Endocrine

PRIMARY ACQUIRED HYPOALDOSTERONISM WITH A SELECTIVE KALIURETIC DEFECT IN RESPONSE TO EXOGENOUS MINERALOCORTICOIDS*

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Juha P. Kokko

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INTRODUCTION

Chronically elevated serum potassium concentration is rare in the absence of severe renal failure. When hyperkalemia is documented in association with metabolic acidosis and renal salt wastage, it is suggestive of either selective hypoaldosteronism or failure of target organs to respond normally to aldosterone (pseudo-hypoaldosteronism). Both selective hypoaldosteronism and pseudo-hypoaldosteronism may be inborn biosynthetic errors or acquired defects. To date the inborn error in infancy has received the most attention due to its dramatic presentation and a more common recognition; however, acquired aldosterone defects in adult patients are being increasingly recognized. This manuscript describes a previously unreported combination of acquired selective hypoaldosteronism and a failure of kaliuresis in response to exogenously-administered mineralocorticoids. Of further interest in this case is the maintenance of normal antinatriuretic and increased hydrogen secretory response to intramuscular mineralocorticoids.

Case Report

A 57-year-old retired beautician was referred to Parkland Memorial Hospital on January 16, 1984, for evaluation and treatment of persistent hyperkalemia. She had been in excellent health until May 1972 when she underwent a laminectomy for a herniated nucleus pulposus. Her surgery was uneventful and her convalescence uncomplicated except that she lost 70 lbs (178 to 108 lbs) during the seven-month period she was in a body cast. When her cast was removed in 1973 she had her first syncopal episode. A complete evaluation in another hospital in 1973 suggested

that her syncope was the result of orthostatic hypotension. Pertinent aspects of her work-up included normal EMG, EKG, SPEP, and UGI. Laboratory findings revealed a Hct 42%, TP 8.3 gm%, albumin 5.3 gm%, BUN 9 mg%, T_3RU 25%, T_4 4.8, and 24-hr urine 17-OH steroids 12 mg/24 hr (nl <10 mg/24 hr) and 17 ketosteroids 7 mg/24 hr (nl 5-15 mg/24 hr). Serum electrolytes were reported as "normal". She was discharged on 0.1 mg 9-α-fluorocortisol.

Patient continued to complain of dizziness and had a number of other hospital admissions between 1974 and 1976. Her standing BP dropped to 60/30 mmHg. Again, neurological work-ups were unrevealing and her electrolytes were normal with Na 132 mEq/L, K 4.5 mEq/L, CO_2 24 mEq/L, and BUN 18 mg%. She then was treated with various combinations of Ephedrine, elastic stockings, and an anti-gravity suit. The does of 9-α-fluorocortisol was gradually increased to 0.6 mg/day.

In June 1976 she was documented for the first time as being hyperkalemic with serum K of 5.7 mEq/L. In 1978 an endocrine work-up at another hospital showed "non-detectable" 24-hr urinary aldosterone on low Na diet, serum aldosterone of 2 ng/dl after 4 hr of upright posture plus diuretic, plasma cortisol of 2 μg/dl at 4 PM after ACTH injection. She was also said to have an "abnormal" response to 8-hr ACTH infusion but a reportedly "normal" metyrapone test showed an increase in 11-DOC (to 3 μg/dl) and a slight decrease in serum cortisol. It was recommended at that time to increase 9-α-fluorocortisol to 1.0 mg/d.

Since 1979 she has not only been hypotensive, but also severely hyperkalemic with numerous serum K concentrations over 7.0 mEq/L with the highest recorded value of 9.9 mEq/L. When her serum K has been over

9.0 mEq/L she is symptomatic with generalized weakness and occasional frank paralysis. These values have occurred in spite of sodium polystyrene sulfonate (Kayexelate®) therapy. However, her course has been complicated by occasional hypokalemia when her cation exchange resin was increased with a combination of decreased intake of potassium. Creatinine clearance in 1979 was 55 cc/min and a repeat endocrine evaluation in December 1979 revealed: supine plasma aldo 3 ng% (nl 3-10 ng%), upright plasma aldo 2 ng% (nl 5-30 ng%), 24-hr urine aldo 3 µg/24 hr (nl 4-20 µg/24 hr), 24-hr urine 17 ketosteroids 4.8 mg/24 hr (nl 5-15 mg/24 hr), 24 hr-urine 17-OH-steroids 10.6 mg/24 hr (nl 4-8 mg/24 hr), supine plasma renin 3.5 ng/ml·hr (nl 0.5-1.6 ng/ml·hr), 2 hr upright plasma renin 18.4 ng/ml/hr (nl 1.9-3.6 ng/ml/hr), plasma cortisol 30.7 µg% at 0800, 20.4 µg% at 1200 (nl 7-27 µg% at 0900). In review of the chart it is not clear what her serum K was at the time of the endocrine work-up. However, the most consistent diagnosis at that time would be isolated hyperreninemic hypoaldosteronism.

In 1983 she again had periods of weakness with documented drops of serum Na to 106 mEq/L and rises of K to 7.5 mEq/L. Despite high doses of sodium polystyrene sulfonate and 9-α-fluorocortisol, her symptoms have persisted and her metabolic abnormalities have been difficult to control. It was for these reasons she was admitted to the Clinical Research Center of Southwestern Medical School at the Parkland Memorial Hospital on January 16, 1984.

On physical examination she was a pleasant white female appearing her stated age. The blood pressure supine was 80/60 and sitting 60/ unobtainable. Respective pulse rates were 60 and 98. The respiratory

rate was 18/min. She was afebrile. The rest of the physical examination was within normal limits.

The laboratory findings the next morning were: Hct 38.1%, MCV 102.2 μ^3, Na 127 mEq/L, K 6.3 mEq/L, Cl 104 mEq/L, CO_2 content 15 mEq/L, Ca 9.5 mg%, phosphorus 3.8 mg%, BUN 33 mg%, Cr 1.7 mg%. Arterial blood gas pH of 7.25 with urine pH 6.5, sp gr 1.025, and a normal urinary sediment. Serum lipids were normal. B_{12} <100 pg/ml (nl 210-920 pg/ml), folic acid 3.2 ng/ml (nl 2-14 ng/ml). Electrocardiogram, chest x-ray, and abdominal computerized tomographic scan were all normal.

Because of her salt-depleted state she was placed on a 410 mEq Na (9.4 gm) and 10 mEq K diet for the first two days and subsequently changed to 260 mEq Na (6 gm) and 10 mEq K metabolic diet with 3000 cc per day fluid intake. Stools were analyzed on q3d collections while serum and urine were analyzed daily.

The pertinent metabolic balance data are summarized in Figures 1 and 2. She came into Na balance on the third hospital day.

Endocrine work-up consisted of measurement of plasma renin activity, catecholamines, cortrosyn (synthetic ACTH) infusion test and angiotensin infusion test for the measurement of baseline and stimulated plasma steroid concentrations for the assesment of zona glomerulosa and fasciculata activity. These results are summarized in Table I and indicate that the renin values were quite high and aldosterone and its precursor 18-OH β concentrations were low when interpreted in the face of hyperkalemia. Furthermore, these latter values had a suboptimal response to posture and ACTH infusion, and also to angiotensin II infusion at a time when there was a definite pressor response. The

glucocorticoid values had normal to high baseline values and increased in response to ACTH infusions, Table I. Thus, it was concluded that the patient had selective unresponsiveness of zona glomerulosa with normal response of the zona fasciculata.

Therefore, it was decided to treat her with intramuscular desoxycorticosterone acetate (DOCA) at high concentrations (10 mg IM bid.) in view of her previous apparent unresponsiveness to oral 9-α-fluorocortisol. DOCA was initiated on the eighth hospital day. The metabolic responses to this therapy are outlined in Figures 1 and 2. Of interest is an immediate antinatriuretic response with a positive Na balance and associated weight gain. The BP returned to 115/70 with this therapy, constituting presumptive evidence that her hypotension was the result of previous volume depletion due to renal salt wastage. Also, the urine pH which had been stable at 6.25 to 6.5 immediately began to drop to less than 5.5. Similarly, the plasma bicarbonate concentration rose to 23 mEq/L and there was increased excretion of ammonia, titratable and net acid. However, neither the stool nor urinary K concentration or excretion rate increased during the subsequent four days of metabolic studies nor die the urinary K excretion rate increase during a month-long follow up on chronic DOCA therapy. Her urinary K concentration has consistently been less than 7 mEq/L with a 24-hr urinary K excretion rate of less than 14 mEq. Thus, in regard to K secretion, the patient has a selective end-organ unresponsiveness to mineralocorticoid while maintaining a normal response to Na reabsorption and H secretion.

Failure of kaliuresis in response to aldosterone may be the consequence of a defective response to the hormone or an intrinsic epithelial defect for K secretion. To test for this the patient will be infused with one liter of 4% sodium sulfate containing 44 mEq/L sodium bicarbonate. The results of these studies as well as the renal biopsy, which is scheduled for March 13, 1984, will be discussed. The results of these studies cannot be included in this presentation since these studies have not been conducted at the writing of this report.)

DISCUSSION

The described patient has a constellation of clinical findings not previously recognized. The ACTH and angiotensin infusion studies strongly support the view that the biosynthetic defect in this patient is an unresponsiveness of the adrenal zona glomerulosa to secrete aldosterone, while the balance studies demonstrate a selective physiological unresponsiveness of the kidney to increase potassium excretion at a time when aldosterone expresses its expected effect on the kidney to increase sodium reabsorption and hydrogen secretion.

Recent reports have made it evident that acquired hypoaldosteronism with normal glucocorticoid secretory rate is not as uncommon as once thought. Hypoaldosteronism can be the result of a decreased signal to the adrenal gland to secrete aldosterone or due to an intrinsic defect of the adrenal gland to secrete aldosterone. A frequent clinical association in diabetic patients is the finding of hypoaldosteronism secondary to hyporeninemia (1-7). Hypoaldosteronism can also result from adrenal insensitivity to angiotensin II mediated either at a receptor level or due to the destruction of zona glomerulosa. Among the

more common causes of acquired primary hypoaldosteronism as a result of primary zona glomerulosa defect are heparin therapy (8,9), auto-immune disorders (10-14) and in critically ill patients with hypotension (15).

Patients have also been recognized whose metabolic profile simulates hypoaldosteronism, i.e., renal salt wasting, hyperkalemia, and hyperchloremic acidosis. These patients have normal or elevated values of renin and aldosterone but the renal distal tubule fails to respond to aldosterone. While pseudohypoaldosteronism of infants is well described (16), acquired cases in adults are recognized more commonly and would include circumstances such as renal amyloidosis (17), methicillin interstitial nephritis (18) and other disease processes where the distal tubule is primarily affected (19).

Recent studies have greatly extended our understanding concerning the pathophysiology of the metabolic abnormalities associated with hypoaldosteronism, salt wastage, hyperkalemia, and hyperchloremic acidosis.

One of the cardinal features of hypoaldosteronism is a negative sodium balance. Quantitatively, the most important factor is increased renal wastage of sodium. In vitro microperfusion studies have localized the cortical collecting tubule as the principle site where both acute and chronic mineralocorticoid exposure leads to an increase in net reabsorption of sodium (20-26). Cortical collecting tubules harvested from adrenalectomized rabbits and perfused in the absence of mineralocorticoids demonstrate negligible Na reabsorption leading to tubular rejection of sodium. Indeed, the patient described in this presentation was chronically in a salt-depleted state as evidenced by persistent hypotension and elevated renin values. The day after she was placed on

10 mg DOCA IM twice a day, she went into positive Na balance as evidenced by a decrease in urinary Na and a gain in weight, Figures 1 and 2.

The cellular mechanism by which aldosterone increases Na absorption is schematically summarized in Figure 3 (27). In this model aldosterone gains access to cytoplasmic receptors where it initiates a series of biochemical steps culminating in synthesis of a protein (permease) which increases the luminal membrane entry of Na. The increased intracellular entry of Na, in turn, secondarily increases Na-K ATPase activity. In addition, studies are consistent with the view that aldosterone enhances the capacity of mitochondrial energy production (28), Figure 3. The increased entry of Na and the increased activity of the Na pump (Na-K ATPase) will lead to increased net transport of Na from the collecting duct lumen into blood.

Hyperkalemia is a common finding in untreated patients with a severe degree of hypoaldosteronism. Indeed, persistent hyperkalemia in the absence of chronic renal failure, acid-base disturbances, and specific drugs affecting K secretion should lead the physician to consider hypoaldosteronism.

Whether mineralocorticoids have a direct effect on K secretion has been difficult to establish. An exhaustive review has concluded that most of the clearance studies have failed to demonstrate an acute effect of aldosterone on K secretion (29). The studies at the isolated tubule level are interesting. Recent in vitro studies have demonstrated that collecting tubules harvested from adrenalectomized rabbits do not increase K secretion within 120 minutes in response to in vitro addition

of aldosterone at a time when increased net Na reabsorption could be demonstrated (26). Thus, these studies support the view that mineralocorticoids do not have a direct acute effect on K secretion across the cortical collecting tubule. However, when tubules are dissected from rabbits which have received chronic doses of DOCA, these tubules have a higher secretory rate of K than tubules from rabbits not receiving DOCA (22, 24). Indeed, there seems to be a nice correlation between plasma levels of aldosterone and K secretory rate of the cortical collecting tubule (24). Thus, the view is developing that cortical collecting tubule responds to aldosterone in a biphasic manner (26). Aldosterone has been shown to stimulate net Na reabsorption acutely without effect on K secretion, but aldosterone chronically stimulates both Na reabsorption and K secretion. The mechanism of increased K secretion has not been established but probably involves increased passive diffusion down a favorable electrical gradient and perhaps also adied by an increased apical cell membrane conductance to K (30).

Our patient did not increase her urinary K excretion after one month of DOCA administration. While failure to increase K excretion in response to mineralocorticoids has been described in patients with severe renal disease (GFR's well below 10 cc per minute), our patient's glomerular filtration rates of approximately 50 cc per minute make this possibility a highly unlikely pathogenesis for defective kaliuretic response to mineralocorticoids.

Hyperchloremic acidosis is not an infrequent finding with hypoaldosteronism. While debate has existed whether gluco- or mineralocorticoids primarily affect hydrogen secretion, a number of patients with

hyporeninemic hypoaldosteronism have been reported where a physiologic concentration of 9-α-fludrocortisone substantially ameliorated prior hyperchloremic acidosis (19). Similarly, the patient in this report, in response to IM DOCA, decreased her urine pH, increased her net acid excretion, and corrected toward normal her serum bicarbonate concentration, Figures 1 and 2. Thus, the findings in this patient constitute support for the view that mineralocorticoids stimulate renal hydrogen secretion.

The site and mechanism of renal tubular response of hydrogen secretion to mineralocorticoids is interesting. In vitro microperfusion studies have shown that aldosterone may enhance hydrogen secretion either by direct or indirect mechanisms. The studies of Lombard et al (31) have recently demonstrated that the medullary collecting duct (in contrast to the cortical collecting tubule) has the highest distal capacity to secrete hydrogen. Furthermore, the recent studies of Stone et al (32) and Laski and Kurtzman (33) have demonstrated that the proton secretory process does not depend on Na and that aldosterone, by a primary Na-independent process, stimulates hydrogen secretion across the medullary collecting duct (32), Figure 4. Preliminary evidence suggests that the hydrogen secretory process is the result of H-activated ATPase on the luminal membrane of the medullary collecting duct. Hydrogen secretion is also stimulated in the cortical collecting tubule by aldosterone, but this process appears to depend on Na and probably occurs down a favorable potential gradient generated by aldosterone-stimulated Na reabsorption (34). Thus, this process is different from the medullary collecting duct.

The physiologic responses to mineralocorticoids are interesting since it now is clear that aldosterone has different effects in different nephron segments. In cortical collecting tubule it stimulates primary active Na reabsorption with secondary passive stimulation of H and K secretion. On the other hand, across the medullary collecting duct, aldosterone stimulates primary active H secretion without significant effect on Na or K transport. At the present time it appears that the affinity of the cytoplasmic receptors for aldosterone are similar in these two segments (35) and that under normal circumstances aldosterone expresses simultaneously a physiological effect across both segments.

Of interest in our patient is an apparent antinatriuretic and hydrogen secretory response to aldosterone without any effect on potassium secretion. There does exist an interesting report where a number of family members had hyperkalemia, low renin values, normal aldosterone values, and normal renal Na conservation. These patients also failed to demonstrate a kaliuretic response to exogenous mineralocorticoids (36). Thus, while these family members share some common renal features to our patient, these patients' renin-aldosterone axis showed completely different characteristics from our patient. The pathogenesis of the physiological findings in our patient cannot be explained on the currently available information. Perhaps they suggest the existence of aldosterone receptors with differing post-receptor pathways for the regulation of specific ion transport processes.

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TABLE I*

Plasma Steroid Concentrations as Influenced by Posture, ACTH, and AII Infusions

Procedure	Date & Time	Aldosterone ng/dl	Cortisol µg/dl	DOC ng/dl	Corticosterone ng/dl	18-OHB ng/dl	18-OHDOC ng/dl
Normal $\bar{x}$ Values Range		7.3±2.7 (4-13)	9.9±2.9 (4-16)	7.4±2.8 (2-13)	292±127 (38-546)	22.9±8.2 (7-39)	6.0±3.6 (1-13)
	1/20/84						
Supine	0600	6.8	22.2	41.6	1517	37.7	13.2
Upright	1000	8.0	24.8	63.7	2277	39.4	16.4
ACTH Infusion Control	1/21/84 1005	4.6	18.6	15.8	930	20.0	4.5
60' sample		6.9	21.6	44.4	2088	33.4	10.5
	1/23/84						
AII Infusion	Baseline 1520	3.6	16.7	17.2	490	16.8	4.5
	14 ng/kg/min 1655	4.7	12.8	14.1	814	14.0	3.0

*Values determined by Dr. Morris Schambelan, San Francisco General Hospital. Normal values reflect values determined in his laboratory (7).

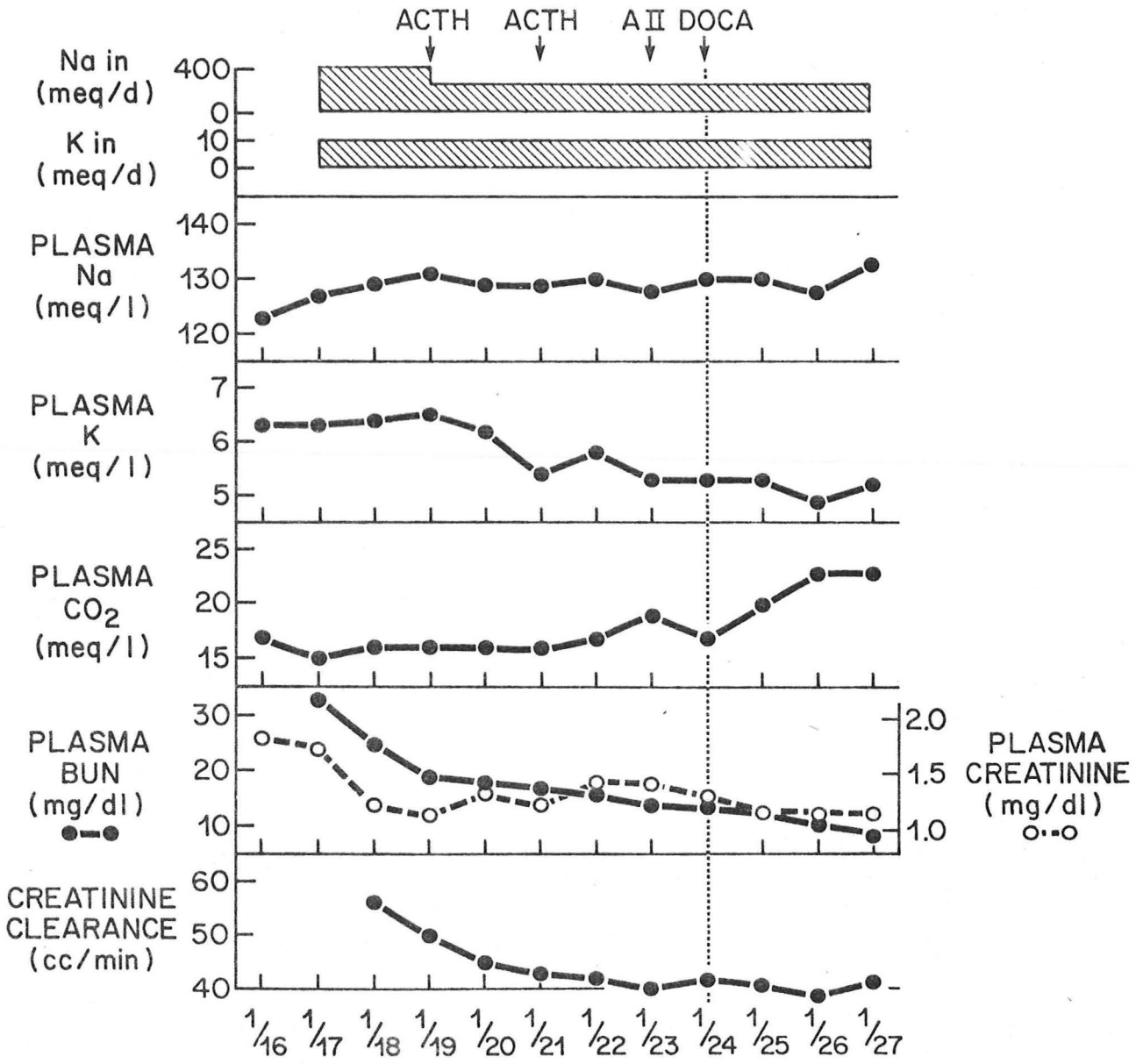

FIGURE 1. Effect of intramuscularly administered DOCA (10 mg IM bid) on plasma sodium, potassium, total CO_2, urea nitrogen, creatinine and on creatinine clearance.

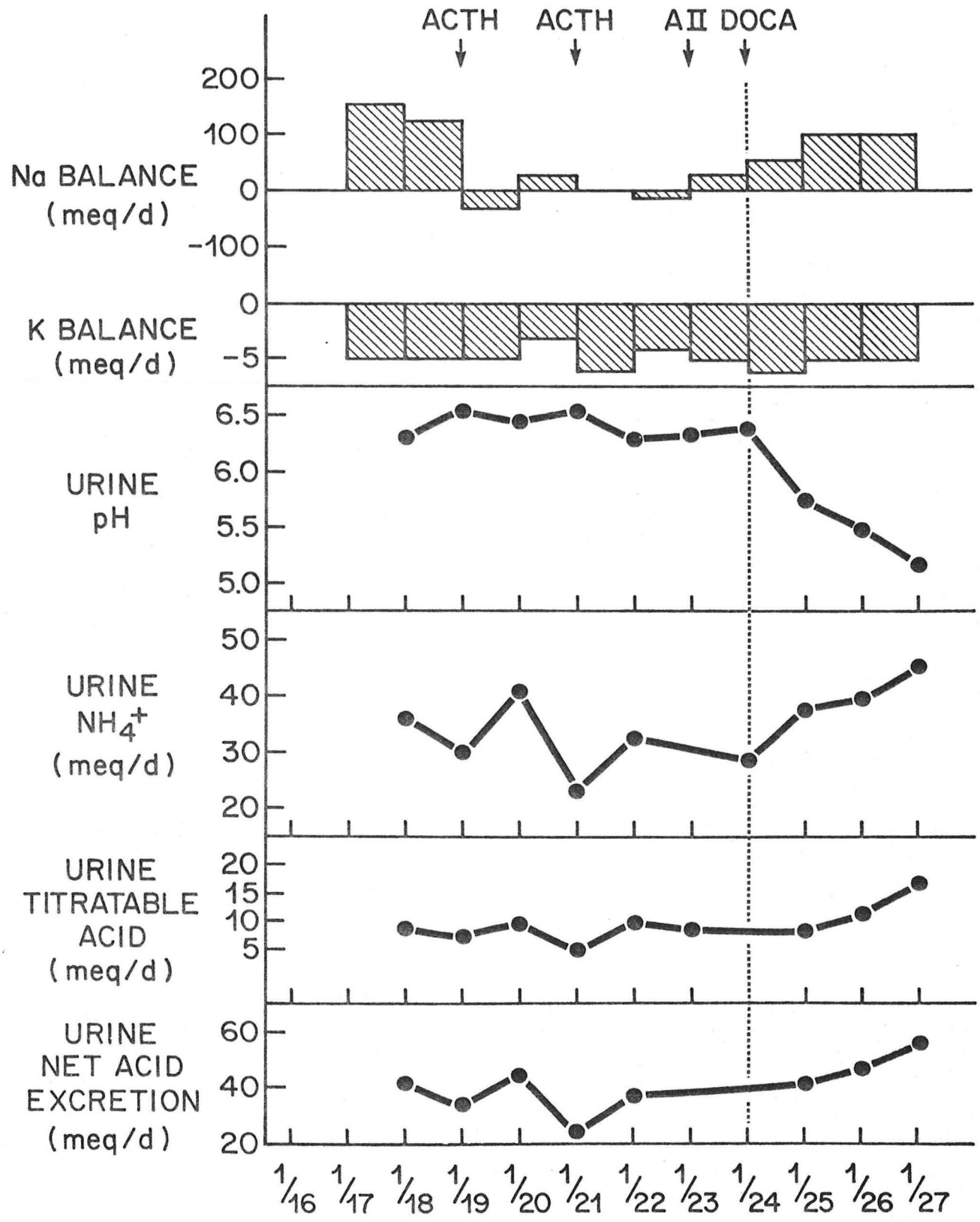

FIGURE 2. Effect of intramuscularly administered DOCA (10 mg IM bid) on sodium balance, potassium balance, urine pH, urine ammonia, urine titratable acid, and urinary net acid excretion.

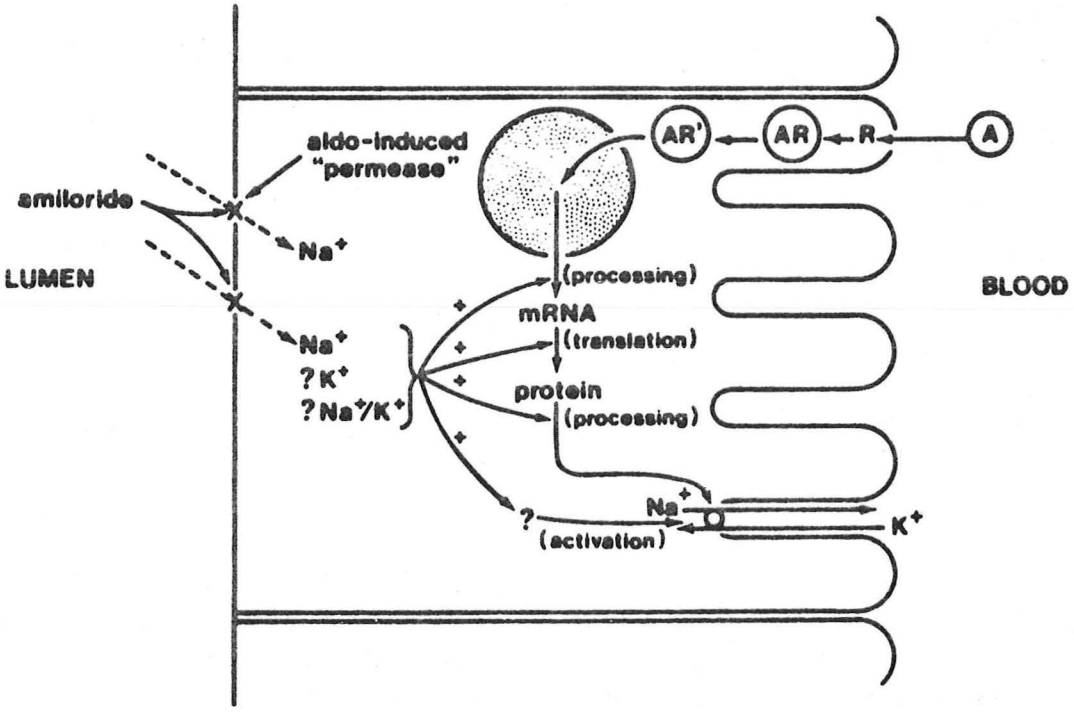

FIGURE 3. Model for secondary enhancement of Na-K ATPase by aldosterone, A. R is the cytoplasmic mineralocorticoid receptor. In this model an increase in intracellular Na activity leads to a secondary activation of ATPase which can be blocked by amiloride (27).

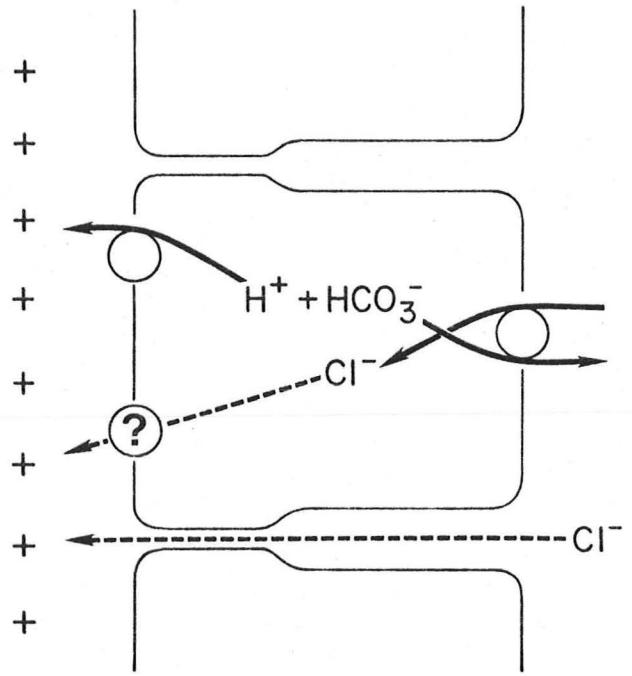

FIGURE 4. Schematic model of hydrogen secretion by the medullary collecting tubule. Lumen positive potential is represented by a +.