

## Factors Influencing the Increase in Na-K-ATPase in Compensatory Renal Hypertrophy

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An increase in Na-K-ATPase in kidney homogenates usually accompanies compensatory renal hypertrophy. While it may be evident in both the cortex and medulla of the kidney, it is most marked in the outer medulla and may be present only in that region. The increase in enzyme activity does not depend on an intact adrenal cortex and can be elicited in the absence of adrenal glucocorticoids. It is not seen in the form of renal hypertrophy produced by potassium depletion, in which the transport of sodium and potassium by the kidney is not increased. When present in compensatory renal growth, the enzyme change is correlated with an increase in the reabsorption of sodium, or the excretion of potassium, or both, per unit of renal tissue. It proceeds in the presence of either, but not in the absence of both.

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An increase in the specific activity of sodium-potassium-activated adenosine triphosphatase (Na-K-ATPase) in homogenates of kidney tissue is a regular feature of compensatory renal hypertrophy in the rat. The change in enzymatic activity has special interest since it is not accompanied by similar increases in many other enzymes thought to be bound to plasma membranes, mitochondria or microsomes of renal cells. The factors responsible for this striking change have not been entirely clear, but it is natural to speculate that they have to do with the transport function of the enzyme. At the time the observation was first made, it seemed likely that the increase in enzymatic activity per unit of kidney tissue was caused by the increase in sodium reabsorption per gram of kidney tissue in the remaining hypertrophying kidney of unilaterally nephrectomized rats [1]. This is, of course, a corollary of the increase in glomerular filtration rate that occurs after one kidney is removed [2]. A second hypothesis was that the increase in enzyme was connected, not with the transport of sodium, but with the increased excretory load of potassium required per nephron after renal ablation [3,4]. A third possibility was that the enzyme changes were secondary to changes in endocrine secretions after partial renal excision, adrenal and thyroid hormones in particular having been shown to influence Na-K-ATPase activity in the kidney [Charney AN, Silva P, Epstein FH: unpublished data; 5]. Finally, it seemed conceivable that a burst of renal growth *per se* might be associated with an increase in the specific activity of Na-K-ATPase, even though changes in the transport of sodium and potassium were prevented.

I should like to review a number of experiments, performed in various laboratories including our own, dealing with these questions. The development of several models for experimental renal insufficiency and compensatory hypertrophy has provided an experimental approach that permits the dissection and isolation of individual factors that might be expected to contribute to enhanced enzyme activity in compensatory hypertrophy.

### UNILATERAL NEPHRECTOMY (50% ABLATION) (Figs. 1 and 2)

When one kidney is removed from a male Sprague-Dawley rat weighing 250–300 grams, there is a gradual increase in both glomerular filtration rate and renal weight. The increase in GFR outstrips the increase in renal weight by the end of 1–2 weeks and by three weeks after unilateral nephrectomy, the filtered load of sodium per gram of kidney tissue (and therefore the sodium reabsorbed by renal tubules per gram of kidney tissue) is 20–30 percent higher than in sham-operated pair-fed controls [2]. This increase in the reabsorptive work for sodium per unit of kidney tissue is paralleled by an increase in the Na-K-ATPase activity in kidney homogenates [1]. The increase is most marked in the red medulla of the kidney, though it may be seen in the cortex as well [Unpublished data; 6].

### URETEROPERITONEOSTOMY

It should be pointed out at once that merely increasing the filtration rate per unit of kidney mass (and therefore the quantity of sodium necessarily reabsorbed by renal tubules) is no guarantee in itself that Na-K-ATPase activity will automatically increase. Such a correlation has been observed in high protein feeding to rats [1] and also in the pregnant rat [9]. However, an increase in glomerular filtration rate in one kidney can equally well be produced by ureteroperitoneostomy. It is well established that this maneuver does not produce hypertrophy of the intact kidney [10]. Instead, the remaining kidney may double its glomerular filtration rate. In the experiments of Weinman et al. [7], tubular reabsorption of sodium increased from  $110 \pm 13$  to  $221 \pm 37 \mu\text{Eq}/\text{min}/\text{g}$  kidney by one week after ureteroperitoneostomy. Nevertheless, as Fanestil first reported [8], Na-K-ATPase of renal cortex and medulla remains unchanged. It is conceivable that inflammatory changes induced by peritoneal irritation might have inhibited enzyme induction in some of these experiments, but in

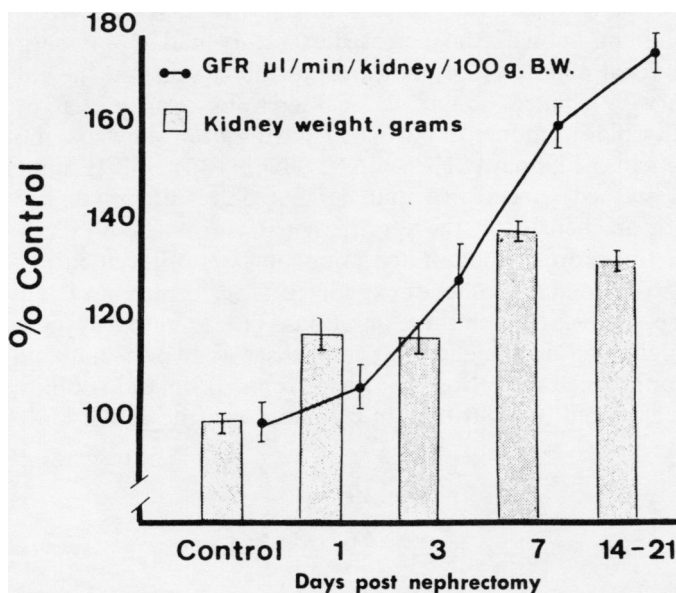


FIG. 1. Relationship between glomerular filtration rate and weight of the remaining kidney following contralateral nephrectomy. (From [2]; reproduced by permission).

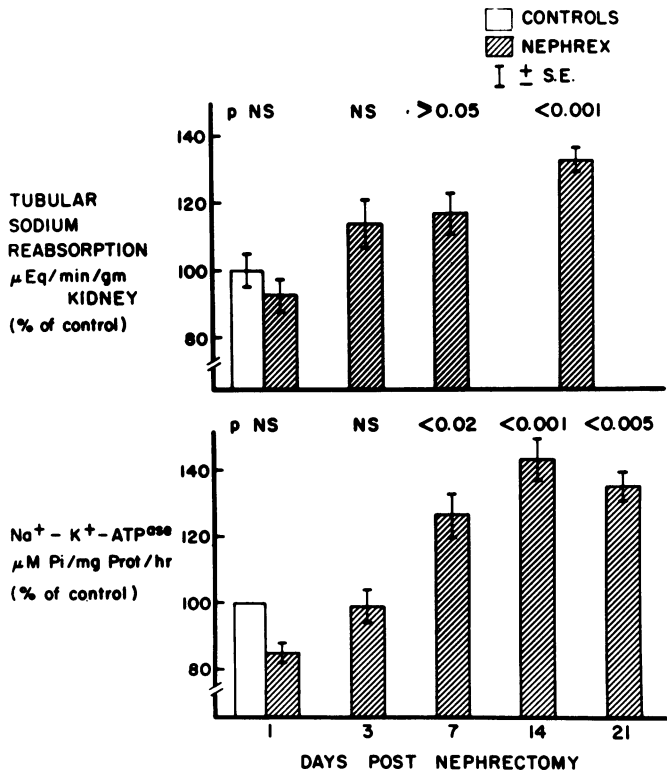


FIG. 2. Changes in renal Na-K-ATPase related to changes in sodium transport after removal of one kidney. (From [2]; reproduced by permission).

similar ones performed by Hayslett, Weinman and Kashgarian, the same results were obtained and inflammation of the peritoneum was carefully looked for and not found. Evidently, an increase in tubular transport, even if sustained for 7-8 days, is not by itself completely sufficient to induce a rise in Na-K-ATPase.

### VARIATIONS IN THE PATTERN OF RENAL GROWTH AFTER NEPHRECTOMY

(Table 1)

The pattern described above, in which GFR and sodium reabsorption per unit of kidney weight is increased after unilateral nephrectomy, is seen in adult rats, usually weighing 250-300 grams. This sequence of events can be modified in several ways, some of the influential variables being age, diet, and extent of removal of kidney tissue. Moreover, the results obtained may vary slightly with different batches of rats even in the same laboratory. In younger rats, the capacity for renal growth is greater than in older ones. In weanlings, for example, compensatory renal growth is so pronounced that as early as one week after nephrectomy there is no change in the ratio of glomerular filtration to renal weight—both have increased in parallel [11]. Even in rats weighing 150 grams, hypertrophy of the kidney, though lagging behind the spurt in GFR at one week, has caught up at four weeks, so that sodium transport per unit of kidney weight is normal, rather than increased. Nevertheless, Na-K-ATPase activity is always significantly elevated in the outer medulla of the hypertrophying kidney.

TABLE 1  
Sodium Reabsorption/Renal Mass in the Course of Renal Hypertrophy  
(% of normal value in control rats)

	1 Week	2 Weeks	3-4 Weeks
50% Nephrectomy			
Adult [2]	119	128	130
Weanling [11]	100		95
75% Nephrectomy			
Adult [4,12; present paper]	140	91	57

A similar phenomenon is seen in older rats after more extensive nephrectomy. If the left kidney plus half of the right kidney are excised, both GFR and kidney weight start to increase. At one week, filtration is considerably ahead, so that net sodium reabsorption per gram of kidney is increased. But by two and four weeks, hypertrophy has caught up. At this time, net sodium transport per unit of kidney tissue is at or below the control level of pair-fed, sham-operated rats. It is difficult under these circumstances to ascribe the increase in Na-K-ATPase per unit of kidney tissue that is present 2-4 weeks after 75 percent nephrectomy to an increase in sodium transport (Fig. 3).

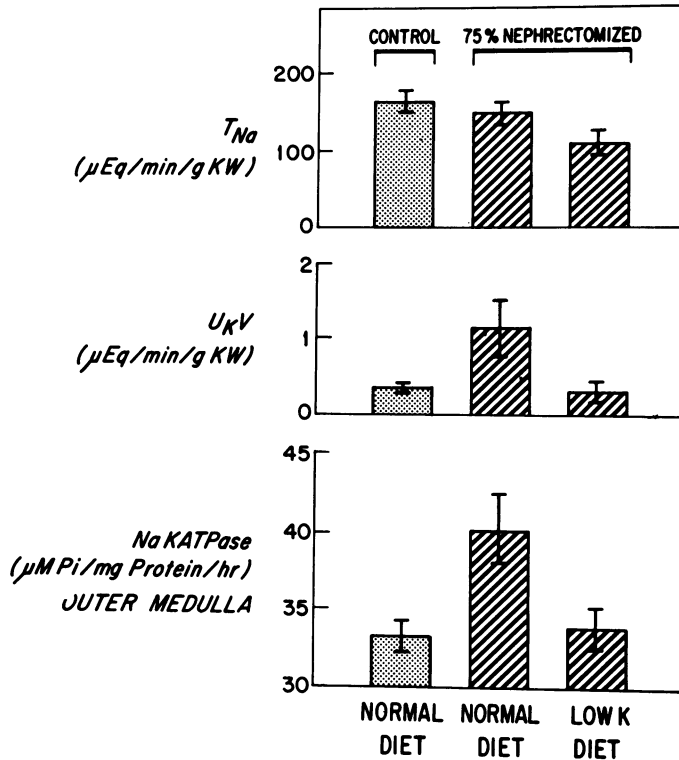


FIG. 3. Na-K-ATPase and renal hypertrophy two weeks after 75 percent nephrectomy. Potassium restriction prevents the increase in enzyme activity.

### INFLUENCE OF THE EXCRETORY LEVEL OF POTASSIUM. 75% NEPHRECTOMY AND UNILATERAL HYDRONEPHROSIS

The observation that a high potassium diet stimulates an increase in renal Na-K-ATPase in normal rats [3] suggested that the transport of potassium, rather than that of sodium, might be the major influence controlling enzyme adaptation in uremia. Most, if not all, of excreted potassium arrives in the urine via tubular secretion, and this secreted load must increase in direct proportion to the quantity of kidney tissue removed, if dietary intake remains constant. The excretory load of potassium per gram of kidney tissue tends to be considerably elevated, therefore, in all forms of compensatory renal hypertrophy secondary to kidney ablation. Figure 3 illustrates an experiment performed by Schon, Silva and Hayslett [4] on adult rats subjected to 75 percent nephrectomy and studied at two weeks after the operation. Note that at this time, renal hypertrophy had caught up with the early increase in glomerular filtration, so that the reabsorption of sodium per gram of kidney was at or below control levels. The excretion of potassium per gram of kidney tissue was, however, elevated in rats given a standard diet, and the Na-K-ATPase activity in the red medulla of the hypertrophied kidney remnant was significantly increased.

The increase in Na-K-ATPase could be entirely prevented, however, by restricting dietary potassium in proportion to the decrease in functioning renal tissue. Under these circumstances, potassium excretion per gram of kidney tissue (presumably a rough measure of secretory load) remained normal. Renal growth was not prevented by the change in diet. The necessity for potassium excretion, then, appeared to be the major and possibly the sole reason for the increase in Na-K-ATPase in this model of renal hypertrophy, studied two weeks after 75 percent nephrectomy.

Is potassium, then, the only explanation for the changes in Na-K-ATPase in hypertrophy? Evidently not. Figure 4 illustrates the results of experiments in which rats subjected to 75 percent nephrectomy were studied after only one week. At this time, the increase in GFR in the remnant kidney still exceeded the increase in kidney weight, so that the sodium reabsorptive load was elevated. Potassium excretion per gram of kidney tissue was also high. Restriction of potassium returned the potassium excretory burden per gram of hypertrophied kidney to normal, but the load of sodium filtration and reabsorption remained high. Na-K-ATPase in the renal medulla was increased, and remained high despite potassium restriction. The difference between these experiments and the preceding ones lies in the rate of sodium reabsorption per gram of kidney tissue, which in the one-week rats may have stimulated and sustained transport enzyme activity despite removal of the potassium stimulus.

A similar conclusion can be drawn from the experiments illustrated in Fig. 5. The left ureter of adult rats weighing 250–300 grams was tied and one week later they were studied. Again, there is an increase in sodium reabsorption as well as in potassium excretion per gram of kidney tissue. Na-K-ATPase activity is elevated in the medulla of the kidney remnant. Here, too, restriction of potassium does not affect enzyme activity, which in this model of renal compensation is apparently responding to the increased demands for tubular sodium reabsorption.

### EFFECT OF ADRENALECTOMY

Both glucocorticoids and mineralocorticoids appear to have a direct effect upon renal Na-K-ATPase (though perhaps in different portions of the tubule) [13]. It was therefore of interest to see whether Na-K-ATPase would increase as a result of renal hypertrophy that developed in the absence of the adrenal glands. It had previously

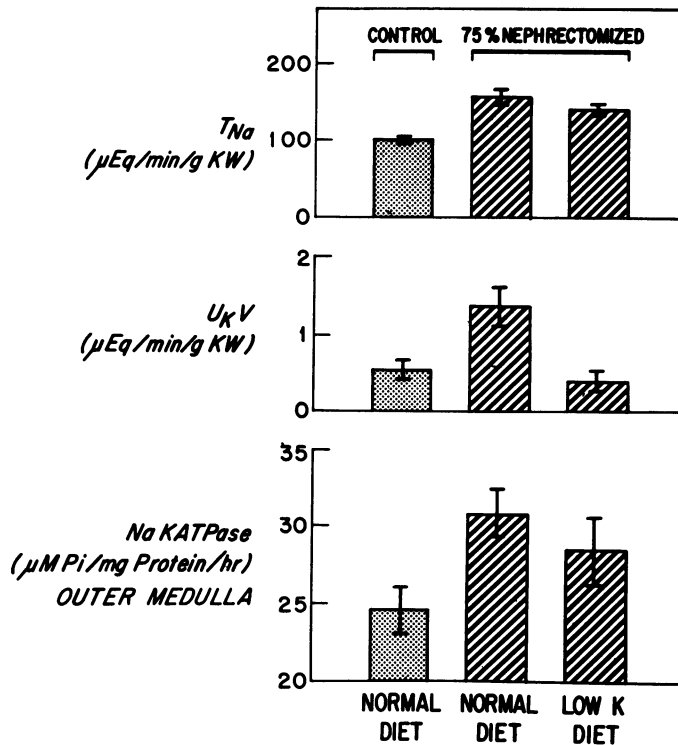


FIG. 4. Na-K-ATPase and renal hypertrophy one week after 75 percent nephrectomy. Sodium reabsorption per gram of kidney is elevated, and potassium restriction does not prevent an increase in Na-K-ATPase activity.

been shown that adrenalectomy did not prevent compensatory renal hyperplasia from occurring, if dietary intake of food and water was maintained [14]. Rats were adrenalectomized and maintained on daily injections of desoxycorticosterone acetate, then studied two weeks after 75 percent nephrectomy. Adrenalectomy, as expected, resulted in a fall in Na-K-ATPase activity by about one-third in both medulla and cortex. During compensatory renal hypertrophy, enzymatic activity in the medulla (but not the cortex) rose significantly, from  $24 \pm 1.9$  to  $29 \pm 1.5$   $\mu\text{MPi}/\text{mg protein}/\text{hr}$ , though not quite to the level of that in control rats with intact adrenals. The increase in Na-K-ATPase activity that accompanies compensatory hypertrophy, therefore, can occur independently of an increase in secretions from the adrenal cortex.

**HYPERTROPHY WITHOUT AN INCREASE IN NA-K-ATPASE:  
RENAL GROWTH CAUSED BY POTASSIUM DEPLETION  
(Table 2)**

Does the process of renal growth itself elicit an increase in Na-K-ATPase, regardless of the transport demands placed on the kidney? The answer to this question should lie in the study of still other models of renal hypertrophy, unassociated with marked changes in filtration or excretion of sodium and potassium. One way to stimulate this kind of hypertrophy of the kidneys in rats is to place them on a potassium-free diet. After a week or two, both kidneys have increased in size by

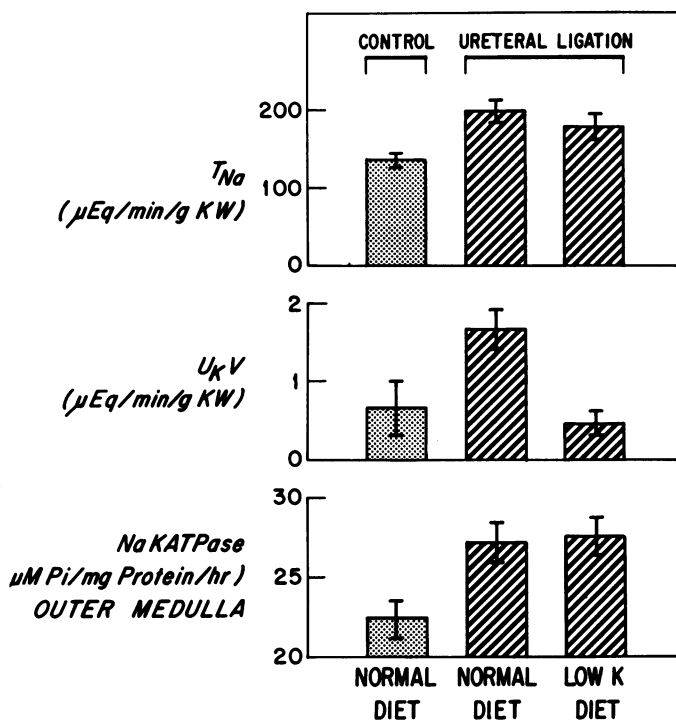


FIG. 5. Na-K-ATPase one week after ureteral ligation. Sodium reabsorption per gram of kidney is elevated and potassium restriction does not prevent an increase in Na-K-ATPase activity.

about 25 percent. Glomerular filtration rate, however, is unchanged, so that the reabsorption of sodium per gram of kidney may actually be lower than normal, and potassium secretion is probably turned off. Under these circumstances, Na-K-ATPase of kidney medulla and cortex remains at control levels. Evidently renal hypertrophy *per se* is not a sufficient stimulus to increase Na-K-ATPase.

### SUMMARY

An increase in Na-K-ATPase activity in homogenates of kidney tissue regularly accompanies renal hypertrophy induced by loss of nephrons in the rat. While the increase in enzyme activity is usually associated with an increase in GFR and sodium reabsorption per unit of renal mass, this is not in itself sufficient to induce a rise in

TABLE 2  
Effect of Renal Hypertrophy Caused by  $K^+$  Depletion on Na-K-ATPase

	Control	1 Week K-depletion
Rt. kidney weight		
% body wt	0.46 ± 0.01	0.55 ± 0.02
Na-K-ATPase, $\mu\text{M Pi}/\text{mg prot}/\text{hr}$		
Cortex	11.8 ± 0.7	11.4 ± 1.0
Medulla	22.4 ± 1.3	24.0 ± 1.2

Values are mean ± s.e.  $n = 7$ .

Na-K-ATPase. Enzyme levels do not change in ureteroperitoneostomy, a condition in which GFR is increased but kidney size is unchanged. Renal hypertrophy that is not accompanied by a change in reabsorptive transport as seen, for example, in potassium depletion, also leaves Na-K-ATPase activity unaltered.

When present in rat kidneys undergoing compensatory growth, the increase in Na-K-ATPase activity appears to be an adaptive response to an increase in the reabsorption of sodium, or the excretion of potassium, or both, per unit mass of renal tissue. It proceeds in the presence of either but not in the absence of both. The increase in enzyme activity does not depend on an intact adrenal cortex and can be elicited in adrenalectomized animals.

#### ACKNOWLEDGEMENTS

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