

The Molecular Physiology of the Urinary Concentrating Mechanism

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Current progress in renal physiology has been driven by progress in molecular biological methods which have led to cloning of cDNAs corresponding to most of the major solute and water transporters expressed along the renal tubule. The Human Genome Project will complete the task, giving us a comprehensive set of primary protein structures. Scientists worldwide are now focussing on development of novel ways to exploit the new sequence information. Our approach to this problem, in the context of renal physiology, is based on two facts: 1) most functions of the cell are mediated by proteins, and not other types of macromolecules; and 2) most important regulatory processes in renal physiology and pathophysiology involve a large array of specific proteins, not a single protein. Consequently, we have developed a strategy to exploit the information from molecular cloning, based on the design and production of ensembles of peptide directed polyclonal antibodies that recognize the major renal transporters involved in specific regulatory process. To study the regulation of the urinary concentrating process, we have developed an ensemble of peptide-directed antibodies recognizing proteins involved in NaCl accumulation in the renal medulla and countercurrent multiplication (aquaporin-1 and all major cation transporters of the thick ascending limb of Henle), urea accumulation in the renal medulla (UTA urea transporter), and collecting duct water transport (aquaporins-2, -3, and -4). These ensembles of antibodies are being employed in immunoblotting and immunocytochemical studies to understand at a molecular level the basis of several complex processes such as 1) the vasopressin-escape phenomenon, 2) the antidiuretic effect of cyclooxygenase inhibitors, 3) the transient defect in concentrating ability associated with prolonged water diuresis, 4) the development of hyponatremia in hepatic cirrhosis and congestive heart failure, and 5) the polyuria associated with lithium-treatment, hypokalemia and hypercalcemia.