Effect of Adrenal Steroids on a Na⁺- and K⁺-requiring Adenosine Triphosphatase from Rat Kidney

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SUMMARY

In the rat, kidney adenosine triphosphatase activity levels in the presence of sodium and potassium ([Na⁺ + K⁺]-ATPase) fall slowly after adrenalectomy, reaching a minimum on the 6th or 7th postoperative day. Kinetic data from kidney microsomal preparations indicate that this result from a decrease in enzyme levels rather than an alteration in the Kₐ values for ATP, sodium, or potassium.

The administration of aldosterone (10 μg) to adrenalectomized rats produced no detectable changes in kidney (Na⁺ + K⁺)-ATPase levels after 3 hours, even though maximal sodium retention may be observed at that time. However, corticosterone, when given in doses equivalent to the adrenal output, brought the kidney (Na⁺ + K⁺)-ATPase levels of adrenalectomized rats back to normal in 2 to 3 days.

The transport of sodium and potassium ions across cell membranes against an electrochemical gradient is an energy-dependent active process. In the squid axon, energy for active cation transport can be supplied by adenosine triphosphate or one of its precursors, e.g. phosphoenolpyruvate or arginine phosphate (1). The transport of sodium and potassium ions across the red cell membrane is also dependent upon ATP as an energy source (2, 3). It therefore seems reasonable that cell membranes contain a system capable of converting chemical energy into a form in which it can be used for cation transport. When cellular organization is destroyed, this system is thought to manifest itself as a Mg⁺⁺-dependent adenosine triphosphatase (ATPase) which can be stimulated by the simultaneous presence of sodium and potassium ions (1). The existence of (Na⁺ + K⁺)-ATPase¹ was first demonstrated by Skou (4) in a microsomal fraction from crab peripheral nerve, and it has subsequently been found in mammalian tissues, particularly those with nervous or secretory functions (5).

Well documented evidence now exists to support Skou's original hypothesis that (Na⁺ + K⁺)-ATPase could provide an enzymatic basis for the active transport of cations across cell membranes (6, 7).

In the kidneys of warm blooded animals active transport apparently carries sodium ions from the glomerular filtrate back into the circulation, since perfusion of the organ with cardiac glycosides causes loss of sodium (8, 9). In the normal rat essentially all of the sodium in glomerular filtrates is reabsorbed, and after adrenalectomy about 98% (10). Because of the high filtration rates this 2% decrement in reabsorption is large enough to account for the increased sodium excretion observed after adrenalectomy. Restoration of the deficient reabsorption in the distal tubule appears to be the mechanism by which aldosterone exerts its antinatriuretic effect in the adrenocortical animal (11). This effect can be abolished by pretreating the animal with actinomycin D (12). Edelman, Bogoroch, and Porter (13, 14) have convincingly demonstrated that in the toad bladder a ribonucleic acid-mediated synthesis of protein precedes the increase in sodium transport caused by aldosterone. Further complications are introduced by the observations of Lockett and Roberts (15) that growth hormone is required for the full expression of the aldosterone effect. In any case it would appear that the steroid is stimulating the synthesis of an enzyme system involved in the active transport of sodium. If (Na⁺ + K⁺)-ATPase is the enzyme involved, it might be expected that changes in its level would be either so small or so localized anatomically that detection of these changes would be difficult. In view of these observations it is somewhat surprising that Landon and Forte (16) observed a very marked decrease in the (Na⁺ + K⁺)-ATPase activities of kidney microsomes from rats which had been adrenalectomized or treated with aldactone, an aldosterone antagonist. Since so little is known of the effects of steroids on this enzyme, it seemed advisable to examine the levels of the kidney ATPase after the administration of various adrenocortical steroids before embarking on further studies of the hormonal control of transport. A preliminary report of this work has already appeared (17).

EXPERIMENTAL PROCEDURE

Corticosterone, d-aldosterone, and hydrocortisone were obtained from Calbiochem. Growth hormone (NIH-GH-S-3 ovine, 1 U.S.P. unit per mg) was kindly supplied by Dr. Peter Condiffe. Terminally labeled ATP²P (specific activity, 5 to 10 mCi per μmole) was prepared by the method of Pfeiderer (18) as modified by Gibbe, Roddy, and Titus (10) and was diluted with

¹ In this paper, ATPase activity measured in the presence of Mg⁺⁺ alone will be referred to as Mg⁺⁺-ATPase. The increment in activity observed when sodium and potassium are also present will be designated (Na⁺ | K⁺)-ATPase.
carrier ATP obtained from Sigma to give a specific activity of 10 to 20 μCi per mmole. All other chemicals were obtained from commercial sources and were of reagent grade.

Both normal and adrenalectomized rats (male, Sprague-Dawley) were purchased from Hormone Assay Laboratories and were fed Purina rat chow. Adrenalectomized animals were allowed a 5% glucose-1% sodium chloride solution ad libitum. In preliminary experiments several groups of adrenalectomized rats were maintained on tap water for 24 to 48 hours before removal of the kidneys. Since levels of kidney ATPase were not different from those of animals receiving NaCl, it seemed unnecessary to maintain precise control of salt intake.

Single doses of aldosterone (10 μg) were administered intravenously in 0.2 ml of 0.9% NaCl solution; controls received NaCl only. Growth hormone (100 μg) was given intramuscularly in 0.2 ml of 0.9% NaCl adjusted to pH 9.0. In the chronic experiments aldosterone (5 and 10 μg), corticosterone (1 and 2 mg) and hydrocortisone (0.08 and 0.15 mg) were given intramuscularly in sesame oil (0.1 ml). Controls received sesame oil (0.1 ml) only.

The rats were sacrificed by a blow on the head, and the kidneys were removed and dissected free of adipose and connective tissue. They were then homogenized for 1 min (1200 rpm) in 0.2 ml of 0.9% NaCl. In the chronic experiments aldosterone (5 and 10 μg), corticosterone (1 and 2 mg) and hydrocortisone (0.08 and 0.15 mg) were given intramuscularly in sesame oil (0.1 ml). Controls received sesame oil (0.1 ml) only.

The unique cation requirements of (Na+ + K+)-ATPase make it possible to estimate the total amount of this enzyme in rat kidneys by assaying the activity of whole homogenates. Fig. 1 shows the effects of eatoms and ouabain on the crude rat kidney preparation used in this investigation. A high concentration of ouabain (1 μM) was used because the rat enzyme is very insensitive to this glycoside. In contrast to the rat kidney microsomal preparation of Landon and Norris (21), dialysis was not necessary for the demonstration of (Na+ + K+)-ATPase activity. This was undoubtedly due to the inclusion of deoxycholate in the homogenizing medium. Järnefelt (26) has reported that this detergent removes bound sodium and potassium ions from rat brain microsomal preparations which then become sensitive to the addition of exogenous cations.

Both the kidney microsomes (Fig. 2) and the whole homogenates release inorganic phosphate from ATP in a linear fashion with respect to enzyme concentration up to 8 min of incubation provided that not more than 20% of the substrate is hydrolyzed. The ATPase activities of the crude homogenates are reported in millimoles of P i formed per hour per mg of wet kidney weight. This method of expressing the results is valid since neither adrenalectomy nor the administration of steroids appears to alter the degree of kidney hydration (17, 26). This was confirmed by measurement of the protein content of the homogenates by the method of Lowry et al. (22). In a typical experiment, preparation of endoplasmic reticulum free of intact mitochondria and large mitochondrial fragments (21). Fresh microsomal preparations hydrolyzed ATP at the rate of 60 to 70 μmoles per hour per mg of protein; half of this activity was sodium and potassium sensitive. Approximately 30% of the (Na+ + K+)-ATPase activity present in the whole homogenates was recovered in the microsomal fraction.

**Protein Determinations—** These were carried out by the method of Lowry, Rosebrough, Farr, and Randall (22).

**Kidney ATP Determinations—** Five adrenalectomized rats (120 to 140 g, 7th postoperative day) were injected intravenously at zero time with 10 μg of aldosterone dissolved in NaCl (0.2 ml). Controls received NaCl (0.2 ml) only. After 3 hours the rats were sacrificed by a blow on the head, and the kidneys were removed quickly into liquid nitrogen. This technique was found to produce kidney ATP levels not significantly different from those obtained in rat kidneys which had been completely immersed in liquid nitrogen.

The frozen kidneys were dissected free from adhering adipose and connective tissue and weighed quickly on a torsion balance. Each kidney was pulverized in a tissue disintegrator (23) in the presence of 1 ml of 0.3 M perchloric acid, and the mixture was allowed to thaw and was then treated with a further 4 ml of cold 0.3 M perchloric acid. After standing at 0° for 15 min, the extract was washed into a megazomer with 10 ml of cold distilled water, briefly homogenized, and then centrifuged for 10 min at 3000 × g. The supernatant was carefully decanted into a chilled beaker containing 10 ml of cold 0.2 M glycyglycine buffer (adjusted to pH 8.0 with 1.0 N KOH), and the pH was adjusted to 7.5 with 1.0 N KOH. After centrifugation of the precipitated KClO 4, the extract was quantitatively transferred to a chilled 50-ml volumetric flask and made up to volume with distilled water. Aliquots of this neutralized extract were assayed for ATP by the luciferin-luciferase method (24).

**RESULTS**

Kidney Microsomal Fraction—The whole kidney homogenates were centrifuged at 37,000 × g for 40 min. The supernatant was then centrifuged at 100,000 × g for 120 min. The pellet was resuspended in half the original volume of histidine buffer (0.08 M histidine-0.25 M sucrose-0.001 M EDTA, pH 6.8) and stored at -20°. This procedure has been found to produce a preparation of endoplasmic reticulum free of intact mitochondria and large mitochondrial fragments (21). Fresh microsomal preparations hydrolyzed ATP at the rate of 60 to 70 μmoles per hour per mg of protein; half of this activity was sodium and potassium sensitive. Approximately 30% of the (Na+ + K+)-ATPase activity present in the whole homogenates was recovered in the microsomal fraction.
ADDITIONS

\[
\begin{array}{cccc}
\text{Na}^+ & \text{K}^+ & \text{Mg}^{++} & 1 \\
\text{Na}^+ & \text{K}^+ & \text{Mg}^{++} & 2 \\
\text{Na}^+ & \text{K}^+ & \text{Mg}^{++} & 3 \\
\text{Mg}^{++} & \text{OUABAIN} & 4 \\
\text{Mg}^{++} & \text{OUABAIN} & 5 \\
\end{array}
\]

Fig. 1. The effect of ouabain and cations on the ATPase activities of rat kidney homogenates. Tubes contained 0.1 M imidazole, pH 7.2, and 2 mM ATP. MgCl_2 was 6 mM; NaCl, 100 mM; KCl, 20 mM; and ouabain, 1 mM. The results are the mean values of preparations from five animals with the standard error represented by a horizontal bar.

No change in ouabain and cations on the ATPase activities of rat kidney homogenates (Experiment 6, Table II), kidney homogenates from the control adrenalectomized rats contained 0.77 ± 0.03 mg of protein per ml. Kidney homogenates from the rats receiving hydrocortisone (0.08 mg twice daily for 5 days) contained 0.75 ± 0.02 mg of protein per ml, whereas those receiving aldosterone (5 μg twice daily for 5 days) contained 0.76 ± 0.02 mg of protein per ml.

The whole homogenates were found to lose Mg^{++}-ATPase activity slowly on standing at 0°, while the (Na^+ + K^+)-ATPase levels remained unchanged (Fig. 3). This decay of Mg^{++}-ATPase has been observed by other workers (27) and may account for the different levels of this enzyme observed in experiments carried out on different days (see Table I). Within one experiment, however, the Mg^{++}-ATPase levels were found to be constant, thus providing a steady base line from which to measure (Na^+ + K^+)-ATPase activity. All measurements of (Na^+ + K^+)-ATPase activities were made within 2 hours of the preparation of the homogenate.

Adrenalectomy caused a 40 to 50% reduction in the (Na^+ + K^+)-ATPase activities of rat kidney homogenates without significantly affecting the Mg^{++}-ATPase levels (Experiments 1 and 4, Table I). London and Forte (16) have also found lower (Na^+ + K^+)-ATPase levels in dialyzed kidney microsomal preparations from adrenalectomized rats. As may be seen from Fig. 4, the fall of kidney (Na^+ + K^+)-ATPase levels after adrenalectomy is very slow in weanling rats, reaching the previously observed level (Experiment 4, Table I) on the 7th postoperative day. Kidney (Na^+ + K^+)-ATPase levels in older rats (120 to 140 g) also fall slowly after adrenalectomy, reaching a minimum on the 6th or 7th postoperative day. Other experiments (17) have shown that the fall in (Na^+ + K^+)-ATPase activity occurs to the same extent in both the cortex and the medulla. Microsomal preparations from the kidneys of normal and adrenalectomized rats reflect the same differences observed in the whole homogenates (Fig. 2).

Although maximal sodium retention may be observed 3 hours after the administration of aldosterone (10 μg intravenously) to an adrenalectomized rat (28), no change in (Na^+ + K^+)-ATPase levels could be detected at that time (Table I). Growth hormone (100 μg intramuscularly), which has been reported to be necessary for the complete restoration of sodium reabsorption in rats (15), did not alter (Na^+ + K^+)-ATPase levels when given alone or in combination with aldosterone (10 μg intravenously). Increased doses of aldosterone up to 100 μg per rat were also without effect (17). Epinephrine (10 μg subcutane-
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TABLE I
Effect of adrenalectomy and acute administration of steroids on rat kidney (Na+ + K+)-ATPase

Aliquots of the whole kidney homogenates (containing 1 mg of kidney, wet weight) were incubated at 37° for 4 min with 2 mM ATP and 0.1 M imidazole-HCl, pH 7.2. MgCl₂ was 5 mM; KCl, 20 mM; and NaCl, 100 mM. The (Na+ + K+)-ATPase activity was calculated by subtracting the enzyme activity obtained in the presence of MgCl₂ alone (Mg++-ATPase) from that obtained with MgCl₂, NaCl, and KCl. Numbers in parentheses indicate the days after adrenalectomy. Results are expressed as the mean from five animals followed by the standard error. Rats received the dose of drug indicated 3 hours before sacrifice.

<table>
<thead>
<tr>
<th>Rat</th>
<th>Mg++-ATPase</th>
<th>(Na+ + K+)-ATPase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmoles P_i/hr/mg kidney</td>
<td></td>
</tr>
<tr>
<td>Experiment 1</td>
<td>Adrenalectomized (7)*</td>
<td>1.53 ± 0.22</td>
</tr>
<tr>
<td>Normal*</td>
<td>1.98 ± 0.12</td>
<td>2.87 ± 0.10</td>
</tr>
<tr>
<td>Experiment 2</td>
<td>Adrenalectomized (11)*</td>
<td>2.05 ± 0.04</td>
</tr>
<tr>
<td>Adrenalectomized (11), aldosterone, 10 µg, i.v.</td>
<td>2.00 ± 0.04</td>
<td>1.94 ± 0.04*</td>
</tr>
<tr>
<td>Experiment 3</td>
<td>Adrenalectomized (6)*</td>
<td>1.35 ± 0.05</td>
</tr>
<tr>
<td>Adrenalectomized (6), aldosterone, 10 µg, + 100 µg growth hormone, i.m.</td>
<td>1.20 ± 0.00</td>
<td>1.28 ± 0.04*</td>
</tr>
<tr>
<td>Adrenalectomized (6), growth hormone, i.m.</td>
<td>1.42 ± 0.08</td>
<td>1.07 ± 0.07*</td>
</tr>
<tr>
<td>Experiment 4</td>
<td>Adrenalectomized (9)*</td>
<td>1.77 ± 0.09</td>
</tr>
<tr>
<td>Normal*</td>
<td>1.85 ± 0.06</td>
<td>2.49 ± 0.05</td>
</tr>
</tbody>
</table>

* Weight, 120 to 140 g.
* p < 0.001.
* p > 0.05.
* Weight, 50 to 70 g (weanlings).
* p < 0.01.

In view of these results, it became of interest to determine whether normal (Na+ + K+)-ATPase levels could be reestablished in adrenalectomized animals by the chronic administration of steroids. Aldosterone, corticosterone, and hydrocortisone were therefore administered separately to groups of five rats for 5 days. In experiments with corticosterone and hydrocortisone, each rat received twice daily a dose of steroid equal to the reported daily output of the adrenal gland (31).

TABLE II
Effect of chronic administration of steroids on rat kidney (Na+ + K+)-ATPase

Incubation conditions were the same as in Table I. Rats received the dose of drug indicated intramuscularly twice daily for 5 days. Activity was measured on the 5th day. Numbers in parentheses indicate the days after adrenalectomy at the beginning of the experiment. Results are expressed as the mean from five rats followed by the standard error.

<table>
<thead>
<tr>
<th>Rat</th>
<th>Mg++-ATPase</th>
<th>(Na+ + K+)-ATPase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmoles P_i/hr/mg kidney</td>
<td></td>
</tr>
<tr>
<td>Experiment 1</td>
<td>Adrenalectomized (14)*</td>
<td>2.20 ± 0.04</td>
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<tr>
<td>Adrenalectomized (14), corticosterone, 2.0 mg</td>
<td>2.20 ± 0.04</td>
<td>2.27 ± 0.10*</td>
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<tr>
<td>Experiment 2</td>
<td>Adrenalectomized (12)*</td>
<td>1.59 ± 0.06</td>
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<tr>
<td>Adrenalectomized (12), hydrocortisone, 0.15 mg</td>
<td>1.77 ± 0.04</td>
<td>1.18 ± 0.04*</td>
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<td>Experiment 3</td>
<td>Adrenalectomized (15)*</td>
<td>2.15 ± 0.08</td>
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<td>Adrenalectomized (15), aldosterone, 10 µg</td>
<td>2.15 ± 0.03</td>
<td>1.60 ± 0.08*</td>
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<tr>
<td>Experiment 4</td>
<td>Adrenalectomized (5)*</td>
<td>1.35 ± 0.03</td>
</tr>
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<td>Adrenalectomized (5), aldosterone, 100 µg</td>
<td>1.35 ± 0.04</td>
<td>1.05 ± 0.08*</td>
</tr>
<tr>
<td>Experiment 5</td>
<td>Adrenalectomized (7)*</td>
<td>1.61 ± 0.05</td>
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<tr>
<td>Adrenalectomized (7), hydrocortisone, 0.08 mg</td>
<td>1.64 ± 0.08</td>
<td>2.30 ± 0.05*</td>
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<tr>
<td>Adrenalectomized (7), corticosterone, 1.0 mg</td>
<td>1.85 ± 0.10</td>
<td>3.11 ± 0.05*</td>
</tr>
<tr>
<td>Experiment 6</td>
<td>Adrenalectomized (7)*</td>
<td>2.04 ± 0.16</td>
</tr>
<tr>
<td>Adrenalectomized (7), aldosterone, 5 µg</td>
<td>2.06 ± 0.09</td>
<td>1.98 ± 0.10*</td>
</tr>
<tr>
<td>Adrenalectomized (7), hydrocortisone, 0.08 mg</td>
<td>2.29 ± 0.08</td>
<td>2.95 ± 0.10*</td>
</tr>
</tbody>
</table>

* Weight, 120 to 140 g.
* p < 0.001.
* p < 0.01.
* Weight, 50 to 70 g (weanlings).
Aldosterone was given twice daily in a dose (10 µg) equivalent to four times the reported daily adrenal output (32). The results from these experiments may be found in Table II. It may be seen that corticosterone brought the (Na⁺ + K⁺)-ATPase levels back to normal in the older rats (120 to 140 g) while hydrocortisone was without effect. Aldosterone significantly increased kidney (Na⁺ + K⁺)-ATPase levels at both doses tested but in neither case were normal levels attained.

In the weanling adrenalectomized rats, corticosterone also significantly increased (Na⁺ + K⁺)-ATPase levels (Table II). The effect of hydrocortisone in weanling rats is not clear since in one experiment (Na⁺ + K⁺)-ATPase levels were increased (Experiment 6, Table II) while no significant change could be demonstrated in other experiments (Experiment 5, Table II). Aldosterone had no effect at the dose level tested. It will be noted that in these experiments the (Na⁺ + K⁺)-ATPase levels in the control adrenalectomized weanling rats (Table II and Fig. 5A) were slightly higher than those observed previously (Table I and Fig. 4). This discrepancy could not be accounted for and may represent the variation between different batches of animals.

It may be seen from Fig. 5B that in the older adrenalectomized rats (120 to 140 g) the response of kidney (Na⁺ + K⁺)-ATPase to exogenous corticosterone is not apparent until the 2nd day.

Fig. 5. The effect of corticosterone on rat kidney ATPase levels. The weanling rats (A) were given 1 mg of corticosterone intramuscularly twice daily, while the older rats (B) received 2 mg twice daily. Injections were commenced on day zero, and the rats were sacrificed on the days indicated. All animals were 7 days postoperative at the commencement of the experiment. ATPase activities of the whole kidney homogenates were estimated with ATP, MgCl₂, NaCl, KCl, and buffer concentrations as in Fig. 1. Each point is the mean from five animals with the standard error represented as a vertical line. ○, (Na⁺ + K⁺)-ATPase; ●, Mg⁺⁺-ATPase.

Normal kidney (Na⁺ + K⁺)-ATPase levels were observed on the 3rd day. The response of weanling adrenalectomized rats to corticosterone was slightly faster, reaching a maximum on the 2nd day (Fig. 5A).

To ascertain the effect of adrenalectomy on the kinetic behavior of rat kidney (Na⁺ + K⁺)-ATPase, the Km values for ATP, sodium, and potassium were measured. These determinations were made on microsomal preparations rather than whole homogenates since the latter showed pronounced changes in activity on freezing and thawing. The microsomes, on the other hand, were stable for several months when stored at -20°. Kinetic data for kidney microsomes (Na⁺ + K⁺)-ATPase from normal and adrenalectomized rats are presented in Figs. 6 and 7 and summarized in Table III. The linearity of the Lineweaver-Burk plot for ATP (Fig. 6) suggests that the interaction of this substrate with (Na⁺ + K⁺)-ATPase can adequately be described by simple Michaelis-Menten kinetics. Adrenalectomy results in a reduction of the specific activity (Vₘₐₓ) of the preparation while the Km for ATP is not significantly altered (Table III). The Mg⁺⁺-ATPase is not influenced by adrenalectomy (Table III). It is of interest to note that for Mg⁺⁺-ATPase the Km for ATP is 3 to 4 times lower than for (Na⁺ + K⁺)-ATPase. This is in contrast to previous reports for beef and guinea pig brain microsomal preparations (19, 33).

Lineweaver-Burk plots for Na⁺ and K⁺ showed a pronounced upward bending, indicating a deviation from simple Michaelis-Menten kinetics. Reliable estimates of the Km value for these
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The (Na+ + K+)-ATPase activity of rat kidney homogenates was significantly lowered by adrenalectomy (Table I). Kinetic data obtained from microsomal preparations seem to indicate that this is the result of a decrease in enzyme levels rather than an alteration in the $K_m$ values for ATP, sodium, or potassium. In the rat, kidney (Na+ + K+)-ATPase levels fall slowly after adrenalectomy, reaching a minimum on the 6th or 7th postoperative day. Thus, it would appear that the enzyme may be turning over very slowly. It is also possible that the messenger RNA concerned with synthesis de novo is very long lived.

The administration of aldosterone (10 µg) to adrenalectomized rats produced no change in kidney (Na+ + K+)-ATPase levels after 3 hours even though maximal sodium retention may be observed at that time (28). If aldosterone exerts its antinatriuretic effect by control of (Na+ + K+)-ATPase, the induced changes must be very small or very highly localized. Experiments with the toad bladder (37) have suggested that aldosterone may control the supply of metabolic energy to the cation-transporting mechanism. Figmonari, Kasbekar, and Edelman (38), for example, have reported that if the toad bladder is incubated with aldosterone (7 x 10^{-8} M), the level of ATP is increased by 30%. In the mouse ascites tumor cell, it has been shown that active transport is linearly related to the intracellular level of ATP (39). In the mouse ascites tumor cell, it has been shown that active transport is linearly related to the intracellular level of ATP (39). The administration of aldosterone (100 µg intraperitoneally) increases the levels of cytochrome oxidase and succinic dehydrogenase in rat kidney, it seemed possible that this steroid could control active transport by altering the level of ATP in the tubule cells. No increase in kidney ATP levels was observed, however, after the administration of aldosterone (10 µg intravenously) to adrenalectomized rats. It should be pointed out, however, that the doses used by Feldman et al. were high enough for the glucocorticoid effects of aldosterone to be seen.

The data provided here do indicate that, in the rat, corticosterone, and not aldosterone, is responsible for maintaining kidney (Na+ + K+)-ATPase levels. The physiological significance of this finding is not at present clear, although it is known that corticosterone is the main steroid secreted by the rat adrenal (31). It would be of interest, therefore, to investigate the role of corticosterone in other species, e.g. hamster, dog, where hydrocortisone is the main component of adrenal secretion.

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