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Aquaporins and Vasopressin Signaling in Kidney Health and Disease: Introduction

One of the most satisfying aspects of scientific endeavor is to be involved in areas of research in which new basic discoveries suggest potentially novel strategies for therapeutic intervention, as well as for understanding underlying physiologic processes. This has certainly been the case for the field of body fluid and electrolyte homeostasis via vasopressin signaling and water channel function over the past few years. Although the existence and role of water channels (aquaporins) in biological membranes had been known for decades, based on pioneering studies by many superb physiologists and biophysicists, the discovery of the molecular identity of the first water channel by Peter Agre and his colleagues in 1991 has led to a veritable flood of research in this area. Most importantly, it has attracted a great deal of bright, young talent into the field, and has reawakened interest in understanding the mechanisms by which physiologic processes are regulated in health and disease. Much of this exciting research is now taking place under the umbrella of coordinated research activities known as *systems biology* in major institutions throughout the world.

New developments in aquaporin biology, structure, function, and physiology in just about every family of living organism that inhabits the earth appear with great regularity in the scientific literature. In many cases, information generated in one species, organ, or cell type can be applied directly or indirectly to one's own favorite experimental model. This exchange of information has been critical to the aquaporin field, and has contributed greatly to the advances that have been made in the specific area of aquaporins and vasopressin signaling in the kidney, which is covered by this special issue of *Seminars in Nephrology*. The role of water channels in the urinary concentrating mechanism under the influence of the antidiuretic hormone, vasopressin, has been the subject of extensive work that began in the 1950s using model systems such as the amphibian urinary bladder and epidermis. With the discovery of aquaporin 2 (AQP2), the signaling cascade that leads to the incorporation of water channels into the plasma membrane of kidney collecting duct principal cells has been examined in great detail over the past few years. However, some critical questions remain unanswered—notably, what is the precise role of vasopressin-stimulated AQP2 phosphorylation in determining its intracellular location, and how do the multiple phosphorylation sites on AQP2 interact to regulate this process? Nevertheless, research has now matured to the stage at which several clinical applications to correct urine concentrating defects such as nephrogenic diabetes insipidus (NDI) can be envisioned more clearly. Furthermore, recent developments related to vasopressin signaling have led to important potential breakthroughs in hyponatremia and polycystic kidney disease therapy. This issue of *Seminars in Nephrology* brings together short reviews from many leading laboratories in the world. The articles were chosen to provide a concise and timely snapshot of research that is of actual and potential clinical relevance in the domain of renal aquaporins and the vasopressin signaling cascade.

This collection of reviews begins with the contribution of the Verkman laboratory, who have developed several transgenic and knockout mouse models from which suspected and unsuspected roles of various aquaporins have emerged in many organs including the kidney. The most obvious effect of blocking aquaporin

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function in the kidney is DI, a disease of urine concentration characterized in human beings by the daily production of many liters of dilute urine. NDI results from a failure of collecting duct principal cells to appropriately accumulate AQP2 in their apical plasma membrane when the serum osmolality increases and vasopressin is released into the circulation. NDI can be acquired or inherited, usually as an X-linked disease. The review by Nielsen et al summarizes our understanding of lithium-induced NDI, which is a common side effect resulting from treatment of bipolar disorder with lithium therapy. The inherited forms of NDI are discussed in detail in the articles by Bichet and Deen. The former stresses the importance of genetic testing and early treatment in hereditary NDI that results from mutations in the vasopressin receptor (X-linked NDI), while the latter focuses on mutations in AQP2 itself that lead to autosomal forms of hereditary NDI. Both discuss potential strategies to rescue misfolded mutant proteins (vasopressin type 2 receptor [V2R] or AQP2) by driving cell surface expression that could restore signaling and/or water channel function to principal cells. Using a different approach, Bouley et al combine our knowledge of intracellular signaling and recycling pathways to propose ways of bypassing defective vasopressin receptors to induce cell surface accumulation of AQP2 in principal cells.

The vasopressin/AQP2 axis has a central role in other aspects of fluid and electrolyte homeostasis and kidney function. Three articles discuss the use of vasopressin-receptor antagonists (vaptans) as therapeutic agents for various conditions. Kumar and Berl address the use of vaptans in restoring normal electrolyte balance in cases of hyponatremia, most often caused by inappropriate secretion of vasopressin, or by extracellular volume depletion. Schrier also summarizes the use of vasopressin antagonists to understand and treat several water-retaining states both in animal models and in the clinic, including cardiac failure, cirrhosis, and pregnancy, as well as thyroid and adrenal disorders. Procino et al tackle the relationship between AQP2 and hypercalciuria via the calcium-sensing receptor, which may help devise strategies for reducing the risk of nephrocalcinosis, nephrolithiasis, and renal insufficiency. Finally, Torres summarizes exciting data showing that vaptans reduce cyst formation and even reverse cyst growth in mouse models of autosomal-dominant polycystic kidney disease, and provides an update on clinical trials that are based on these data.

These contributions provide a small taste of some practical outcomes that are currently emerging from our deeper basic understanding of how fluid and electrolyte balance is regulated by the kidney. It is to be expected that we will have both success and disappointment as we travel the long and often rocky road from the bench to the bedside. Our final destination may yet seem to be a faint light glimmering over the horizon, but this collection of data shows that it grows brighter every day. I believe that I speak for everyone in this field when I say that we are certainly enjoying the journey, and we are learning much along the way.

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