

Katz A I & Epstein F H. The role of sodium-potassium-activated adenosine triphosphatase in the reabsorption of sodium by the kidney. *J. Clin. Invest.* 46:1999-2011, 1967.

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Selective and concordant changes in sodium-potassium-adenosine triphosphatase (Na-K-ATPase) activity of renal microsomes were observed when tubular sodium reabsorption was chronically increased or diminished by various experimental maneuvers. These adaptive responses supported the concept that the enzyme plays a physiologic role in active sodium transport by the kidney. [The SCJ® indicates that this paper has been cited in over 295 publications.]

The Sodium Pump in Renal Transport

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I joined Franklin H. Epstein's laboratory at Yale University in the fall of 1965, just as he was returning from a sabbatical at the University of Oxford during which he had worked on Na-K-ATPase. By that time Epstein had developed a keen interest in the possible role of this ubiquitous component of cell membranes in renal transport. Up to 1965 the best work on Na-K-ATPase was done with red blood cells, and, while it was known that the enzyme is found in abundance in the kidney, relatively little was known about what it does in this organ.

I had just completed my house staff training and was interested in renal physiology but knew little biochemistry and next to nothing about Na-K-ATPase. Epstein's enthusiasm was, however, contagious, and I was soon immersed in work on the subject of this week's *Citation Classic*. Our working hypothesis was simple (and perhaps simplistic): If Na-K-ATPase indeed participates in the bulk transfer of sodium across the renal tubule, increasing or

decreasing the reabsorptive sodium load (i.e., the traffic across the pathway catalyzed by the enzyme) will tend to enhance or suppress its activity. We were pleased to see this prediction validated in a variety of experimental conditions in which alterations in net sodium reabsorption were accompanied by parallel changes selectively in Na-K-ATPase.

While this work was in progress, Epstein thought to test its basic premise in a model in which sodium transport fluctuates much more than it ever could in the kidney even under the most extreme conditions. In collaboration with the late Grace Pickford, we measured Na-K-ATPase activity in gills of the euryhaline killifish (*Fundulus heteroclitus*), a creature equally at home in fresh- and seawater. To our delight we found the enzyme activity in gills of fish adapted to seawater, which markedly increase sodium excretion in response to this osmotic stress, to be sevenfold higher than in gills of fish living in freshwater.¹

These joint studies were followed by others done separately, by Epstein at Yale and later at Harvard University, and by me at the University of Chicago. Epstein and colleagues were the first to show that Na-K-ATPase also mediates renal potassium secretion,² and I learned in the laboratory of F. Morel in Paris to microdissect the nephron and measure the enzyme in single pieces of tubule,³ an improvement over existing techniques utilizing whole tissue homogenates. The function of this and other transport ATPases in the kidney has been reviewed by us^{4,5} and others in subsequent years.

The probable reason this paper has been cited often is that it was among the first to examine in systematic fashion the behavior of the renal enzyme under diverse physiologic conditions and to point to its role in sodium reabsorption—one of the cardinal functions of the kidney. Other contributing factors may be found in the widespread and increasing interest in the Na:K pump in general,^{6,7} which coincided with the remarkable growth of renal physiology and nephrology as independent disciplines in the last 25 years.

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3. Katz A I, Doucet A & Morel F. Na-K-ATPase activity along the rabbit, rat, and mouse nephron. *Amer. J. Physiol.* 237:F114-F120, 1979. (Cited 150 times.)
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5. ———. Distribution and function of classes of ATPases along the nephron. *Kidney Int.* 29:21-31, 1986. (Cited 15 times.)
6. Skou J C, Norby J G, Maunsbach A B & Esmann M, eds. *The Na⁺, K⁺-pump. Part A: molecular aspects.* New York: Liss, 1988. 655 p.
7. ———, eds. *The Na⁺, K⁺-pump. Part B: cellular aspects.* New York: Liss, 1988. 497 p.

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