Vasopressin and Aquaporin 2 in Clinical Disorders of Water Homeostasis

Robert W. Schrier, MD

Summary: Impaired urinary dilution leading to water retention and hyponatremia may occur in patients with cardiac failure, cirrhosis, pregnancy, oxytocin administration, hypothyroidism, glucocorticoid, and mineralocorticoid deficiency. The mechanisms for these defects predominantly involve the nonosmotic stimulation of arginine vasopressin release with up-regulation of aquaporin 2 water channel expression and trafficking to the apical membrane of the principal cells of the collecting duct. These perturbations are reversed by V2 vasopressin receptor antagonists. In contrast, urinary concentration defects leading to polyuria are vasopressin resistant. They may involve several factors, such as impaired countercurrent concentration secondary to down-regulation of Na-K-2Cl cotransporter. Vasopressin-resistant down-regulation of aquaporin 2 expression has also been described as a factor in impaired urinary concentration.
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The cloning of the V2 vasopressin receptor was a major advance in understanding the mechanisms involved in regulation of solute-free water excretion by arginine vasopressin (AVP).[1] Subsequently, mutations of the V2-receptor gene were found to account for approximately 85% of cases of congenital nephrogenic diabetes insipidus.[2] The mechanisms whereby AVP activates the V2 receptor on the basolateral membrane of the principal cells of the collecting duct and leads to increased water permeability of the apical membrane were, however, quite perplexing. The water transport across the bilipid apical membrane of the principal cells was too fast to be caused by diffusion alone. Thus, the shuttle hypothesis was proposed whereby theoretic water channels would be moved from the cytoplasm to the apical membrane of the principal cells by AVP.[3] The discovery of the first water channel, aquaporin 1 (AQP1), by Agre et al[4] led to great excitement in the biomedical community and the awarding of the Nobel Prize in Chemistry in 2003 to Peter Agre. Subsequently, AQP2 was identified by the Sasaki group[5] in the principal cells of the collecting duct. Further investigations have shown that AVP is the major regulator of the AQP2 water channels.[6] Activation of the V2 receptor on the principal cells of the collecting duct by AVP is associated with a cascade of events involving adenylyl cyclase–mediated cyclic adenosine monophosphate (Fig. 1),[7] which leads to both short-term and long-term regulation of AQP2.[8,9] The short-term regulation of AVP involves shuttling the AQP2-containing vesicles from the cytoplasm to the apical membrane. With suppression of vasopressin these apical AQP2 water channels then undergo endocytosis into the cytoplasm.[6] The 5' flanking region of the AQP2 gene has a cyclic adenosine monophosphate response element that is involved in the long-term up-regulation of AQP2 protein expression by AVP.[6]

The discovery of nonpeptide antagonists to the V2 receptor have added yet another important dimension to the understanding of total body water homeostasis.[10] These V2-receptor antagonists are agents that specifically block the action of AVP in human beings. The several V2-receptor antagonists presently involved in clinical studies

Division of Renal Diseases and Hypertension—School of Medicine, Department of Medicine, University of Colorado at Denver Health Sciences Center, Denver, CO

Address reprint requests to Robert W. Schrier, Division of Renal Diseases and Hypertension—School of Medicine, Department of Medicine, University of Colorado at Denver Health Sciences Center, 4200 E Ninth Ave, Box B173, Denver, CO 80262-3706. E-mail: Robert.Schrier@UCHSC.edu

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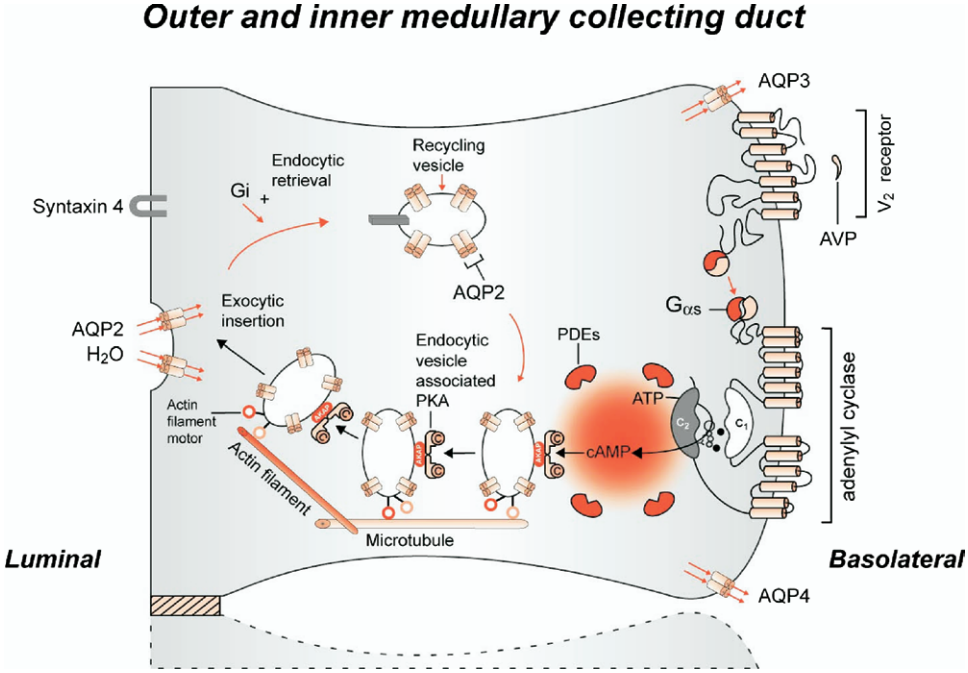

Figure 1. The intracellular action of the antidiuretic hormone, arginine-vasopressin. Reprinted with permission from Bichet.[7]

are shown in Table 1.[11] In contrast to diuretics, which enhance urine water and electrolyte excretion, the V2-receptor antagonists increase electrolyte-free water excretion.

A relative excess of total body water to cation concentration leads to hyponatremia in many clinical circumstances. In fact, hyponatremia is the most frequent electrolyte disturbance in hospitalized patients.[12] V2-receptor antagonists have substantial clinical implications because the majority of the hyponatremic states are caused by the nonosmotic release of AVP.[13] These V2-receptor antagonists also have been important vehicles to understand several water-retaining states including cardiac failure, cirrhosis, and pregnancy, as well as thyroid and adrenal disorders. These disorders are discussed in this review.

CARDIAC FAILURE

Hyponatremia is common in patients with advanced cardiac failure and, in fact, pretreatment hyponatremia is a major risk factor for mortality in patients with congestive heart failure.[14] The degree of hyponatremia and, thus, hypoosmolality in these patients would be expected to maximally suppress AVP in normal subjects. However, plasma AVP, as assessed by radioimmunoassay, is not maximally suppressed in hyponatremic patients with heart failure.[15,16] If indeed baroreceptor-mediated, nonosmotic stimulation of vasopressin is responsible for the hyponatremia in cardiac failure, then the expression and membrane trafficking of AQP2 should be increased. Experimental studies in cardiac failure rats were, therefore, undertaken to examine this possibility.[17,18] The results indeed showed an up-regulation of AQP2 protein expression and increased AQP2 trafficking to the apical membrane of principal cells of the collecting duct. Moreover, the excess water retention and hyponatremia in these heart failure animals was reversed by a V2-receptor antagonist.[17] Subsequently, several studies with orally active, nonpeptide V2-receptor antagonists have been shown in heart failure patients to enhance electrolyte-free water reabsorption and improve serum sodium concentration.[19–21] AQP2 can be detected in the urine in the presence of AVP as a result of movement into the nephron lumen from the apical membrane of collecting duct principal cells.[22] In this regard, a V2-receptor antagonist was shown to decrease urinary AQP2 in heart failure patients.[23]

Table 1. Vasopressin-Receptor Antagonists

	Company	Approval Stage	Description/Mode of Administration	Purpose
Satavaptan (SR-121463)	Sanofi-Synthelabo (Paris, France)	Phase III	Vasopressin V2-receptor antagonist Selective, orally active, nonpeptide	Euvolemic* and hypervolemic† hyponatremia
Lixivaptan (VPA-985)	Cardiokine (Philadelphia, PA)	Phase III	Vasopressin V2-receptor antagonist Selective, orally active, nonpeptide	Euvolemic and hypervolemic hyponatremia
Tolvaptan (OPC-41061)	Otsuka Pharmaceutical (Tokyo, Japan)	Phase III	Vasopressin V2-receptor antagonist Selective, orally active, nonpeptide	Euvolemic and hypervolemic hyponatremia
Conivaptan (YM-087) Vaprisol	Astellas (Tokyo, Japan)	Approved	Vasopressin V1- and V2-receptor antagonist Nonselective, intravenous, limited to 4 days	Euvolemic hyponatremia and cardiac failure
Mozavaptan, (OPC-31260) Physuline	Otsuka Pharmaceutical	Approved	Vasopressin V2-receptor antagonist Selective, orally active, nonpeptide	Paraneoplastic syndrome of antidiuretic hormone secretion

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*Euvolemic hyponatremia (near-normal total body sodium without edema).
†Cirrhosis and heart failure: hypervolemic hyponatremia (an increase in total body sodium, causing edema).

The long-term Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) study in heart failure patients showed an early improvement in dyspnea[24] associated with long-term safety.[25] An effect to decrease mortality in heart failure patients with tolvaptan, a V2-receptor antagonist, however, was not observed.[25]

CIRRHOSIS

The renal regulation of sodium and water excretion resides primarily in the arterial circulation.[26,27] Of total circulating blood volume, approximately 85% resides on the venous side of the circulation, with the remaining 15% in the arterial circulation. Stretch arterial baroreceptors in the carotid artery, aortic arch, and glomerular afferent arterioles sense arterial underfilling and activate the neurohumoral axis as a compensatory response to maintain arterial perfusion. In low-output cardiac failure this compensatory reflex is activated by a decrease in cardiac output. With cirrhosis, however, cardiac output is increased in the presence of continued sodium and water reabsorption and ascites formation. Early in cirrhosis, however, arterial vasodilation occurs in the splanchnic circulation secondary to portal hypertension.[27] Arterial underfilling can occur by either a decrease in cardiac output or systemic arterial vasodilation, thereby activating the neurohumoral response including the nonosmotic release of AVP (Fig. 2).[28] Thus, both cardiac failure and cirrhosis show arterial underfilling despite an increase in total blood volume secondary to expansion on the venous side of the circulation. The increase in

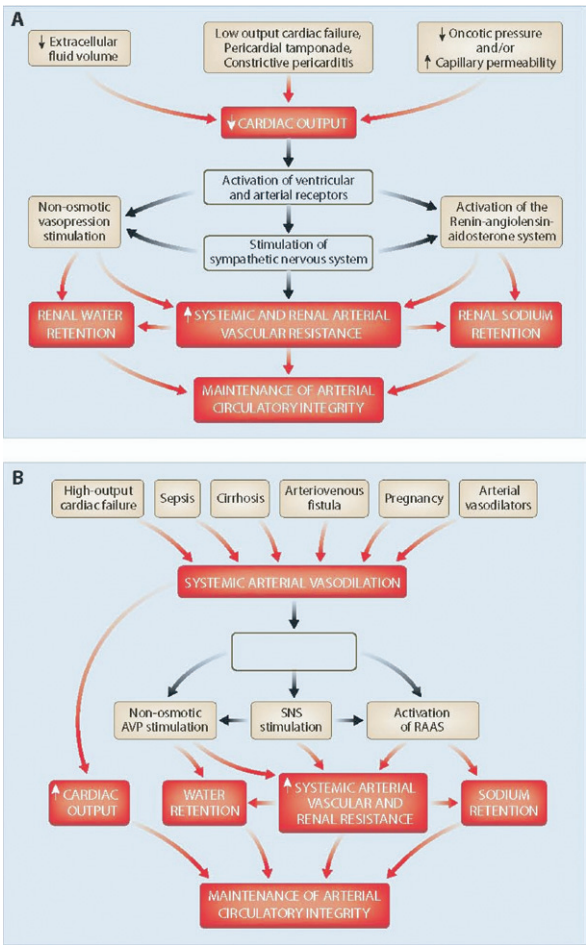

Figure 2. (A and B) Clinical conditions in which a decrease in (A) cardiac output and (B) systemic arterial vasodilation causes arterial underfilling with resultant neurohumoral activation and renal sodium and water retention. In addition to activating the neurohumoral axis, adrenergic stimulation causes renal vasoconstriction and enhances sodium and fluid transport by the proximal tubule epithelium. Reprinted with permission from Schrier.[28]

cardiac output in cirrhotic patients occurs secondary to arterial vasodilation and the resultant decreased cardiac afterload.

On the background of this pathophysiology of cirrhosis, the nonosmotic stimulation of AVP should be involved in the excessive water retention and hyponatremia. Again, as with cardiac failure, pretreatment hyponatremia is a major risk factor for increased mortality in patients with advanced cirrhosis.[29] Plasma AVP, as assessed by radioimmunoassay, has been shown not to be suppressed by an acute water load in hyponatremic cirrhotic

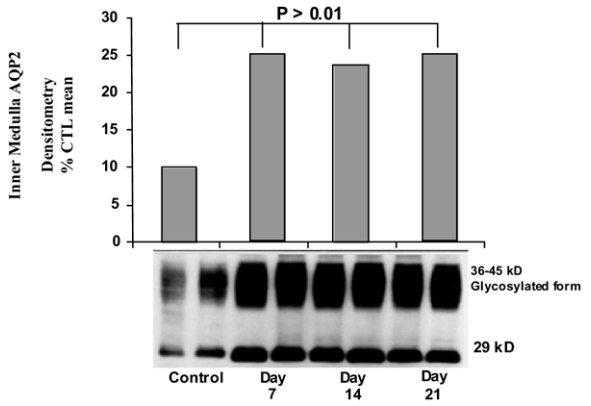

Figure 3. Protein expression of inner medullary AQP2 in pregnancy. Reprinted with permission from Ohara et al.[37]

patients.[30] In advanced experimental cirrhosis, an up-regulation of inner medullary AQP2 expression has been shown.[31] An increase in urinary AQP2 also has been found to be present in cirrhotic patients.[32] Orally active V2-receptor antagonists have been used to treat hyponatremia in cirrhotic patients.[21,33] These studies clearly have shown that an enhanced electrolyte-free water excretion and an increase in plasma sodium concentration occur with V2-receptor antagonist administration in hyponatremic cirrhotic patients.

PREGNANCY

Early in normal pregnancy, plasma osmolality decreases by about 10 mOsm/kg in association with an increase in thirst and water intake.[34] Studies have shown that pregnancy is also a state of arterial underfilling secondary to systemic arterial vasodilation.[35,36] In the presence of hypoosmolality plasma AVP is not suppressed and the renin-angiotensin-aldosterone axis is activated early in pregnancy. In pregnant rats inner medullary AQP2 is up-regulated during the first trimester (Fig. 3)[37] and a V2-receptor antagonist is associated with urinary dilution and increased electrolyte-free water excretion. Thus, pregnancy, as with cirrhosis, is another example in which arterial underfilling occurs secondary to systemic arterial vasodilation with the nonosmotic AVP stimulation and up-regulation of AQP2 expression. In both cirrhosis and pregnancy there is evidence for a

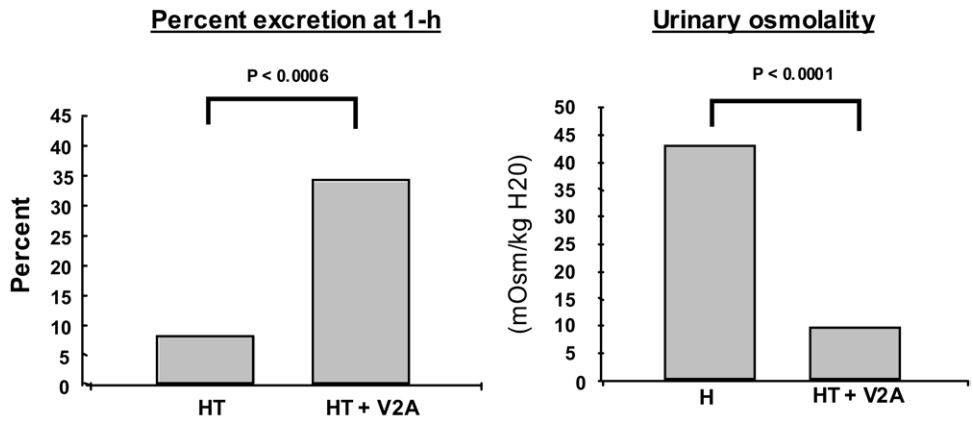

Figure 4. Reversal of impaired water excretion during hypothyroidism (HT) with V2-receptor antagonist (V2A). Reprinted with permission from Chen et al.[44]

role of nitric oxide in mediating the arterial vasodilation.[38,39]

Exogenous oxytocin is used to stimulate labor in pregnant women and can be associated with hyponatremia.[40] This water-retaining effect of oxytocin has been shown in Brattleboro rats, which have no detectable circulating AVP.[41] In Brattleboro rats oxytocin increased AQP2 expression and trafficking to the apical membrane.[42] Moreover, the antidiuresis and AQP2 effects were completely reversed by a V2-receptor antagonist. There was no effect of an oxytocin antagonist. The effect of oxytocin on electrolyte-free water excretion and AQP2 therefore appears to be primarily caused by activation of the V2 receptor.

HYPOTHYROIDISM AND HYPERTHYROIDISM

Patients with advanced primary hypothyroidism may be hyponatremic and fail to suppress plasma AVP with an acute water load.[43] Advanced hypothyroidism may be associated with a decrease in blood pressure secondary to diminished myocardial contractibility and heart rate. These hemodynamics are mimicked in hypothyroid rats and are reversed with thyroxin replacement.[44] These impaired systemic hemodynamics would be expected to activate baroreceptor-mediated, nonosmotic AVP release and indeed this is the case. In this rat model of hypothyroidism the increase in plasma AVP was associated with up-regulation of AQP2. Moreover, a V2-receptor antagonist has been shown in this rat model of hypothyroidism to reverse the increased AQP2 and the impaired response to an acute water load (Fig. 4).[44] The hypothyroid rats also showed a diminution in maximal urinary concentration that was associated with a defect in the countercurrent concentrating mechanism.[45] This defect was related to diminished maximal medullary osmolality and down-regulation of the cotransporter, NA-K-2Cl, which initiates the countercurrent concentrating mechanism.

Hyperthyroid patients may show polyuria[46] and this also has been shown to occur in the hyperthyroid rat.[47] Somewhat surprising, however, this polyuria in the hyperthyroid rat is associated with an up-regulation of the Na-K-Cl transporter. The animals are, however, hypertensive and have an increase in solute excretion, even in the presence of control of water and food intake, most likely secondary to increased blood pressure and catabolism. The diminished urinary concentration and polyuria in hyperthyroid rats was associated with a down-regulation of AQP2 and a persistent solute diuresis.[47] Both of these potential mediators of polyuria associated with hyperthyroidism may be related to the effect of the increase in blood pressure, which has been shown to increase salt and water delivery to the distal nephron[48] and decrease AQP2 expression.[49]

GLUCOCORTICOID DEFICIENCY AND MINERALOCORTICOID DEFICIENCY

The disorders of water homeostasis in glucocorticoid deficiency and mineralocorticoid defi-

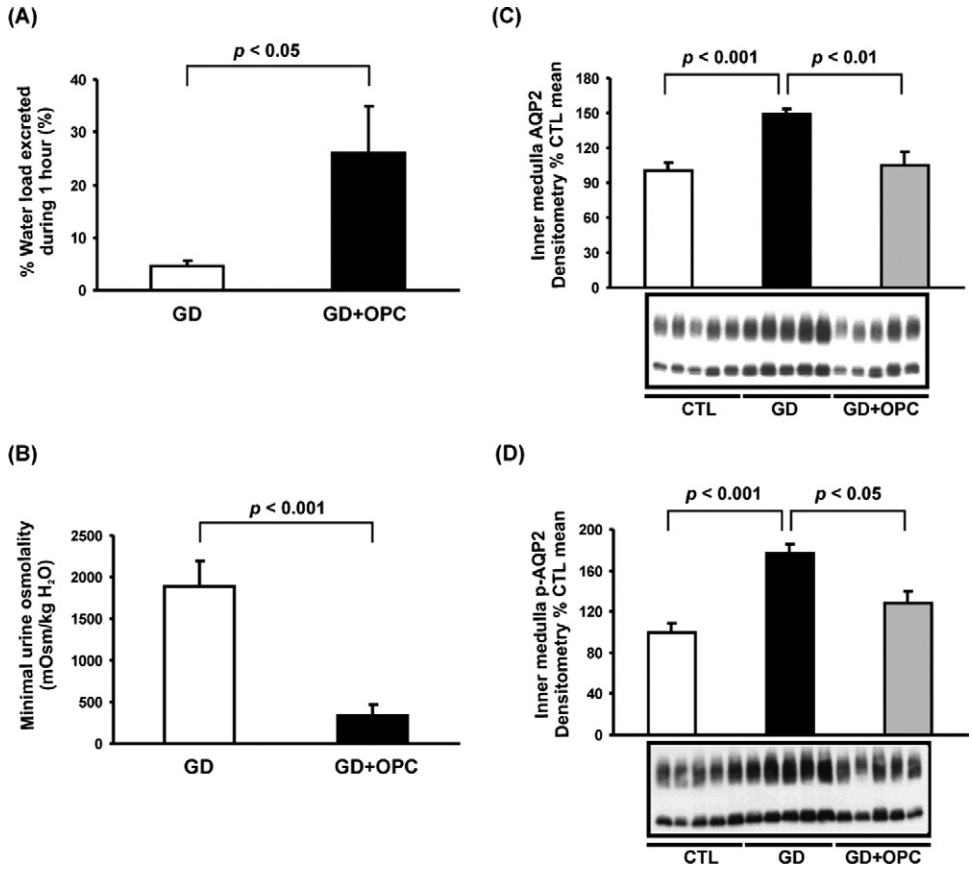

Figure 5. Effect of V2-receptor antagonist (OPC) in glucocorticoid-deficient rats to reverse the (A) impaired water excretion and (B) urinary dilution, as well as the (C) increased AQP2 and (D) phosphorylated AQP2 expression. Reprinted with permission from Wang et al.[56]

ciency appear to be mediated by different mechanisms.[50,51] Both of these disorders show hyponatremia associated with increased plasma AVP concentrations. Mineralocorticoid deficiency is associated with renal salt wasting, extracellular fluid volume deletion, and a decrease in cardiac output and blood pressure. In rats with mineralocorticoid deficiency these alterations are associated with water retention, hyponatremia, and up-regulation of AQP2 expression, effects that were totally reversed by avoidance of sodium depletion.[52] In contrast, glucocorticoid deficiency is, if anything, mildly sodium retaining. A decrease in blood pressure, however, occurs secondary to diminished cardiac output and an impaired systemic vascular response to hypotension.[53] The hyponatremia of hypopituitarism (ie, selective glucocorticoid deficiency) can be reversed with physiologic doses of hydrocortisone.[54] In addition to the baroreceptor-mediated, nonosmotic AVP release secondary to hemodynamic alternations, there is also experimental evidence that glucocorticoid hormone is necessary for maximal suppression of vasopressin synthesis in the hypothalamus.[55] In experimental selective glucocorticoid deficiency, the increase in plasma AVP was associated with an up-regulation of vasopressin-mediated AQP2 water channels.[56] V2-receptor antagonism was associated with reversal of the impaired water excretion and increase in AQP2 expression (Fig. 5).[56] Thus, the impaired water excretion and hyponatremia with primarily adrenal insufficiency (ie, Addison's disease) is caused by both glucocorticoid and mineralocorticoid deficiency via nonosmotic stimulation of AVP but by different pathways.

In summary, much has been learned about the mechanisms of disorders of water homeostasis with the nonosmotic AVP stimulation and AQP2 up-regulation playing a pivotal role in the defects in urinary dilution leading to hyponatremia. The urinary concentrating defects are

more likely to involve defects in the countercurrent concentrating mechanism such as down-regulation of Na-K-2Cl and diminished maximal medullary osmolality.

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