemoreceptors [51], and a cerebral emetic center [52]. However, no experimental data in support of these proposed pathways has yet been demonstrated [13,42]. It is conceivable that any effect of pain and nausea on ADH release may be mediated through baroreceptor pathways [13], since these events are no doubt associated with altered autonomic neural tone. Figure 5 is a

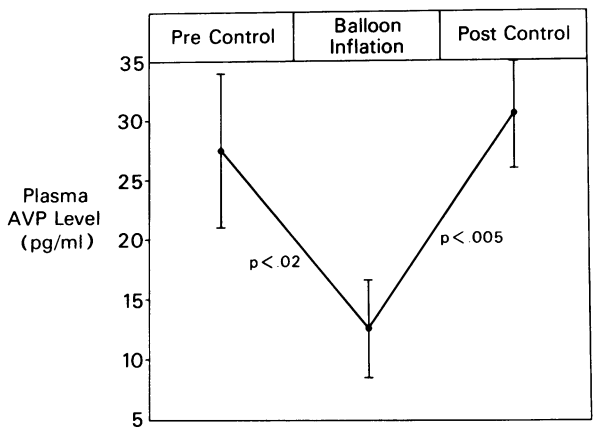

FIG. 4. Effect of an increase in left atrial pressure on plasma arginine vasopressin concentration in intact dogs. (With permission from [43].)

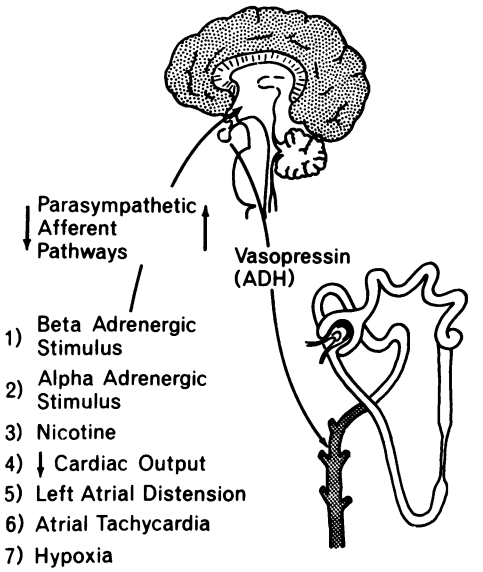

FIG. 5. Schematic representation of stimuli that result in ADH release via baroreceptor pathways. (With permission from [13].)

schematic representation of the various experimental stimuli which have been demonstrated in our laboratory to alter nonosmotic release of ADH through the baroreceptor pathways.

RELATIONSHIP BETWEEN OSMOTIC AND NONOSMOTIC PATHWAYS FOR ADH RELEASE

Some understanding of the interaction between the osmotic and nonosmotic pathways for ADH release has recently been obtained. Some of this knowledge has accrued from the study of patients who have been classified as having "essential hypernatremia" [53]. These patients appear to have an intact pathway for nonosmotic release of ADH but lack an osmoreceptor-mediated pathway. Adipsia is present in these patients, thus indicating ablation of the thirst center. Hypothalamic lesions have been demonstrated in most cases. One can reasonably conclude from this information that the sites of the osmoreceptor and thirst center are located in close proximity in the hypothalamus, both of which must be anatomically separate from the baroreceptor pathways for the nonosmotic control of ADH. The magnocellular nuclei in the supraoptic and paraventricular nuclei must also be anatomically separate from the osmoreceptor cells, since ADH synthesis and release was normal in response to a nonosmotic stimulus, i.e., drug-induced hypotension.

Further insight into the interaction between the osmotic and nonosmotic pathways has been obtained from electrophysiological data [54]. Studies performed by Kannan and Yagi [54] on supraoptic neurons in rats have demonstrated that both nonosmotic and osmotic stimuli can evoke electrical activity, which correlates with ADH release, from the same supraoptic neuron. From the information gleaned from this study and that of patients with "essential hypernatremia" the following model has been proposed (Fig. 6). The same supraoptic and paraventricular nuclei receive inputs from anatomically separate osmotic and nonosmotic pathways [13]. Knowledge of this relationship may explain many cases of "reset osmostat" in which competitive osmotic and nonosmotic input occurs. Specifically, the presence of a persistent nonosmotic stimulus for vasopressin may cause water retention until the hypo-osmolality is of a sufficient degree that the osmoreceptor pathway then predominates

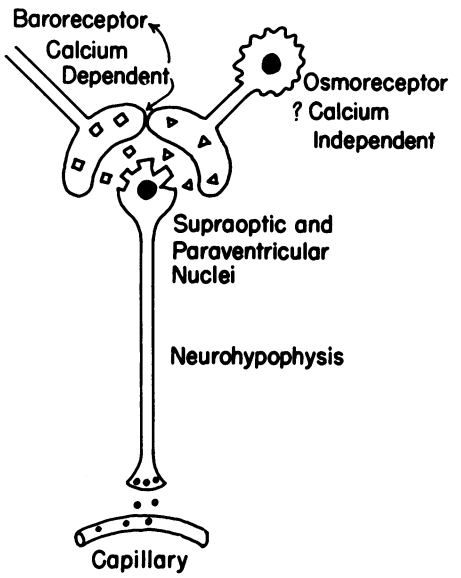

FIG. 6. Representation of a model for osmotic and nonosmotic control of ADH release. (With permission from [13].)

and vasopressin release is then suppressed. On the other hand, some nonosmotic stimuli are so potent that the hypo-osmolality is not sufficient to suppress vasopressin release. The former situation has been termed "reset osmostat" and the latter situation the "syndrome of inappropriate antidiuretic hormone secretion." In fact, both of these clinical circumstances may fall within the same spectrum in which the ultimate balance between opposing osmotic and nonosmotic stimuli dictates the level of plasma osmolality rather than any intrinsic "resetting" of the hypothalamic osmoreceptors.

The details of central neurotransmission for ADH release have not been well delineated. Currently, important roles have been claimed for cyclic nucleotides [13], catecholamines [3,55,56], calcium [57,58], and acetylcholine [3,55,59]. Miller et al. have shown that catecholamines may have an *in vivo* role as potential neurotransmitters in the release of ADH [56]. Rats with depleted brain catecholamines secondary to intraventricular 6-OH dopamine injection had decreased responses in urine osmolality and smaller rises in radioimmunoassayable titers of ADH with both osmotic and nonosmotic stimuli (Figs. 7 and 8). This study did not differentiate between a role for norepinephrine versus dopamine in this neurotransmission of ADH, and thus further studies are needed in this area. Since catecholamines have been found in some tissues to enhance calcium movement into cells [60], it is quite provocative that Handelman et al. have recently implicated cellular calcium influx in the nonosmotic release of ADH *in vivo* [58]. In this study, two different inhibitors of cellular influx were shown to blunt the nonosmotic release of ADH.

VASCULAR EFFECTS OF ADH

The knowledge that ADH or vasopressin has vasoconstrictor properties when given in large doses has been known for many years. Very recent data suggests that, like catecholamines and angiotensin II, ADH induces vasoconstriction *in vivo* by enhancing transcellular calcium influx [61]. The recent availability of an agent, 1-deamino penicillamine, 2-(0-methyl) tyrosine vasopressin, which specifically antagonizes the vascular effects of ADH, supports the role of an endogenous vascular

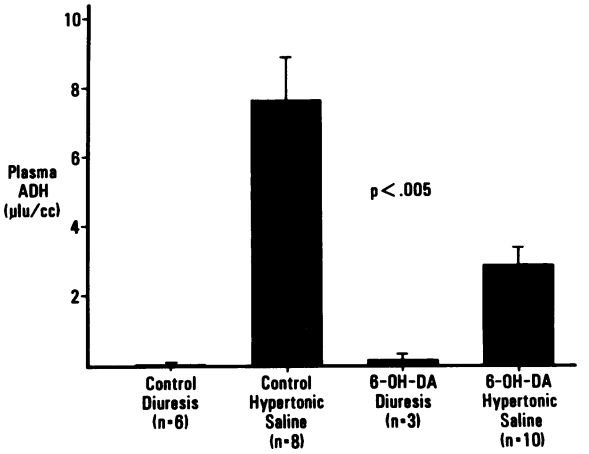

FIG. 7. Plasma ADH levels in water-diuresing animals before and after hypertonic saline infusion. The results in the control rats are depicted in the left two bars and the 6-OHDA results are shown in the right two bars. Values are expressed in microinternational units per milliliter. (With permission from [56].)

effect of ADH [62]. When the ADH vascular inhibitor was used in water diuresing rats with undetectable ADH levels, blood pressure did not fall and ADH levels were undetectable. However, in fluid deprived rats that were shown to have elevated ADH plasma levels of approximately 20 pg/ml, blood pressure significantly declined in the presence of this vascular inhibitor of ADH. This study [63], therefore, supports a role for endogenous ADH contributing to the maintenance of blood pressure in fluid deprived states in the rat.

ABNORMAL WATER EXCRETION IN EDEMATOUS, ADRENAL, AND THYROID DISEASE

A wide variety of clinical disorders are commonly associated with hyponatremia secondary to a defect in water regulation [65] (Fig. 9). Regulatory factors which may influence normal renal dilution include: glomerular filtration rate, renal solute excretion, tubular fluid delivery to the distal nephron, ADH release, ADH-induced water permeability of the collecting duct, papillary tissue solute concentration, and proper functioning of the distal nephron [65]. The understanding of the pathogenesis of impaired water excretion associated with hypothyroidism, adrenal insufficiency, and edematous disorders has been an area of interest for many years [66,67]. Current concepts on the pathogenesis of the renal dilution defect associated with these disorders will be the primary focus of the remainder of this paper.

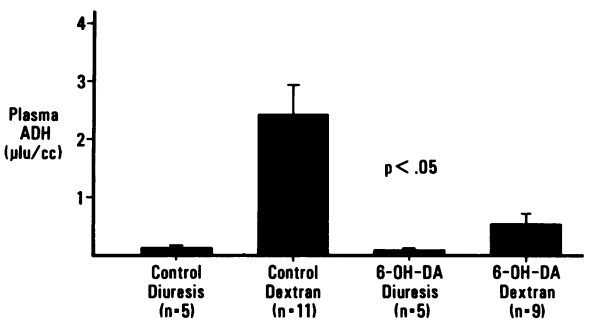

FIG. 8. Plasma ADH levels for water-diuresing (columns labeled "control diuresis" and "6-OHDA diuresis") and dextran-stimulated (columns labeled "control dextran" and "6-OHDA dextran") animals. Neither water-diuresing group had ADH levels significantly different from zero. Values are expressed in microinternational units per milliliter. (With permission from [56].)

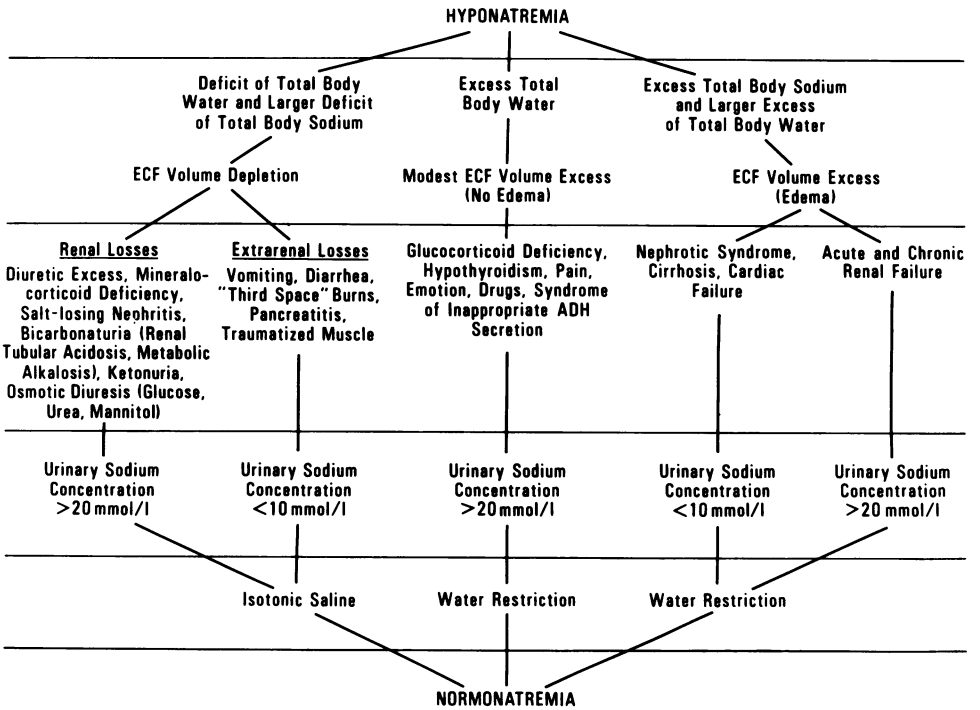

FIG. 9. Clinical approach to the patient with hyponatremia. (With permission from Schrier RW, Berl T: Disorders of water metabolism, Chapt. 1. In Renal and Electrolyte Disorders, 2nd ed. Edited by RW Schrier. Boston, Little Brown Co, 1980.)

EDEMATOUS DISORDERS: CONGESTIVE HEART FAILURE AND CIRRHOSIS

Cirrhosis of the liver and congestive heart failure are commonly associated with water and sodium retention. In both of these disorders, decreased glomerular filtration rate, increased proximal tubular fluid reabsorption, and elevated plasma ADH levels have all been proposed as possible mechanisms for diminished renal water excretion [67]. A decrease in "effective circulating blood volume" is believed to be the precipitating factor which may activate both the intrarenal (decreased glomerular filtration rate and increased proximal fluid reabsorption) and extrarenal (increased ADH) mechanisms which restrict water excretion [67].

Congestive Heart Failure

Bennett et al. have demonstrated decreased distal delivery of tubular fluid in patients with congestive heart failure [68]. Several animal models of congestive heart failure have also demonstrated increased proximal tubule reabsorption of tubular fluid [40,69]. Studies performed by Anderson and associates [40], however, support a mechanism for acute water retention in experimental low output failure that is predominantly mediated by decreased afferent parasympathetic tone from baroreceptors, which results in ADH release. As previously mentioned, Yaron and Bennett also produced an ADH dependent antidiuresis in conscious dogs with acute pulmonary hypertension and right ventricular failure [49]. Recent studies utilizing the radioimmunoassay for ADH have also shown, in patients with congestive heart failure, persistently elevated levels of ADH in spite of hypoosmolality and marked

hyponatremia that would normally suppress ADH release in normal subjects [70]. Conscious rats with high output failure from an aorta-caval fistula demonstrated an inability to excrete a water load while water excretion was normal in ADH-free Brattleboro rats with the same degree of high output failure [69]. Present clinical and experimental evidence therefore suggests that both intrarenal factors and persistent ADH release contribute to the abnormal water excretion commonly seen in heart failure [66].

Cirrhosis

An impaired ability to excrete a water load occurs in a significant number of patients with advanced cirrhosis of the liver [71,72]. Improvement in water excretion occurs with maneuvers that expand extracellular fluid volume which has been shown also to improve renal hemodynamics and distal nephron delivery [72]. However, it is also a possibility that expansion of the extracellular fluid space may also suppress baroreceptor-mediated nonosmotic release of ADH [13,66].

A decrease in free water clearance and an increase in urinary osmolality has been shown to occur with acute portal vein constriction in the dog [73]. Following acute hypophysectomy, portal vein constriction produced less of a diminution in free water clearance and urinary osmolality failed to increase. These studies consequently incriminate both intrarenal and extrarenal (ADH) mechanisms for impaired water excretion. Similar results have been shown in animal models of chronic liver disease produced by carbon tetrachloride (CCl_4) [74] or chronic bile duct ligation [75]. In the CCl_4 rat model, elevated serum ADH levels were still detected following a water load despite hypoosmolality. The defect in water excretion could not be detected in ADH-free Brattleboro rats with CCl_4-induced cirrhosis. Therefore, as seen with congestive heart failure, there is evidence that suggests a dominant role for nonosmolar-induced ADH release causing abnormal water excretion in chronic liver disease [66]; however, intrarenal factors may also contribute.

HYPOTHYROIDISM

Impairment of water excretion and hyponatremia has been described in patients [76] and animals [77] with hypothyroidism. Thyroid hormone replacement has been shown to significantly improve this dilution abnormality [77]. Diminished renal blood flow and glomerular filtration have been noted in the hypothyroid state, suggesting important intrarenal mechanisms for the dilutional defect [66,76]. In the myxedematous patient the most likely etiology of the renal hypoperfusion and augmented proximal tubule reabsorption is the decreased systemic hemodynamics which has been observed [66]. In hypothyroid patients receiving an oral water load a modest increase in minimum urinary osmolality occurs associated with a marked limitation in urine flow rate [76]. These findings are most consistent with intrarenal factors having a dominant role in altered water excretion in hypothyroidism [66]. Studies, however, using radioimmunoassay measurements of ADH and ADH-free Brattleboro rats also support the contention that vasopressin-independent renal factors limit water excretion in hypothyroid states [66,76]. However, Skowsky's studies also revealed that in some patients, despite hypoosmolality, there were elevated levels of ADH, thus implicating enhanced vasopressin secretion in at least some patients with hypothyroidism [76]. Other studies in rats [78] and sheep [79] also indicate a role of ADH in the impaired water excretion associated with hypothyroidism. Decreased cardiac output in advanced hypothyroidism with activation of the baroreceptors is the most likely explanation for this enhanced ADH secretion. The

relative roles of ADH and intrarenal factors apparently depend therefore on the severity of the hypothyroid state. Mild hypothyroidism causes diminished water excretion predominantly secondary to intrarenal factors while ADH release also becomes involved in more severe hypothyroidism.

ADRENAL INSUFFICIENCY

Adrenal insufficiency is another pathological state associated with a dilutional defect. It appears that separate roles have been defined for mineralocorticoid and glucocorticoid deficiencies [67].

Mineralocorticoid Deficiency

Early studies by Kleeman and associates corrected the abnormal water excretion in primary adrenal insufficiency with the administration of glucocorticoids [80]. Unfortunately, pharmacological doses of steroids were used which could have conceivably occupied mineralocorticoid receptors and thereby corrected the altered water excretion [66]. In this regard, other investigators replaced the extracellular fluid volume, but not glucocorticoid hormone, in Addisonian patients and demonstrated improvement in the ability to excrete a dilute urine [81].

With the aid of bioassay measurements of ADH, Share and Travis [82] were able to show that either volume expansion with sodium chloride supplements or glucocorticoid replacement could inhibit ADH secretion in dogs with adrenal insufficiency. Ufferman et al. studied conscious adrenalectomized dogs replaced with physiological doses of glucocorticoids [83]. These animals were shown to have an impaired response to a water load and develop hyponatremia. This hyponatremia was associated with extracellular fluid volume depletion. Either saline drinking water or chronic mineralocorticoid replacement in physiological doses corrected the defect in water excretion. Radioimmunoassay levels of ADH in similar animals demonstrated elevated titers in spite of a hypoosmolar state [84]. The persistent elevation of plasma ADH was no doubt secondary to the known nonosmotic stimulus of ECF volume depletion.

As in the previous pathological conditions discussed, intrarenal mechanisms have also been implicated in the water excretion defect seen in isolated mineralocorticoid deficient animals. ADH-free Brattleboro rats display a defect in water excretion that is corrected by mineralocorticoid replacement or normalization of the extracellular fluid volume [85].

Glucocorticoid Hormone Deficiency

Isolated glucocorticoid deficient states also have been shown to have impaired water excretion [67,86]. As with the previous pathological conditions discussed both intrarenal and extrarenal factors have been determined to play major roles in the altered dilution process [87,88].

Elevated plasma ADH levels measured by radioimmunoassay have been shown in both glucocorticoid deficient rats [88,89] and dogs [90] with abnormal water excretion (Fig. 10). A decrease in cardiac function has been seen in both glucocorticoid deficient rats and dogs and is the most likely stimulus for the nonosmotic release of ADH [88,90]. The pathogenesis for the altered cardiac function is currently not understood, but has been clearly dissociated from extracellular volume depletion. In this regard, there is evidence that glucocorticoid deficiency directly impairs myocardial function [88,90].

Studies in Brattleboro rats with hereditary hypothalamic diabetes insipidus have

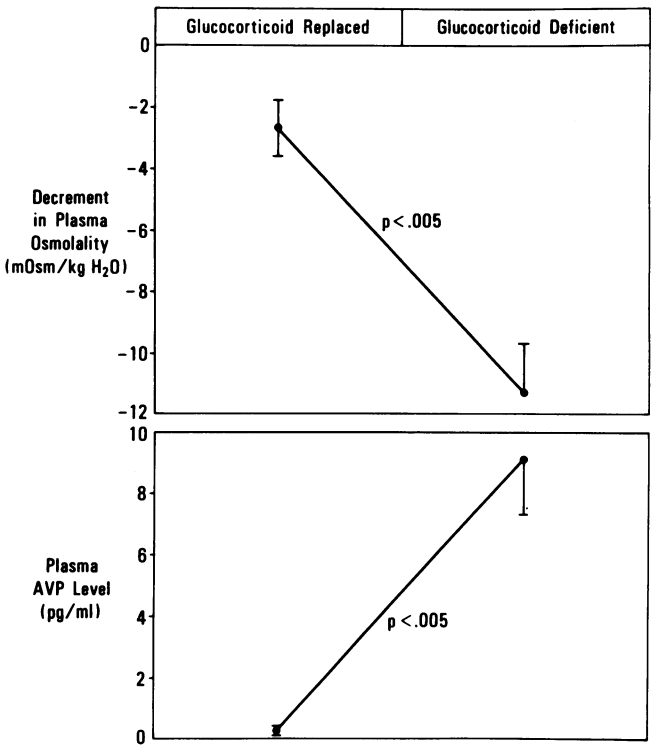

FIG. 10. Effect of an acute water load on Posm and plasma AVP in group I studies (*left panel*) and group II studies (*right panel*). Despite a greater decrement in Posm as compared to group I, plasma AVP remained elevated in the group II studies. (With permission from [90].)

also provided evidence for ADH independent mechanisms of impaired water excretion with glucocorticoid deficiency [85,88]. Both Linas and associates [88] and Green et al. [85] have shown that with prolonged glucocorticoid deficiency intrarenal factors impair water excretion. This effect is probably secondary to marked decreases in both systemic and renal hemodynamics [88,90].

It has been suggested that deficiency of glucocorticoid hormones increases water permeability of the distal nephron [80,91]. Using an isolated perfused renal papilla preparation, Rayson et al. [92] have provided direct evidence against this postulate. Moreover, in anuran membranes glucocorticoid hormone enhances, rather than diminishes, osmotic water movement [93]. The evidence of increased papillary 3′,5′-adenosine monophosphate (cyclic AMP) in papillas from adrenalectomized rats might suggest a direct effect of glucocorticoid deficiency on collecting duct water permeability. However, the observation that this effect on papillary cyclic AMP could be abolished by *in vivo* but not *in vitro* ADH administration is compatible with an effect of glucocorticoid deficiency which is mediated by persistent release of ADH.

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