

Effects of Adrenalectomy and Chronic Adrenal Corticosteroid Replacement on Potassium Transport in Rat Kidney

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Abstract

Clearance experiments were carried out in pair-fed rats to examine the long-term effects of adrenalectomy and selective adrenal corticosteroid replacement in physiological amounts on renal potassium transport. To this end, clearance studies were conducted in rats that were sham operated, or adrenalectomized (ADX). ADX animals were given either vehicle, aldosterone (0.5 $\mu\text{g}/100$ g body wt per day), dexamethasone (1.2 $\mu\text{g}/100$ g body wt per day), or aldosterone and dexamethasone, by osmotic minipump for 7–9 d whereupon clearance experiments were conducted. After chronic hormone treatment, during basal conditions when only Ringers solution was infused, all groups excreted similar amounts of potassium. However, in all ADX animals without mineralocorticoid replacement, the maintenance of urinary potassium excretion at control levels was associated with hyperkalemia, increased urine flow, and natriuresis; all are factors known to stimulate urinary potassium excretion. During acute potassium infusion, the increase in urinary potassium excretion was less in ADX rats than in controls. This functional deficiency in potassium excretion was partially corrected by dexamethasone and was uniformly associated with a significant increase in urine flow. Aldosterone replacement or aldosterone and dexamethasone given together chronically, sharply increased potassium excretion but did not restore excretion to control levels. Only acute aldosterone infusion (0.2 $\mu\text{g}/100$ g body wt bolus plus 0.2 $\mu\text{g}/100$ g body wt per hour), superimposed upon chronic aldosterone and dexamethasone treatment, fully restored potassium excretion to control levels. This aldosterone induced enhancement of potassium excretion, both chronic and acute, was not associated with hyperkalemia, and increased urine flow or natriuresis. Thus, physiological levels of both classes of adrenal corticosteroids stimulate renal potassium excretion albeit by different mechanisms. Mineralocorticoids stimulate tubular potassium excretion directly, whereas glucocorticoids augment excretion indirectly by increasing fluid and sodium delivery along the distal nephron.

Introduction

Adrenal corticosteroids play an important role in potassium homeostasis (reviewed in 1–4). Chronic adrenal insufficiency

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is associated with hyperkalemia and with a decreased ability to excrete an acute potassium load (5–11). Young et al. (12–14) have demonstrated the importance of chronic aldosterone replacement in adrenalectomized dogs in maintaining potassium homeostasis. Thus, restoration of plasma aldosterone in glucocorticoid replete, aldosterone-deficient animals lowers plasma potassium to basal levels and normalizes the relationship between plasma potassium concentration and urinary excretion of potassium. Acute administration of mineralocorticoids or glucocorticoids to animals alleviates the hyperkalemia associated with adrenal insufficiency and acute potassium loading, and increases, but does not fully restore, the ability of the kidney to excrete potassium (5–11, 15–24).

There are several unresolved issues concerning the role of adrenal corticosteroids in the regulation of potassium handling by the kidney. First, there is considerable controversy concerning the nature of the selective effects of mineralocorticoids vs. glucocorticoids on potassium excretion (reviewed in 1–4). Previous investigators often employed supraphysiologic or pharmacologic doses of steroids that were likely to result in nonspecific effects through binding to both glucocorticoid and mineralocorticoid receptors in the kidney (4, 25–27). These large doses of corticosteroids often increase the rate of glomerular filtration (6, 15, 20, 28, 29) and fluid delivery into the distal tubule (17). Additionally, changes in the concentration of sodium in tubular fluid in the distal tubule and in the cortical collecting duct may enhance urinary potassium excretion indirectly (30–32). A final point concerns the possible role of changes in the potassium content of the diet during the evaluation of the role of adrenal steroids on potassium excretion (18, 19, 22, 33, 34). Frequently, dietary potassium and steroid levels were changed simultaneously. Thus, the specific effects of alterations in potassium intake and of adrenal steroids could not be evaluated separately.

There is also little information available concerning the effects of fixed, chronic physiological replacement of mineralocorticoids and glucocorticoids on the ability of the kidney to excrete an acute potassium load. In particular, it is not known whether the kidney's ability to excrete such a potassium load requires an acute rise in corticosteroid levels coincident with the rise in plasma potassium levels or simply requires a chronic daily replacement dose of corticosteroids.

This study was designed to resolve some of these issues. Thus, we examined the chronic effects of adrenalectomy and of selective, continuous replacement of physiological levels of adrenal corticosteroids on renal potassium excretion in rats maintained on a constant potassium intake. Renal function studies were performed under basal conditions during infusion of Ringers solution or during acute potassium loading. During infusion of Ringers solution, control, adrenalectomized (ADX),¹

1. Abbreviations used in this paper: ADX, adrenalectomized; FE_K , fractional excretion of potassium; FE_{Na} , fractional excretion of sodium;

and various hormone-treated animals excreted similar amounts of potassium, although at different plasma potassium levels and at varying urinary flow rates. During an acute potassium load, aldosterone sharply increased potassium excretion, independent of alterations in plasma potassium levels and fluid and sodium excretion. However, chronic aldosterone replacement failed to restore potassium excretion to levels observed in intact animals. Chronic replacement of both classes of corticosteroid hormones also failed to restore to normal the ability of the kidneys to excrete an acute load of potassium; for this to occur, an additional acute increase in plasma aldosterone was also required just before the infusion of the acute potassium load. In contrast, a moderate stimulation of potassium excretion by dexamethasone was accompanied by an increase in plasma potassium levels and urinary fluid and sodium excretion. Results of an ultrastructural analysis of the principal cell type, to be reported in a separate paper (35), show that only aldosterone increased basolateral membrane length of these cells in the initial collecting duct.² Dexamethasone was without any effect on this cell type. These ultrastructural results are consistent with the renal function studies in demonstrating that mineralocorticoids but not glucocorticoids have a direct stimulatory effect upon potassium transport by the initial and cortical collecting tubule.

Methods

Pretreatment of animals. Male Sprague-Dawley rats (Charles River, Boston, MA), weighing 237–248 g, were divided into six groups as outlined in Table I. Under Nembutol anaesthesia (60 mg/kg i.p.) animals underwent either a sham adrenalectomy (group 1) and served as adrenal-intact controls, or were bilaterally adrenalectomized (groups 2–6) 7–9 d before renal function studies were performed. At the time of initial surgery, an osmotic minipump (Alzet #2002; Alza Corp., Palo Alto, CA) was inserted subcutaneously in the neck of each animal. Fluid delivery was 11 μ l/d. In the six groups of animals, vehicle or hormone replacement for 7–9 d was as described in Table I and below:

Group 1, control, $n = 10$. Vehicle (polyethylene glycol 400; J. T. Baker, Phillipsburg, NJ). Group 2, adrenalectomy, $n = 10$. Vehicle. Group 3, adrenalectomy plus dexamethasone, 1.2 μ g/100 g body wt per day, $n = 11$.

Dexamethasone was chosen as a representative glucocorticoid because it binds more selectively to the glucocorticoid receptor (type II) than does corticosterone, the predominant endogenous glucocorticoid in the rat (25–27). A dexamethasone dose of 1.2 μ g/100 g body wt was chosen because we observed, in preliminary experiments, that this was the lowest dose to maintain normal weight gain, normalize glomerular filtration rate, and maintain normal fasting plasma glucose and insulin levels (Stanton, B., G. Giebisch, G. Klein-Robbenhaar, J. Wade, and R. A. DeFronzo, unpublished observations). Note that this dose is much smaller than that employed by previous investigators (8, 15, 16, 20, 21, 28, 36). Lower doses of dexamethasone resulted in

GFR, glomerular filtration rate; PVP, polyvinyl proline; U_1 , baseline 30-min control urine collection; U_2 , first experimental urine collection; U_3 , second experimental urine collection; U_{K^+V} , urinary excretion of potassium; U_{Na^+V} , urinary excretion of sodium; V, urine fluid excretion.

2. Recent evidence indicates that the superficial late distal tubule is ultrastructurally similar to the cortical collecting tubule and is composed of principal and intercalated cells (45, 50, 51). Thus, we have chosen to refer to this segment of the distal tubule, which is the site of potassium excretion (40, 45), as the initial collecting tubule (45, 50).

Table I. Pretreatment of Animals

Group	Surgical treatment	Hormone replacement
1	Control	Vehicle
2	ADX	Vehicle
3	ADX	Dexamethasone 1.2 μ g/100 g per day
4	ADX	Aldosterone 0.5 μ g/100 g per day
5	ADX	Aldosterone and dexamethasone as above
6	ADX	Aldosterone and dexamethasone as above with acute aldosterone* \ddagger

Six groups of animals were studied. Animals were either sham-adrenalectomized (control) or were adrenalectomized (ADX). Hormones were replaced continuously by implantable osmotic minipumps for 7–9 d.

* 0.2 μ g/100 g body wt bolus and continuous infusion of 0.2 μ g/100 g body wt per hour.

\ddagger Given 75 min before potassium infusion.

fasting hypoglycemia and hypoinsulinemia, and decreased both glomerular filtration rate (GFR) and growth rate. Higher doses of dexamethasone, on the other hand, were associated with loss of weight or decreased weight gain, fasting hyperglycemia, and fasting hyperinsulinemia.

Group 4, adrenalectomy plus aldosterone, 0.5 μ g/100 g body wt per day, $n = 10$. This replacement dose is comparable to the daily secretory rate of aldosterone and resulted in normal plasma levels of this hormone (37–39; and see Results).

Group 5, adrenalectomy plus aldosterone and dexamethasone, $n = 9$. The hormone doses are as described in groups 3 and 4.

Group 6, adrenalectomy plus aldosterone and dexamethasone, as in Group 5; plus acute aldosterone, $n = 9$. The acute infusion of aldosterone was begun at the conclusion of the surgical preparation for renal function studies, which were performed 7–9 d after initiation of the continuous hormone infusion (see below and Fig. 1 for details of the renal function studies). The bolus of aldosterone (0.2 μ g/100 g body wt dissolved in 0.05% ethanol) was given 75 min before starting the potassium infusion and 105 min before starting the first experimental urine collection (U_2) during the potassium infusion (Fig. 1). A continuous infusion of aldosterone, 0.2 μ g/100 g body wt per hour, was maintained throughout the experiment. The purpose of this supplemental aldosterone infusion was to mimic the increase in plasma aldosterone concentration that occurs after anesthesia and potassium chloride infusion in intact control rats (17, 40; and see Results). In five separate rats this

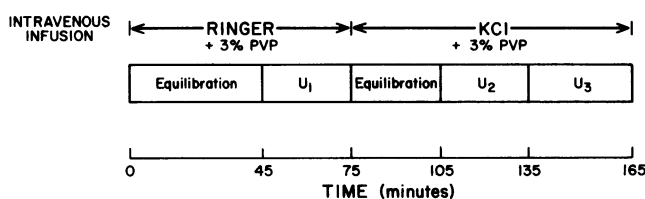


Figure 1. Protocol for renal clearance studies. At time zero an infusion of Ringers solution was initiated. In groups 2 and 4 the Ringers solution contained 3% PVP. After 45 min of equilibration, a 30-min urine collection (U_1) was begun. At 75 min, a KCl infusion (7 μ eq/min) was started and was maintained throughout the experiment. After a 30-min KCl equilibration period, two 30-min urine samples were collected (U_2 and U_3).

small amount of ethanol necessary to dissolve aldosterone for its acute administration did not change any of the renal functional parameters that were measured in this study.

Experimental protocol for clearance experiments. After the sham-operation or adrenalectomy and implantation of the minipumps, all rats were maintained on 18 g/d of standard rat chow (Ralston Purina Co., St. Louis, MO) (total daily sodium and potassium intake equal to 2.9 and 4.8 meq/d, respectively). Rats consumed the entire 18 g of rat chow each day. There were no significant differences in weight gain among the experimental groups. Animals in group 1 (control) received distilled water to drink, whereas ADX animals in groups 2–6 drank a solution containing 0.9% NaCl and 1.5% glucose.

On the day of clearance studies rats were anesthetized with Inactin (Byk Gluden Konstanz, Germany), 100 mg/kg body wt i.p., and a tracheostomy tube was inserted to ensure adequate ventilation. Throughout the study, body temperature was maintained at 37–38°C. The left carotid artery and right external jugular vein were cannulated with PE-50 tubing for the withdrawal of blood samples and the infusion of all test substances, respectively. Bladder catheterization was performed to allow the complete collection of urine.

Fig. 1 summarizes the essential steps of the clearance protocol. After surgery, all rats received a bolus of 0.9% NaCl in an amount equal to 1% of body weight. This was followed by a maintenance Ringer infusion (145 mM NaCl, 5 mM KHCO₃) at the rate of 3.3 ml/h during the basal-Ringer period. At the same time a priming dose (25 μ Ci) of tritiated inulin (New England Nuclear, Boston, MA) was given and sufficient isotope was added to the Ringer solution to provide a sustaining infusion of 25 μ Ci/h. After a 45-min equilibration period, a base-line 30-min control urine collection was obtained (U₁). After the basal-control urine collection, KCl was infused at a rate of 7 μ eq/min. This was accomplished by substituting the Ringer solution with one containing 127 mM KCl, 13 mM NaCl, and 5 mM NaHCO₃. After a 30-min KCl equilibration period, two 30-min experimental urine collections were obtained (U₂ and U₃). Blood samples were obtained before and at the end of the basal-control period, KCl equilibration period, and each of the two 30-min experimental-KCl periods.

In ADX and ADX aldosterone replete animals, (groups 2 and 4), 3% polyvinyl pyrrolidone (PVP) was added to the infusion fluid to improve the GFR (41). It was necessary to use PVP, since in preliminary experiments, animals without PVP had a 63% reduction in GFR compared with intact controls and with animals receiving dexamethasone chronically (groups 3, 5, and 6). In preliminary studies we found that PVP had no significant effect on GFR, urinary flow rate, or on absolute or fractional excretion of potassium in intact-control animals ($n = 6$), thereby confirming earlier observations by Peart and Pessina (41). At the end of the KCl loading period, plasma was obtained for the measurement of pH, HCO₃⁻, pCO₂, and aldosterone and dexamethasone. Plasma potassium concentration was determined at 30-min intervals throughout the study.

Analytical determinations. Plasma and urine sodium and potassium concentrations were measured with a flame photometer using an internal lithium standard (Instrumentation Laboratory, Inc., Lexington,

MA). Inulin concentrations in urine and plasma were determined in a scintillation counter (Analytical 92; Searle & Co., Skokie, IL) using Hydrofluor scintillation fluid. Plasma aldosterone was kindly measured by Dr. Patric Mulrow (Medical College of Ohio, Toledo, OH) by radioimmunoassay (42). Dexamethasone levels were measured in four ADX/dexamethasone replaced animals by including [³H]dexamethasone (specific activity, 38 Ci/mM; New England Nuclear, Boston, MA) with the unlabeled hormone in the osmotic minipump. 10 d after insertion of the pumps into the animals, blood was drawn for determination of radiolabeled dexamethasone. Methods for the determination of blood pH, pCO₂, and bicarbonate concentration have previously been published (43).

Urinary excretion of potassium (U_{KV}) and sodium (U_{NaV}) (μ eq/min per 100 g body wt) were calculated during the basal period (45–75 min, Fig. 1) when Ringers solution was infused and compared with the mean values of electrolyte excretion during the two potassium chloride (KCl) experimental periods (105–165 min, Fig. 1). GFR (ml/min per 100 g body wt), fractional excretion of potassium (FE_K), and fractional excretion of sodium (FE_{Na}), were calculated using standard formulae. Urine volume was measured gravimetrically.

A preliminary inspection of the data was performed using a one way analysis of variance. If there was a significant difference ($P < 0.05$) among means, the least significant test was used to examine statistical significance between means (44). P values are based on least significant test comparisons; all differences are expressed as either $P < 0.05$ or $P < 0.01$. All data shown represent the mean \pm standard error. In the text, means will be considered statistically different only if $P < 0.05$.

Results

Plasma hormone concentrations and acid-base status. In a separate group of rats, plasma was obtained to determine whether the aldosterone replacement protocol restored hormone levels to basal, unstressed control levels (Table II). Basal plasma aldosterone in these intact unstressed controls was 7.2 \pm 1.3 ng/dl. This value is similar to that observed by others under similar conditions (37–39).

Surgical preparation and infusion of potassium into adrenal-intact controls led to a sharp increase in plasma aldosterone to 77.8 \pm 13.0 ng/dl (group 1). In both groups of ADX animals not receiving aldosterone (groups 2 and 3), hormone levels were not significantly different from zero (since hormone levels in both groups were similar, the results were pooled). Replacement of aldosterone by osmotic minipump, at 0.5 μ g/100 g body wt per day in ADX animals increased plasma aldosterone significantly to 4.4 \pm 1.9 ng/dl, a value that was not significantly different from basal adrenal-intact control animals (7.2 \pm 1.3 ng/dl). Since groups 4 and 5 received the same infusion of aldosterone and plasma levels were similar in both groups, we

Table II. Aldosterone Levels Measured by Radioimmunoassay

	Basal (unstressed)	Group 1 (control)	Groups 2 and 3 (ADX and Dex)	Groups 4 and 5 (Aldo and Aldo/Dex)	Group 6 (Aldo/Dex: acute Aldo)
Plasma aldosterone	7.2	77.8*	0.5*‡	4.4	88.8*
ng/dl	\pm 1.3	\pm 13.0	\pm 0.3	\pm 1.9	\pm 24.7
n	6	6	12	16	4

The basal plasma aldosterone samples were drawn from adrenal-intact unstressed controls. Blood was collected from groups 1–6 at the conclusion of renal function studies. Groups 1–6 are the same as in Table I. Results in groups 2 and 3 were pooled as were results in groups 4 and 5 since they received the same aldosterone treatment. Plasma was also drawn from a separate set of group I animals at the end of the Ringers infusion. Aldosterone was 22 \pm ng/dl ($n = 6$). Data are expressed as the mean \pm SEM. * $P < 0.01$ vs. basal and groups 4 and 5; ‡ not significantly different from zero. Aldo, aldosterone; Dex, dexamethasone.

again pooled the data. Acute infusion of aldosterone upon a background of basal hormone replacement reproduced the rise in plasma aldosterone similar to that seen in adrenal-intact controls after the acute infusion of potassium (group 1 vs. group 6).

Tritiated dexamethasone levels were measured in four ADX animals receiving dexamethasone at 1.2 $\mu\text{g}/100$ g body wt per day (group 3). Plasma concentration was 20.7 ± 3.0 nM, a value that is slightly greater than the dissociation constant of the renal glucocorticoid receptor, of 5–10 nM (25–27).

Blood pH, pCO_2 , and bicarbonate concentrations were measured at the end of the KCl period in all groups of animals (Table III). Only small deviations from the normal acid-base status were observed. pH was similar to control values in all experimental groups except group 5, which had a significantly higher pH, 7.44 ± 0.02 , than groups 1–3. Although animals in group 6 were slightly alkalemic compared with controls, the difference was not statistically significant. Blood pCO_2 levels were similar to control (group 1) values in groups 2, 3, and 4. However, both groups receiving aldosterone and dexamethasone (groups 5 and 6) had significantly lower pCO_2 levels than groups 1–4. Blood bicarbonate levels were significantly lower in groups 2, 3, 5, and 6 compared with control. Thus, animals in groups 5 and 6 had a mild respiratory alkalosis with a secondary metabolic acidosis as a compensatory response and those in groups 2 and 3 had a mild metabolic acidosis. Animals in group 4 were similar to controls (group 1). It is apparent that the deviations in acid-base balance in the different experimental groups are small and thus unlikely to have exerted an important effect upon the urinary excretion rates observed.

Renal function: basal-control period. Plasma and urine electrolyte data, as well as glomerular filtration rates during the basal-Ringers infusion period, are summarized in Fig. 2 and Table IV. The most striking observation is that urinary potassium excretion, expressed either as fractional or total excretion rates, was similar in all experimental groups. However, two factors known to influence renal potassium excretion, the rate of fluid and sodium excretion (30–32), were different among the experimental groups. As apparent from inspection of Fig. 2 and Table IV, both urine flow rate and sodium excretion were sharply elevated in groups 2 and 3 compared with the other experimental groups. This is due to the different effects of adrenalectomy, dexamethasone, and aldosterone on urinary fluid and sodium excretion. Whereas relatively high

sodium excretion rates were seen in adrenalectomy (group 2) and dexamethasone (group 3), aldosterone replacement in groups 4, 5, and 6 induced a sharp and statistically significant decrease in sodium and fluid excretion compared with groups 2 and 3. The rate of potassium excretion was not significantly affected by the acute infusion of aldosterone in rats treated chronically with aldosterone and dexamethasone (group 5 vs. group 6). Although sodium excretion fell subsequent to the acute infusion of aldosterone (group 5 vs. group 6), the difference was not statistically significant (Table IV). This is not unexpected since the fully developed antinatriuretic and kaliuretic effect of aldosterone takes longer to become apparent than the duration of the present period of aldosterone infusion (75 min) (1–4, 10). GFR was similar in groups 1–4 and moderately increased in groups 5 and 6.

Plasma potassium concentration, another factor known to influence potassium excretion (17), was also affected by adrenalectomy and subsequent hormone replacement. Plasma potassium levels were higher in aldosterone deficient animals (groups 2 and 3) than in aldosterone-replaced animals (groups 4–6, Table IV). Dexamethasone replacement (group 3) led to a small but significant reduction in plasma potassium (from 5.51 ± 0.14 meq/liter to 4.92 ± 0.15 meq/liter), compared with adrenalectomy (group 2). In animals that received aldosterone chronically (groups 4–6), plasma potassium levels were similar to each other as well as to controls.

We conclude from these studies that during infusion of sodium chloride, potassium balance is maintained by different mechanisms in control compared with dexamethasone, aldosterone-deficient, and aldosterone replete animals. Thus, in

Table III. Summary of Blood Acid-base Status

Group	pH	pCO_2	HCO_3
		mmHg	meq/liter
1: Control (n = 8)	7.40 ± 0.02	46.7 ± 2.1	28.0 ± 0.6
2: ADX (n = 10)	7.38 ± 0.02	43.6 ± 1.6	$25.0 \pm 1.1^*$
3: Dex (n = 10)	7.38 ± 0.01	44.3 ± 2.5	$25.1 \pm 0.9^*$
4: Aldo (n = 8)	7.38 ± 0.01	48.4 ± 0.6	28.0 ± 0.8
5: Aldo/Dex (n = 7)	$7.44 \pm 0.02 \ddagger$	$37.7 \pm 2.9^{*\ddagger}$	$24.0 \pm 0.7^*$
6: Aldo/Dex + acute Aldo (n = 7)	7.43 ± 0.02	$37.1 \pm 1.5^{*\ddagger}$	$24.5 \pm 1.2^*$

Groups are the same as in Table I.

* $P < 0.05$ vs. group 1.

‡ $P < 0.05$ vs. groups 2, 3, and 4. Acid-base status was not assessed in all animals in each group.

Aldo, aldosterone; Dex, dexamethasone.

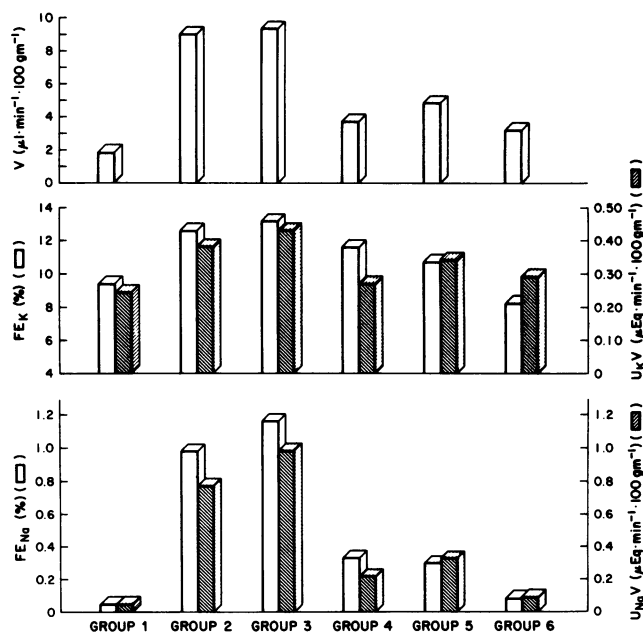


Figure 2. Renal function studies: base-line period during Ringers infusion. Top, urinary fluid excretion (V). Middle, total potassium excretion (U_KV ; □) and fractional potassium excretion (FE_K ; ▨). Bottom, fractional sodium excretion (FE_{Na} ; □) and total excretion of sodium ($\text{U}_{\text{Na}}\text{V}$; ▨). For statistical comparison of means among groups see Table IV. Group 1, control; group 2, ADX; group 3, ADX, dexamethasone; group 4, ADX, aldosterone; group 5, ADX, aldosterone/dexamethasone; group 6, ADX, aldosterone/dexamethasone, acute aldosterone.

Table IV. Summary of Renal Clearance Study During Basal Control Conditions (Ringers Infusion)

Group	GFR <i>ml · min⁻¹ · 100 g⁻¹</i>	V <i>μl · min⁻¹ · 100 g⁻¹</i>	Plasma K <i>meq/liter</i>	Plasma Na <i>meq/liter</i>	FE _K %	U _{KV} <i>μeq · min⁻¹ · 100 g⁻¹</i>	FE _{Na} %	U _{NaV} <i>μeq · min⁻¹ · 100 g</i>
1: Control (n = 10)	0.63±0.04	1.9±0.1	4.45±0.10	145.7±1.0	9.5±1.4	0.250±0.038	0.04±0.01	0.039±0.009
2: ADX (n = 10)	0.55±0.03	9.0±1.1*	5.51±0.14*	138.8±0.8*	12.3±1.5	0.377±0.041	0.98±0.09*	0.765±0.092*
3: Dex (n = 11)	0.65±0.03	9.3±2.2*	4.92±0.15	139.6±1.0*	13.1±2.4	0.430±0.084	1.16±0.43*	0.980±0.307*
4: Aldo (n = 11)	0.55±0.05	3.7±0.5§	4.59±0.14§	144.3±0.8§	11.6±3.2	0.257±0.072	0.33±0.12§	0.219±0.081§
5: Aldo/Dex (n = 9)	0.71±0.03‡	4.9±0.8§	4.43±0.12§	147.9±0.7§	10.8±2.0	0.337±0.073	0.30±0.08§	0.325±0.097§
6: Aldo/Dex/ acute Aldo (n = 9)	0.75±0.03*‡	3.3±0.5§	4.27±0.33§	145.6±0.9§	8.2±1.7	0.291±0.070	0.08±0.03§	0.087±0.030§

Groups are the same as in Table I. Data represent mean±SEM. Differences between means are not significant unless indicated in the table or text. * *P* < 0.005 vs. group 1; ‡ *P* < 0.005 vs. groups 2 and 4; § *P* < 0.005 vs. groups 2 and 3; || *P* < 0.05 vs. group 2.

ADX rats and rats receiving dexamethasone, an elevation in the plasma potassium concentration combined with elevated excretion rates of both fluid and sodium maintained potassium excretion at normal or slightly increased values. These factors thus have a hormone-independent stimulatory effect on potassium excretion by the distal tubule (7, 30, 31, 40).

Renal function: potassium infusion. After the base-line urine collection, potassium was infused to examine the effects of chronic hormone replacement on the ability of the kidney to excrete an acute potassium load. Urinary electrolyte excretion and plasma sodium and potassium concentration data are summarized in Fig. 3 and Table V. In the control group (group 1), FE_K rose from 9.5±1.4% to 54.5±4.0%. In contrast, the rise in FE_K in ADX rats (group 2) was markedly impaired

(12.3±1.5% to 19.1±1.0%) and this was 67% less than in controls (*P* < 0.001). Absolute potassium excretion was similarly impaired in ADX animals.

Dexamethasone replacement (group 3) led to a small but significant increase in FE_K, from 13.1±2.4% to 28.6±1.1%; however, FE_K remained well below the control value of 54.5±4.0%. Absolute potassium excretion was similarly impaired in dexamethasone-replaced animals (Table V) and again remained less than in controls (1.020±0.066 μeq/min per 100 g body wt vs. 1.710±0.081 μeq/min per 100 g body wt). As shown in Table V and Fig. 3, the kaliuresis during chronic dexamethasone replacement was associated with a substantial increase in GFR, and urine fluid and sodium excretion compared with adrenalectomized, unreplaced animals.

Table V. Summary of Renal Clearance Study: Potassium Infusion

Group	GFR <i>ml · min⁻¹ · 100 g⁻¹</i>	V <i>μl · min⁻¹ · 100 g⁻¹</i>	Plasma K <i>meq/liter</i>	Plasma Na <i>meq/liter</i>	FE _K %	U _{KV} <i>μeq · min⁻¹ · 100 g⁻¹</i>	FE _{Na} %	U _{NaV} <i>μeq · min⁻¹ · 100 g</i>
1: Control (n = 10)	0.61±0.02‡	23.9±6.0	5.34±0.19§	143.3±0.7§	54.5±4.0	1.710±0.081¶	0.55±0.13§	0.480±0.123§
2: ADX (n = 10)	0.41±0.02*	18.8±1.5*	7.06±0.10*	134.5±0.9*	19.1±1.0*	0.544±0.030*	2.21±0.25*	1.239±0.133*
3: Dex (n = 11)	0.54±0.04‡	33.3±6.3	6.73±0.19*	136.5±1.1*	28.6±1.1*¶	1.020±0.066*¶	3.00±0.39***	2.244±0.301***
4: Aldo (n = 11)	0.45±0.03*	17.8±1.5*	6.03±0.13*§	141.2±0.9§	41.6±3.2*§	1.087±0.071*¶	1.12±0.20§	0.661±0.101§
5: Aldo/Dex (n = 9)	0.51±0.02*‡	19.0±3.3*	6.02±0.15*	143.7±0.8§	44.3±3.4*§	1.340±0.094*¶‡‡	1.28±0.22*§	0.978±0.187
6: Aldo/Dex + acute Aldo (n = 9)	0.54±0.02‡	14.7±1.6*	5.60±0.12§	143.7±0.8§	50.7±2.4§	1.529±0.081¶‡‡	0.43±0.10§§§	0.333±0.071§

Groups are the same as in Table I. Data represent mean±SEM. Differences between means are not significant unless indicated in table or text. * *P* < 0.05 vs. group 1; ‡ *P* < 0.05 vs. groups 2 and 4; § *P* < 0.05 vs. groups 2 and 3; ¶ *P* < 0.05, groups 4 and 5 vs. 6; ¶¶ *P* < 0.05 vs. group 2; *** *P* < 0.05, group 2 vs. group 3; ‡‡ *P* < 0.05 vs. group 3; §§§ *P* < 0.05, group 6 vs. 2-5; ||| *P* < 0.05, group 6 vs. 2, 3, and 5.

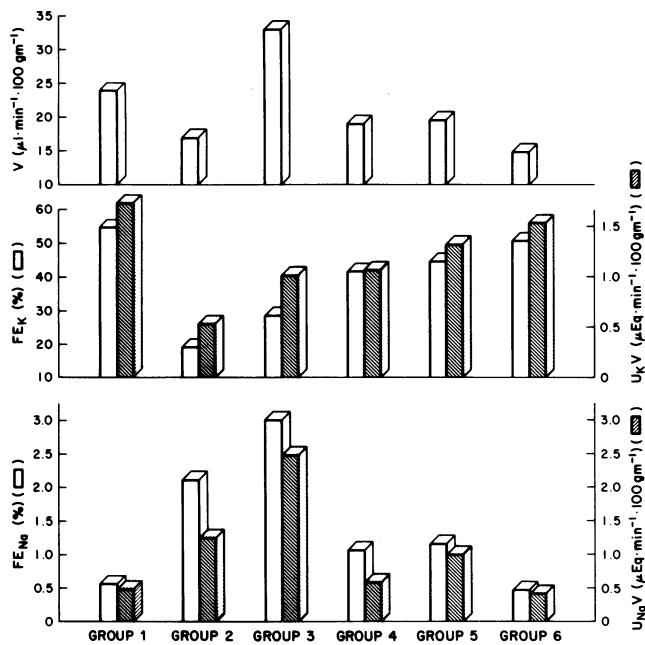


Figure 3. Renal function studies: potassium clearance period. See Fig. 2 for details. For statistical comparisons among groups see Table V. Group 1, control; group 2, ADX; group 3, ADX, dexamethasone; group 4, ADX, aldosterone; group 5, ADX, aldosterone/dexamethasone; group 6, ADX, aldosterone/dexamethasone, acute aldosterone.

The role of the increase in urinary fluid and sodium excretion in eliciting changes in potassium excretion after chronic dexamethasone treatment was further evaluated. In additional experiments in group 2 (ADX chronically unreplaced animals), GFR and urinary fluid and sodium excretion were increased to levels observed in group 3 (chronic dexamethasone treatment) by an acute infusion of dexamethasone. In a previous microperfusion study from our laboratory it was

observed that such an acute infusion of dexamethasone (as the Na-phosphate salt Hexadrol, Oraganon, West Orange, NJ), at 0.2 µg/100 g body wt per h (after an initial bolus of 2 µg/100 g) did not stimulate potassium secretion directly by the distal tubule when tubular flow rate and sodium concentration were held constant by continuous microperfusion (17). As shown in Table VI, acute infusion of dexamethasone in ADX, chronically unreplaced animals (group 2b) sharply increased GFR and urinary fluid and sodium excretion to the same levels observed in group 3 rats who were chronically replaced with dexamethasone. Again this dexamethasone-induced diuresis and natriuresis produced a significant increase in both fractional and absolute urinary potassium excretion. The magnitude, both fractional and absolute, of the increment was similar to that observed in group 3, chronically replaced animals. This observation agrees with previous results from our laboratory (16, 17) and underscores the importance of nonspecific stimulatory effects, such as sodium and fluid delivery along the distal nephron, in the kaliuresis induced by dexamethasone.

As summarized in Table V and Fig. 3, aldosterone replacement sharply increased urinary potassium excretion in all three groups of ADX animals (groups 4–6). Aldosterone replacement alone (group 4) increased potassium excretion from 11.6±3.2% (Ringers infusion) to 41.6±3.2% (KCl infusion), a value, however, that was still less than control animals (54.5±4.0%; group 1). Absolute urinary potassium excretion rates followed a similar pattern. Compared with dexamethasone treatment (group 3), animals receiving aldosterone (group 4) had a higher fractional excretory rate of potassium, 41.6±3.2% vs. 28.6±1.1% during KCl infusion. Absolute potassium excretion, however, was similar in groups 3 and 4. This was due to a significantly lower GFR in group 4 animals compared with group 3, 0.45±0.03 vs. 0.54±0.04 ml/min per 100 g body wt.

When dexamethasone and aldosterone were given together (group 5), GFR was normalized and there was a further modest increase in absolute urinary potassium excretion compared with group 4 animals (from 1.087±0.071 in group 4 to

Table VI. Summary of Renal Clearance Studies During Potassium Infusion

Group	GFR	V	Plasma K	Plasma Na	FE _K	U _K V	FE _{Na}	U _{Na} V
	ml·min ⁻¹ ·100 g ⁻¹	µl·min ⁻¹ ·100 g ⁻¹	meq/liter	meq/liter	%	µeq·min ⁻¹ ·100 g ⁻¹	%	µeq·min ⁻¹ ·100 g
2: Adrenalectomy (n = 10)	0.41±0.02	18.8±1.5	7.06±0.10	134.5±0.9	19.1±1.0	0.544±0.030	2.21±0.25	1.239±0.133
2a: Adrenalectomy and acute dexamethasone (n = 6)	0.50±0.02	38.7±6.6	6.50±0.38	137.3±1.0	34.0±2.2	1.069±0.050	3.146±0.440	2.271±0.350
3: Adrenalectomy and chronic dexamethasone (n = 11)	0.54±0.04	33.3±6.3	6.73±0.19	136.5±1.1	28.6±1.1	1.020±0.066	3.000±0.390	2.244±0.301
Statistical comparison								
2 vs. 2a and 3	P < 0.05	P < 0.05	P < 0.05	P < 0.05	P < 0.05	P < 0.05	P < 0.05	P < 0.05
2a vs. 3	NS	NS	NS	NS	NS	NS	NS	NS

Groups 2 and 3 are the same as in Table I. Group 2a was prepared similarly to group 2 except that dexamethasone was infused during clearance experiments (see text for details). Data represent mean±SEM. Statistical comparisons for each vertical row of data are indicated at the bottom of each row.

1.340±0.094 $\mu\text{eq}/\text{min}$ per 100 g body wt in group 6). Nonetheless, despite chronic aldosterone-dexamethasone replacement, both fractional and total potassium excretion remained significantly less than control levels (groups 5 vs. 1). Thus, chronic aldosterone and dexamethasone administration did not normalize potassium excretion after an acute infusion of potassium to levels observed in adrenal-intact controls.

In the last experimental group, aldosterone was infused acutely into animals who were chronically replaced with aldosterone and dexamethasone. This maneuver was chosen to reproduce the acute rise in plasma aldosterone levels observed in control animals after hyperkalemia and anesthesia (40; and Table II). Acute infusion of aldosterone led to an increase in fractional potassium excretion to 50.7±2.4%, a value not statistically different from the control value of 54.5±4.0%. Similarly, absolute potassium excretion also increased in response to acute aldosterone infusion to 1.529±0.081 $\mu\text{eq}/\text{min}$ per 100 g body wt. This value was also not statistically different from the control excretion rate of 1.710±0.081 $\mu\text{eq}/\text{min}$ per 100 g body wt. These experiments underscore the role of an acute increase in aldosterone levels in maintaining a normal renal response to an acute potassium load.

Additional changes in urinary fluid and electrolyte excretion, GFR, and in plasma sodium and potassium levels were noted in our studies. GFR was significantly reduced during the potassium infusion period in ADX rats (group 2) and in animals receiving aldosterone (group 4), and aldosterone plus dexamethasone (group 5) compared with control (group 1). However, GFR was not significantly less than control values in dexamethasone (group 3) and aldosterone-dexamethasone treated rats that also received aldosterone acutely (group 6). Data on urinary flow rate are shown in Fig. 3 and Table V. Fluid excretion was significantly elevated in dexamethasone-treated animals (group 3) but was similar in all other groups (i.e., groups 2 and 4–6). Accordingly, changes in fluid excretion rate cannot explain hormonally induced alterations in potassium transport in these latter experimental groups.

Renal sodium excretion was also affected by adrenalectomy and subsequent hormone replacements (Fig. 3 and Table V). Dexamethasone replacement in ADX animals led to a significant increase in FE_{Na} and absolute sodium excretion. In groups 4 and 5 (aldosterone replacement), sodium excretion was reduced compared with animals that did not receive aldosterone (groups 2 and 3). Acute infusion of aldosterone into animals treated chronically with both steroid hormones had an additional and potent stimulatory effect on sodium reabsorption. Sodium excretion was reduced from 1.28±0.22% (group 5) to 0.43±0.10% (group 6). Similarly, absolute sodium excretion fell after acute aldosterone infusion from 0.978±0.187 to 0.333±0.071 $\mu\text{eq}/\text{min}$ per 100 g body wt (group 5 vs. group 6). The sodium excretion values in group 6 are similar to observations in control animals (group 1).

Acute potassium infusion led to an increase in plasma potassium concentration in all groups of animals (Table V). The plasma potassium concentration was higher than control values in all experimental groups except group 6. Thus, only the combination of chronic aldosterone plus dexamethasone replacement with acute aldosterone infusion normalized the rise in plasma potassium after acute potassium loading. Plasma potassium concentration was similar in groups 2 and 3, i.e., when aldosterone was absent, and in both groups 2 and 3 it was higher than in all other groups.

Sodium concentrations (Table V) were significantly depressed in aldosterone-deficient animals (groups 2 and 3) compared with adrenal-intact controls and the aldosterone replaced groups (groups 4–6). Sodium concentration was similar to control values in all groups treated with aldosterone (groups 4–6).

Discussion

One of the main conclusions of this study is that different mechanisms are involved in the stimulation of renal potassium excretion after aldosterone and/or dexamethasone replacement in chronically ADX rats. Our data are consistent with the view that, at physiological levels, only aldosterone stimulates potassium secretion directly by the distal and cortical collecting tubule. Dexamethasone, on the other hand, seems to exert its effect on potassium excretion indirectly by increasing GFR and augmenting the delivery of fluid and sodium along the distal tubule and cortical collecting duct. The morphologic effects of the two hormones, to be presented in another paper (35), provide further support for this view. In these morphological studies aldosterone increased specifically the area of the basolateral membrane of the principal cell type in the initial collecting tubule of ADX animals; dexamethasone had no effect. Because similar alterations in membrane area, induced by potassium adaptation, are associated with a sharp increase in potassium secretion by the initial collecting tubule (45), we conclude that augmenting basolateral membrane area in the initial collecting tubule by chronic aldosterone treatment in the present studies indicates a direct effect of aldosterone on the structure and function of this nephron segment.

We did not directly define the nephron sites of action of aldosterone and of dexamethasone in this study. However, a large body of evidence documents that mineralocorticoids stimulate potassium secretion by the "late" distal tubule (initial collecting tubule) and the cortical collecting duct (9, 17, 22, 23, 36, 40, 45–48). Thus, it seems reasonable to assume that alterations in renal potassium excretion represent alterations in potassium secretion by the "late" distal tubule and cortical collecting duct (reviewed in 3). We have also demonstrated in a recent microperfusion study of the distal tubule that an acute elevation of plasma aldosterone stimulates potassium secretion at this tubular site (17). In contrast, dexamethasone did not enhance potassium secretion if care was taken to maintain flow rate constant (17). Thus, the increase in urinary potassium excretion in animals treated with dexamethasone in the present study is most likely related to an increase in the rate of fluid delivery along the distal and collecting tubule as reflected by the sharp augmentation of urinary fluid excretion.³

Basal conditions: Ringer infusion. An important difference was observed concerning the effects of chronic corticosteroid replacement on base-line potassium excretion as opposed to the ability of the kidney to augment potassium excretion after

3. It is likely that at least two mechanisms are responsible for an increase in urinary fluid excretion in dexamethasone treated animals. First, dexamethasone increases the GFR, which may result in an increase in the delivery of fluid into the early distal tubule (28). Second, dexamethasone reduces the water permeability of the distal tubule (24), an effect that would also augment urinary flow rate. Whether dexamethasone has an effect on potassium excretion by a mechanism other than augmenting urinary flow rate is not known.

an acute potassium load. Under basal conditions all groups of animals had similar excretory rates of potassium despite varying replacement protocols of mineralocorticoids and glucocorticoids (Table IV). This observation, however, should not be construed to indicate that adrenal corticosteroids are not important in the regulation of potassium excretion. It is known that hyperkalemia (17), increased urinary fluid excretion, and increased sodium delivery to the distal nephron (30–32) all stimulate potassium excretion. Therefore, we conclude that in the absence of mineralocorticoids, basal potassium excretion is maintained, under the present experimental conditions, by the combined stimulatory effects of hyperkalemia, natriuresis, and augmented urine flow. Note that during chronic treatment with aldosterone (groups 4–6), basal potassium excretion was maintained without an increase in urinary sodium and fluid excretion or hyperkalemia. From this it is safe to infer that aldosterone has a direct stimulatory effect on potassium secretion at the level of the distal and cortical collecting tubule.

In contrast to potassium excretion, the six groups of animals exhibited a wide range of urinary sodium excretion rates during the basal period when only Ringers solution was being infused. These differences are in large part due to the fact that the control animals drank distilled water whereas ADX animals in groups 2–6 ingested a drinking solution containing 0.9% NaCl. Therefore, we will limit our discussion to the effects of aldosterone and dexamethasone on renal sodium transport to the groups of animals receiving saline, i.e., groups 2–6 (Table IV). Chronic dexamethasone replacement (group 3) had no effect on base-line sodium excretion compared with ADX animals, whereas all three groups of animals treated with aldosterone reabsorbed considerably more sodium than did aldosterone deficient animals during the basal period of Ringer infusion. These observations support a large body of evidence that mineralocorticoids stimulate renal sodium reabsorption (reviewed in 1, 3, and 4). Micropuncture and microperfusion studies have localized this effect of aldosterone on sodium reabsorption to the level of the distal and cortical collecting tubule (reviewed in 1, 3, and 4).

Experimental conditions: KCl infusion. In sharp contrast to the effect of chronic aldosterone and/or dexamethasone replacement under basal conditions discussed above, potassium excretion rates were influenced dramatically by adrenalectomy and corticosteroid replacement during potassium chloride infusion. Adrenalectomy resulted in a significant decline in urinary potassium excretion. This defect in acute potassium tolerance confirms observations by others (1–3, 5, 7, 8, 10, 16). Dexamethasone replacement produced a small but significant improvement in fractional potassium excretion, from 19.1% to 28.6%. On an absolute basis, however, these animals excreted much less potassium than controls. Our results thus agree with several previous studies that have demonstrated that glucocorticoids, including dexamethasone, can significantly enhance potassium excretion (6, 11, 15, 16, 19–21). However, in most but not all (16) of these studies, supraphysiologic or pharmacologic doses of glucocorticoids were employed. Receptor binding studies have indicated that even at physiological levels of glucocorticoids there is significant crossover binding of glucocorticoid hormones to the mineralocorticoid receptor (25–27). Thus, the kaliuretic effect of glucocorticoids in ADX animals, particularly at high hormone levels, may result from stimulating the mineralocorticoid receptor.

Additional factors also may contribute to the stimulation

of potassium excretion after glucocorticoid treatment. Glucocorticoid treatment led to a dramatic increase in urine flow in this study as well as in other studies (6, 15, 17, 18). Therefore, it is reasonable to conclude that the associated kaliuresis is, in part, the consequence of the increase in urine flow rate, the latter being a well-known stimulus of potassium excretion (30–32). We investigated this possibility directly by increasing urinary flow rate in ADX, chronically hormone-depleted animals, by the acute administration of dexamethasone; absolute potassium excretion was stimulated by this maneuver. In a previous study we had also shown that this protocol of acute glucocorticoid infusion did not stimulate potassium secretion at the level of the distal tubule, provided distal flow rate was held constant by microperfusion (17). Our results are, therefore, consistent with the view that the stimulatory effect of dexamethasone on potassium excretion is most likely indirect, being mediated by an increase in flow rate and sodium delivery (30–32) through the distal tubule. The results of our ultrastructural analysis of the late distal tubule presented in another paper (35) also suggest that dexamethasone does not have a direct effect at this site because the ultrastructure of principal cells was unaffected by chronic glucocorticoid treatment.

In contrast to the results obtained with dexamethasone treatment, chronic as well as acute aldosterone infusion stimulated urinary potassium excretion without increased fluid or sodium excretion. Chronic aldosterone replacement alone and combined aldosterone and dexamethasone replacement was still insufficient to restore urinary potassium excretion rates to control values. However, when aldosterone was infused acutely into animals given combined hormone replacement, potassium excretion was restored to levels observed in adrenal-intact controls. These results demonstrate that, although maintenance of basal levels of aldosterone are important in potassium homeostasis, they must be associated with an additional acute increase in plasma aldosterone concentration to completely restore the normal physiologic renal response to an acute potassium challenge. This interpretation is consistent with the results of a previous microperfusion study from our laboratory that demonstrated a direct stimulatory effect of an acute elevation of plasma aldosterone on distal tubular potassium secretion independent of changes in tubular flow rate (17).

Physiological alterations in the plasma levels of aldosterone and its glucocorticoid equivalent, dexamethasone, also had significant effects on renal sodium excretion in ADX animals during potassium chloride loading (Table V). Dexamethasone had no stimulatory effect on sodium reabsorption. In fact, it resulted in a further natriuresis. Chronic and acute aldosterone replacement, in contrast, had a potent stimulatory effect on sodium reabsorption. These data confirm the potent effect of physiological levels of aldosterone on sodium transport in the kidney (reviewed in 1–3).

In summary, we have shown that physiological levels of both aldosterone and dexamethasone stimulate renal potassium excretion, albeit by different mechanisms. Mineralocorticoids directly stimulate tubular potassium secretion, whereas glucocorticoids indirectly augment potassium excretion by increasing fluid and sodium delivery along the distal nephron. This dual action of corticosteroids has significant implications. Failure of an acute infusion of aldosterone to stimulate urinary potassium excretion has been observed (2, 3, 10, 16, 17). It is most likely that this is related to the attendant fall in urinary flow and sodium excretion, which oppose a direct stimulatory

effect of the hormone on distal potassium secretion. Indeed, a failure of aldosterone to enhance potassium excretion is always associated with a decline in urinary flow. On the other hand, when urinary flow rate and sodium excretion are prevented from declining, potassium excretion rises after acute aldosterone administration (1–3, 10, 20). Because glucocorticoids such as dexamethasone maintain or elevate glomerular filtration rate, urinary flow rate, and sodium excretion, they will oppose the decline in flow and sodium induced by aldosterone and thereby enhance the sensitivity of the potassium secretory mechanism of the distal nephron to the stimulatory effects of mineralocorticoids. Accordingly, the effective modulation of renal potassium excretion will depend on the appropriate dual action of both classes of steroids, mineralocorticoids, and glucocorticoids.

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