CC/NUMBER16
APRIL 20, 1981

This Week's Citation Classic

Orloff J & Handler J. The role of adenosine 3',5'-phosphate in the action of antidiuretic hormone. *Amer. J. Med.* **42**:757-68, 1967. [Lab. Kidney and Electrolyte Metabolism, Natl. Heart Inst., NIH, Bethesda, MD]

Antidiuretic hormone is responsible for the regulation of water balance in a variety of animals. In man it increases water reabsorption by the kidney, by stimulating production of adenosine 3',5'-phosphate (cyclic-AMP) in specific renal epithelial cells. The nucleotide increases the permeability of the apical membrane of these cells to water, thereby accelerating the reabsorptive process. [The *SCI*® indicates that this paper has been cited over 310 times since 1967.]

Jack Orloff
National Heart, Lung, and
Blood Institute
National Institutes of Health
Bethesda, MD 20205

March 12, 1981

"In 1940 Homer Smith, then professor of physiology at New York University Medical School, kindled my interest in the action of antidiuretic hormone (ADH) that has continued to this day. Ultimately my goal was to understand the biochemical and/or physical changes responsible for the structural alterations in the renal cell membranes that must account for the permeability effects of ADH. Although my initial studies performed at Yale University in the late 1940s and at the National Institutes of Health in the 1950s were in intact animals. Larry Early, who arrived in my lab in 1959, convinced me to switch to a simpler model, the isolated urinary bladder of the toad. The bladder responds to ADH by increasing its permeability to water in a manner indistinguishable from that of the isolated renal collecting tubule of the rabbit as shown by Crantham and Burg in my lab [1] At the time I was aware of Sutherland's second messenger hypothesis,[2] introduced to me by Martha Vaughan, my wife, who was studying the effect of hormones on the activity of glycogen phosphorylase. In addition, I knew that Jim Hilton had reported that high concentrations of ADH mimicked ACTH in the adrenal[3] and I wondered if cyclic-AMP, a second messenger in the action of ACTH, might be involved in the ADH effect in toad bladder and kidney. When I heard him present studies on the mimicry of glucagon by ADH in the liver at a Salt and Water Club meeting, I was convinced that my hypothesis was plausible.

"I returned to Bethesda and together with Joe Handler, who had joined my lab in 1960, began a fruitful collaborative effort that has lasted for more than a decade. In short order we proved that ADH elicited its effect on water permeability of toad bladder via the intermediacy of cyclic-AMP. The nucleotide alone or theophylline, which prevents its degradation, increased water permeability as did ADH. This was the first evidence that the second messenger could elicit a physiologic response in an intact tissue and lent credence to the Sutherland thesis which until then was supported only by biochemical evidence. Subsequently we showed that ADH increased the cyclic-AMP content of target cells

"On rereading our review I realize how lucky and unduly optimistic we were at the time. It was written in the hope that our observations, our views on the problem, would stimulate us as well as our readers to engage in new studies that might accomplish the goal that we outlined, i e , the elucidation of the biochemical and/or physical processes that alter the membrane and account for changes in water flow across cells. Why are we cited? Perhaps to emphasize that neither we nor others have yet succeeded"[4]

1. **Grantham J J & Burg M B.** Effect of vasopressin and cyclic AMP on permeability of isolated collecting tubules. *Amer. J. Physiol.* **211**:255-9, 1%6.
2. **Sutherland E W & Rall T W.** The relation of adenosine 3.5'-phosphate and phosphorylase to the actions of catecholamines and other hormones. *Pharmacol. Rev.* **12**:265-99, l960.
3. **Hilton J G, Scian L F, Westermann C D & Kruesl O R.** Direct stimulation of adrenocortical secretion by synthetic vasopressin in dogs. *Proc. Soc. Exp. Biol. Med.* **100**:523-4, 1959.
4. **Strewler G J & Orioff I.** Role of cyclic nucleotides in the transport of water and electrolytes. *Advan. Cvctic Nucl. Res* **8**:311-61,1977.