PHARMACOLOGY OF VASOPRESSIN AND THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

Elizabeth J. Brant, Albert Q. Lam, and Julian L. Seifter
Renal Division, Brigham and Women's Hospital, Boston, Massachusetts

Pharmacological agents targeted toward renal pathophysiology have had a profound effect in medicine, serving to advance the understanding of both renal disease and normal physiology, and significantly improve disease outcomes in many circumstances. A review of the mechanisms of action of several of these agents will be reviewed here. In addition, new agents active in major hormonal pathways, including antidiuretic hormone (ADH) and the renin–angiotensin system will be introduced.

1 ADH ANTAGONISTS

The antidiuretic hormone (ADH), or vasopressin, is a nonapeptide hormone synthesized in the hypothalamus and secreted by the posterior pituitary [1]. It initiates several physiological mechanisms by acting at any of several receptor types, depending on tissue localization [1–4]. ADH stimulation of V1a receptors results predominantly in cardiovascular changes, including vasoconstriction, platelet aggregation, increased force of cardiac contraction, and increased protein synthesis in the myocardium. V1b receptor stimulation increases adrenocorticotropic hormone (ACTH) secretion by the hypothalamus. The primary function of ADH is maintenance of water balance, which is achieved by stimulation of V2 receptors. The net effect is uptake of free water in the collecting duct of the kidney. ADH receptors are found in numerous other tissues, and the role of ADH continues to be elucidated. However, the important role of ADH in water regulation will be the focus of this discussion.

The system by which ADH facilitates water balance is an elegant one. The distal collecting duct of the kidney is, at baseline, impermeable to water [5]. In the setting of increased plasma osmolality or decreased effective circulating volume, ADH levels rise, with subsequent binding of ADH to V2 receptors on the basolateral membrane of principal cells of the collecting duct [4, 5]. The result of binding is the G-coupled protein-mediated synthesis of cyclic adenosine monophosphate (cAMP), with subsequent activation of protein kinase A. Protein kinase A in turn promotes fusion with the apical membrane of vesicles containing preformed aquaporin-2, rendering the heretofore impermeable collecting duct membrane permeable to water [6]. In addition, the rise in cAMP promotes increased transcription of aquaporin-2 [4]. Simultaneous insertion of aquaporin-3 and aquaporin-4 channels into the basolateral membrane allows for the transcellular movement of water, a process driven by the sodium osmotic gradient. As ADH levels decrease in response to restoration of plasma osmolality and/or volume, the aquaporins are endocytosed, and the collecting duct membrane again becomes impermeable to water.

Disturbance of the ADH-mediated pathway that increases activity of ADH leads to a disruption of water balance, as reflected in the development of hyponatremia, and can be seen in such conditions as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), heart failure, and liver disease. The

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing
Edited by Shayne C. Gad