

# Hyponatremia: More to the story than disordered sodium homeostasis

**T**HE SERUM SODIUM concentration is regulated by thirst and by renal water conservation or excretion. In the kidney, two important events are necessary for normal water homeostasis:

- First, sodium reabsorption in excess of water reabsorption (urinary dilution) occurs in the thick ascending limb and distal tubules, creating hypotonicity of the tubular fluid entering the latter portion of the nephron.
- Second, the neurohormone arginine vasopressin modifies water permeability in the principal cells of the collecting duct.

## ■ INSIGHTS INTO VASOPRESSIN'S ACTIONS

Our understanding of the cellular mechanisms of vasopressin has advanced since the discovery of water channels by Preston et al.<sup>1</sup> Vasopressin produces its effects via binding to a specific receptor (the vasopressin type 2, or V<sub>2</sub>, receptor) on the basolateral surface of the collecting duct principal cells, initiating a sequence of events that results in the phosphorylation of the aquaporin-2 water channels. This causes translocation of the aquaporin-2-containing vesicles from the cytosol to the apical membrane of the collecting duct cell, permitting passive water movement from the tubular lumen to the interstitium along the osmotic gradient created by the countercurrent concentrating mechanism.

## ■ THE VASOPRESSIN–HYPONATREMIA CONNECTION

In the normal individual, variations in plasma osmolality (primarily due to serum sodium concentration) of as little as 1% produce significant changes in vasopressin secretion and water homeostasis, tightly maintaining serum sodium within the range of 136 to 145 mEq/L.

Hyponatremia (serum sodium < 135 mEq/L) is a common clinical disorder that

usually results from the nonosmotic stimulation of vasopressin secretion. It can occur in states of normal sodium balance as well as in conditions associated with sodium depletion and excess, underscoring that disordered sodium homeostasis is not the main explanation for the hyponatremia.

## ■ GETTING A HANDLE ON HYPONATREMIA

This supplement begins with a review by **Dr. Ivor Douglas** in which he summarizes the clinical approach to unraveling the various causes of hyponatremia and addressing their treatment.

### Two distinct hyponatremic populations

Following this overview, two special populations with hyponatremia are discussed—one very healthy and the other very sick.

Hyponatremia associated with prolonged exercise has attracted increased recognition as more and more people participate in long-distance running and other endurance sports. Though the exact mechanisms leading to exercise-associated hyponatremia are not certain, several risk factors have been identified, including inadequate conditioning prior to racing and excess fluid replacement during competition. The article here by **Dr. Robert E. O'Connor** discusses the observed and proposed mechanisms of exercise-associated hyponatremia and suggests preventive measures.

A second population with hyponatremia includes patients with nephrotic syndrome, severe cirrhotic liver disease, and advanced heart failure. In each of these conditions, the decrease in effective (perceived) circulating volume and the upregulation of several hormones, including angiotensin and catecholamines, cause nonosmotic stimulation of vasopressin.

Because these patients are already volume-expanded and sodium-retentive, they are typi-

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cally placed on sodium-restricted diets and permitted only hypotonic fluids. The upregulation of vasopressin impairs the excretion of the hypotonic fluids they receive and initiates and sustains the hyponatremia. Vasopressin (via binding to vasopressin type 1A receptors on vascular smooth muscle and cardiac myocytes) also increases arteriolar vasoconstriction and is mitogenic and inotropic to the cardiac myocyte.

#### ■ EMERGENCE OF VASOPRESSIN-TARGETED THERAPIES

Correction of hyponatremia has been difficult, and clinicians have had to settle for partial correction at best. Because effective correction of vasopressin-mediated water retention/hyponatremia has been poor, it has not been clear whether the vasopressin disorder contributes to other aspects of the morbidity associated with these disorders. The recent development of vasopressin receptor antagonists that can be administered either parenterally or orally has provided an opportunity to analyze the role of vasopressin in these disorders and to observe the benefits of treatment.

Among the subpopulations of hyponatremic patients, it is those with advanced heart

failure in whom the pathophysiologic role of vasopressin and the potential of vasopressin receptor antagonists have been best studied. The supplement's third article, by **Dr. Steven R. Goldsmith**, details the role of increased vasopressin specifically in these patients.

The supplement concludes with a review by **Dr. Joseph G. Verbalis** of available clinical data on the use of vasopressin receptor antagonists to treat hyponatremic patients with severe heart failure or any of the other underlying conditions discussed above.

Advances in the management of hyponatremic disorders appear to be on the horizon. Careful clinical trials must be completed to clarify which patients with which of these disorders will be the greatest beneficiaries.

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#### ■ REFERENCES

1. **Preston GM, Carroll TP, Agre P.** Appearance of water channels in *Xenopus* oocytes expressing red cell CHIP28 protein. *Science* 1992; 256:385-387.

Clinicians treating hyponatremia have had to settle for partial correction at best