Rapid natriuretic action of aldosterone in the rat

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Rad, Abolfazl K., Richard J. Balment, and Nick Ashton. Rapid natriuretic action of aldosterone in the rat. J Appl Physiol 98: 423–428, 2005. First published October 15, 2004; doi:10.1152/japplphysiol.00572.2004.—Rapid, nongenomic actions of aldosterone have been demonstrated in a number of cell types in vitro, including renal cell lines, but there remains little direct evidence that it is able to exert rapid effects on the kidney in the whole animal. Accordingly, the aim of this study was to determine whether aldosterone induces rapid changes in the renal handling of electrolytes or acid-base balance in the anesthetized rat. With the use of a servo-controlled fluid replacement system, spontaneous urine output by anesthetized male Sprague-Dawley rats was replaced with 2.5% dextrose. After a 3-h equilibration and a 1-h control period, rats were infused with aldosterone (42 pmol/min) or vehicle for 1 h. Aldosterone infusion induced a rapid (within 15 min) increase in sodium excretion that peaked at 0.24 ± 0.08 compared with 0.04 ± 0.01 pmol·min⁻¹·100·body weight⁻¹ (P = 0.041) in the vehicle-infused rats. This natriuresis was not associated with changes in glomerular filtration rate; urine flow rate; potassium, chloride, or bicarbonate excretion; or urine pH. The mechanisms involved are unclear, but because we have previously shown that aldosterone stimulates a rapid (4 min) increase in cAMP generation in the rat inner medullary collecting duct (IMCD) (Sheader EA, Wargent ET, Ashton N, and Balment RJ. J Endocrinol 175: 343–347, 2002), we could involve cAMP-mediated activation of the cystic fibrosis transmembrane conductance regulator chloride channel, which drives sodium secretion in the IMCD.

natriuresis; nongenomic; kidney

Conventionally, aldosterone is thought to act on the distal nephron to promote reabsorption of sodium by initiating genomic events that, over a period of several hours, increase transepithelial electrolyte transport. This slow process is central to the kidney’s ability to regulate sodium balance and thus blood pressure. However, in recent years it has become apparent that aldosterone, like other steroids, is able to evoke rapid, nongenomic responses in a variety of cells and tissues (24). Initial reports described rapid changes in sodium flux in canine erythrocytes (32) and human mononuclear leukocytes (39). Aldosterone has subsequently been shown to stimulate rapid responses in vascular smooth muscle cells (4), endothelial cells (29), colon (25), and bronchial epithelium (35). However, there have been fewer studies of the actions of aldosterone in its classic target tissue, the kidney.

Aldosterone has been shown to rapidly increase intracellular calcium in M-1 cortical collecting duct cells (15) and Madin-Darby canine kidney (MDCK) cells (10). The latter was associated with activation of the sodium/hydrogen exchanger NHE (11), which has also been reported in the toad distal tubule (27). Aldosterone has also been shown to increase NHE activity via extracellular signal-regulated kinase 1/2 (ERK1/2) in MDCK-C11 cells (10). Good et al. (13) have shown that aldosterone inhibits bicarbonate absorption in isolated, perfused rat medullary thick ascending limb. This effect was not blocked by actinomycin D, cycloheximide, or spironolactone, suggesting that it is not mediated via the classic mineralocorticoid receptor (MR). Rapid activation of epithelial sodium channel (ENaC) currents has been reported in rabbit, but not rat, cortical collecting duct cells after exposure to aldosterone (42). Furthermore, our laboratory has recently shown that aldosterone stimulates a rapid, dose-dependent increase in intracellular cAMP in isolated rat inner medullary collecting ducts (30). This was not inhibited by the MR antagonist spironolactone, suggesting that this is another nongenomic effect of aldosterone.

Despite the wealth of in vitro evidence demonstrating that aldosterone is able to evoke rapid, nongenomic actions, there is a paucity of data supporting these effects in vivo. Rapid increases in vascular resistance were noted in humans by Klein and Henk as long ago as 1963 (19), and more recently Wehling et al. (40) have reported a rapid increase in systemic vascular resistance coupled with a fall in cardiac output in response to a bolus injection of aldosterone in patients with coronary heart disease. In the dog, baroreceptor neuron discharge frequency has been shown to decrease 15 min after aldosterone administration (38). However, there remains little direct evidence that aldosterone exerts rapid, nongenomic actions on its classic target organ, the kidney, in vivo. Ganong and Mulrow (9) observed a reduction in urinary sodium excretion in adrenalectomized dogs 5–30 min after a bolus injection of aldosterone into the aorta or renal artery. In contrast, our laboratory has previously reported that combined infusion of aldosterone and oxytocin into aldosterone-suppressed rats (adrenalectomy or sodium bicarbonate infusion) resulted in a rapid increase in urinary sodium excretion (26), contrary to the conventional, genomic antinatriuretic actions of aldosterone. Apart from these observations, little is known about the nongenomic actions of aldosterone in the intact animal.

Because genomic changes occur over hours to days, we sought to establish in this study whether aldosterone is able to induce rapid (within minutes) changes in renal function in vivo. Accordingly, we determined the effect of acute aldosterone administration on renal sodium, potassium, and hydrogen handling, because these are the targets of its established classic genomic action.

METHODS

All experiments were performed under the authority of a UK Home Office Project Licence and received local ethical committee approval.

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Animal Preparation

Male Sprague-Dawley rats were purchased from Charles River UK Limited (Margate, Kent, UK) and were held in the School of Biological Sciences for at least 1 wk before experimentation to ensure that the sodium status of all rats was comparable. They had free access to standard rat chow (Beekay Rat and Mouse Standard Diet, Bantin and Kingman, Hull, UK) and water, with a 12:12-h light-dark cycle. The weight of animals at renal function study was between 250 and 350 g. Animals were anesthetized with Intraval (100 mg/kg body wt ip, thiopeptone sodium BP, Link Pharmaceuticals, Horsham, West Sussex, UK) and transferred to a hot plate that maintained body temperature, monitored by a rectal probe, at 37°C throughout the experiment. Cannulas were inserted into an external jugular vein, carotid artery, and the bladder, and a tracheotomy was performed, as described previously (1). Blood pressure was recorded directly from the arterial catheter by using a pressure transducer (model P23XL, Spectramed, Oxnard, CA) and a Grass polygraph recorder (model 79D, Grass Instruments, Quincy, MA). Depth of anesthesia was monitored throughout the experiment, and additional intravenous bolus doses of Intraval (10 mg/kg body weight) were administered as necessary.

Experimental Protocol

The infusion protocol was similar for each experimental series. Euvolemic fluid replacement of spontaneous urine output was achieved using a servo-controlled fluid replacement system, as described previously (1). Briefly, urine flow rate is determined gravimetrically and this information is transmitted via a computer to an adjustable pump. A program developed at the University of Manchester (2) allows the infusion rate of the pump to be automatically adjusted to precisely replace intravenously the volume of fluid lost as urine. The animals in series I and III (see below) also received a clearance marker ([3H]inulin in 2.5% dextrose, 6 µCi/h, Amershams International, Little Chalfont, Bucks, UK) via a second, slow, constant infusion pump (1 ml/h). After surgery, a bolus dose of [3H]inulin (6 µCi) was injected via the venous cannula (animals in series I and III only), and servo-infusion replacement was initiated. All animals were allowed a 3-h equilibration period, after which they were assigned at random to the following experimental series. The aim of series I was to determine whether aldosterone had a rapid effect on urinary sodium and potassium excretion. The aim of series II was to determine whether aldosterone had a rapid effect on urine pH and bicarbonate excretion. The aim of series III was to determine the circulating concentration of aldosterone induced by the infusion rate of 42 pmol/min employed in series I and II.

Series I. Rats either continued to receive vehicle (2.5% dextrose, n = 8) for the remaining 3 h of the experiment or received vehicle for 1 h, followed by aldosterone (42 pmol/min, Sigma-Aldrich, Poole, Dorset, UK) for 1 h and then vehicle for the final hour (n = 9). Our laboratory has shown previously that this dose alters renal function in aldosterone-suppressed rats while inducing circulating concentrations within the physiological range (26). Urine samples were collected for the measurement of electrolytes and [3H]inulin.

Series II. Rats received vehicle (2.5% dextrose, n = 7) for the remaining 3 h of the experiment or received vehicle for 1 h, followed by aldosterone (42 pmol/min) for 1 h and then vehicle for the final hour (n = 10). Urine samples were collected under mineral oil for the measurement of pH and bicarbonate concentration.

Series III. Rats either received vehicle (n = 6) for 1 h and 45 min or they received vehicle for 1 h, followed by aldosterone (42 pmol/min) for 45 min (n = 7) at which time they were killed by decapitation to collect blood for the measurement of the circulating plasma aldosterone concentration. Urine samples were collected from all animals every 15 min after the equilibration period. Blood samples (0.5 ml) were collected once per hour during the final 3 h of the experiment in series I and II. Sodium and potassium concentrations were measured by flame photometry (Corning 480, Corning, Halstead, Essex, UK) and chloride by chloride meter (Corning 925). pH and bicarbonate concentration were measured by using a blood-gas analyzer (model ABL330, Radiometer, Copenhagen, Denmark). [3H]inulin was determined using a 1900CA Tri-Carb liquid scintillation analyzer (Canberra Industries, Meriden, CT) β-counter. Plasma aldosterone was measured by radioimmunoassay using a commercial kit (ALDO-RIACT, CIS Bio International, Yvette Cedex, France).

Statistical Analysis

All data are presented as means ± SE. Statistical analysis was performed by using SPSS for Windows (version 10.1.0, SPSS UK, Surrey, UK). Homogeneity of variance was tested by Levene’s test and, where appropriate, subsequent analysis was performed on log-transformed data. The effects of time and aldosterone treatment were assessed by using a repeated-measures ANOVA design. Where there was no effect of time, comparisons between vehicle- and aldosterone-treated groups were made by using a one-way ANOVA and Duncan’s test. Differences in plasma aldosterone concentrations were tested by independent samples t-test. Significance was assumed at P ≤ 0.05.

RESULTS

Mean arterial blood pressure remained steady over the experimental period (F3,88 = 2.37, P = 0.083) and did not differ between animals receiving vehicle or aldosterone in either of the three experimental series (F1,33 = 0.205, P = 0.654). Similarly, urine flow rates across all three series remained steady (F4,115 = 1.48, P = 0.217) and did not differ between animals receiving vehicle or aldosterone (F1,32 = 2.61, P = 0.116). Consequently, these data have been combined in Table 1.

Table 1. Mean arterial blood pressure, urine flow rate, and the fractional excretion and clearance rates of electrolytes in rats receiving either vehicle or aldosterone infusion

<table>
<thead>
<tr>
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<th>Vehicle</th>
<th>Aldosterone</th>
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<tr>
<td>1st h</td>
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<tr>
<td>MAP, mmHg</td>
<td>98 ± 2</td>
<td>95 ± 2</td>
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<tr>
<td>UV, µl/min</td>
<td>8.3 ± 0.9</td>
<td>9.8 ± 1.0</td>
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<tr>
<td>FENa, %</td>
<td>0.053 ± 0.015</td>
<td>0.035 ± 0.01</td>
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<tr>
<td>CNa, µl/min</td>
<td>0.32 ± 0.08</td>
<td>0.24 ± 0.04</td>
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<tr>
<td>FCK, %</td>
<td>33 ± 10</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>CK, µl/min</td>
<td>154 ± 27</td>
<td>131 ± 16</td>
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<tr>
<td>FECa, %</td>
<td>0.77 ± 0.21</td>
<td>0.50 ± 0.08</td>
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<tr>
<td>CCK, µl/min</td>
<td>3.4 ± 0.5</td>
<td>3.3 ± 0.5</td>
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<td>Blood pH</td>
<td>7.381 ± 0.019</td>
<td>7.375 ± 0.019</td>
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<td>2nd h</td>
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<td></td>
<td>96 ± 2</td>
<td>92 ± 2</td>
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<td>11.1 ± 0.9</td>
<td>13.6 ± 1.3</td>
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<td>0.05 ± 0.01</td>
<td>0.12 ± 0.03</td>
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<td>0.31 ± 0.04</td>
<td>0.88 ± 0.16</td>
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<td>23 ± 4</td>
<td>29 ± 10</td>
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<td></td>
<td>146 ± 25</td>
<td>174 ± 27</td>
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<td>0.38 ± 0.04</td>
<td>0.55 ± 0.11</td>
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<td>2.4 ± 0.2</td>
<td>3.7 ± 0.5</td>
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<td>7.326 ± 0.022</td>
<td>7.354 ± 0.024</td>
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Values are presented as means ± SE, corrected to 100 g body wt where appropriate. MAP, mean arterial blood pressure; UV, urine flow rate; FENa, FENa, and FECl, fractional excretion rates of sodium, potassium, and chloride, respectively; CNa, CCK, and CCK, clearance rates of sodium, potassium, and chloride, respectively. Combined MAP and UV data are shown for animals from all 3 experimental series (vehicle n = 21, aldosterone n = 26). Fractional excretion and clearance data are shown for animals in series I (vehicle n = 8, aldosterone n = 9), and blood pH data are shown for animals in series II (vehicle n = 6, aldosterone n = 7). The 1st h represents the control hour before aldosterone infusion; the 2nd h represents the hour of either aldosterone or vehicle infusion. Statistical comparisons were by 1-way ANOVA and Duncan’s test. *P < 0.001, vehicle- vs. aldosterone-infused rats at the same time point.
differ between animals receiving vehicle or aldosterone \( (F_{1.16} = 1.88, P = 0.189) \). However, aldosterone infusion induced a rapid, marked increase in urinary sodium excretion within 15 min of the start of infusion (Fig. 1B; \( F_{1.15} = 6.15, P = 0.026 \)), which peaked at 0.24 ± 0.08 compared with 0.04 ± 0.01 \( \mu \text{mol}\cdot\text{min}^{-1}\cdot\text{100 body weight}^{-1} \) \( (P = 0.041) \) in the vehicle-infused rats at the same time. The total amount of sodium excreted over the hour of aldosterone infusion was 7.5 ± 2.4 compared with 2.0 ± 0.6 \( \mu \text{mol}/100 \text{ body weight} \) in the vehicle-infused animals \( (P = 0.048) \). The increase in sodium excretion was associated with significant increases in both fractional excretion of sodium \( (P < 0.001) \) and sodium clearance \( (P < 0.001) \) in the aldosterone-infused rats (Table 1). There was an equally rapid offset at the end of the infusion hour, with sodium excretion falling back toward control levels by the end of the third, postinfusion hour.

This increase in sodium output was not accompanied by a change in either potassium (Fig. 2A) or chloride excretion (Fig. 2B). Potassium excretion remained steady over the 3 h of the experiment \( (F_{3.46} = 0.485, P = 0.8) \) and did not differ between the vehicle- and aldosterone-infused groups \( (F_{1.16} = 0.228, P = 0.64) \). Similarly, fractional excretion \( (F_{3.143} = 1.08, P = 0.359) \) and clearance of potassium \( (F_{3.143} = 1.38, P = 0.252) \) were unaltered by aldosterone infusion (Table 1). By the end of the aldosterone infusion hour, there was a tendency toward higher chloride excretion in the aldosterone-infused animals, but this did not achieve statistical significance (maximum chloride excretion rate at the end of the second hour: vehicle 0.37 ± 0.05 vs. aldosterone 0.55 ± 0.1 \( \mu \text{mol}\cdot\text{min}^{-1}\cdot\text{100 body weight}^{-1} \); \( P = 0.143) \). Fractional excretion \( (F_{1.16} = 0.346, P = 0.565) \) and clearance of chloride \( (F_{1.16} = 0.038, P = 0.848) \) were unaltered by aldosterone infusion (Table 1).

**Series II: Effect of Aldosterone on Urinary pH and Bicarbonate Excretion**

Aldosterone infusion had no significant effect on either urine pH (Fig. 3A) or urinary bicarbonate excretion (Fig. 3B). Urine pH remained steady over the 3 h of the experiment \( (F_{3.48} = 1.91, P = 0.137) \) and did not differ between the vehicle- and aldosterone-infused groups \( (F_{1.15} = 2.19, P = 0.16) \). Bicarbonate excretion increased over the experimental period \( (F_{2.32} = 3.31, P = 0.046) \), but there were no significant differences between the vehicle- and aldosterone-infused groups \( (F_{1.15} = 0.753, P = 0.399) \). Blood pH did not change in response to aldosterone either (Table 1; \( F_{3.33} = 1.25, P = 0.31 \)).

**Series III: Circulating Aldosterone Concentration**

The infusion of aldosterone raised the plasma concentration to 501.2 ± 47.3 \( (n = 7) \) compared with 256.2 ± 88.6 \( \mu \text{mol/l} \) \( (n = 6; P = 0.049) \) in the vehicle-infused group. Although the maximal sodium excretion rate observed over this shorter period of aldosterone infusion (45 min) was not statistically
greater than that in vehicle-infused rats (vehicle 0.11 ± 0.03 vs. aldosterone 0.21 ± 0.06 μmol·min⁻¹·100 g body wt⁻¹; P = 0.16), aldosterone still had a significant impact on renal sodium handling. Total sodium output (vehicle 7.3 ± 2.0 vs. aldosterone 35.3 ± 11.3 μmol/100 g body wt; P < 0.05), fractional excretion (vehicle 0.05 ± 0.01 vs. aldosterone 0.16 ± 0.04%; P < 0.001), and clearance of sodium (vehicle 0.49 ± 0.1 vs. aldosterone 1.47 ± 0.2 μl·min⁻¹·100 g body wt⁻¹; P < 0.001) were all significantly higher in the aldosterone-infused group over the 45-min period of observation.

DISCUSSION

This study has clearly demonstrated that aldosterone is able to induce a rapid increase in urinary sodium excretion in the intact rat within 15 min, confirming our laboratory’s earlier observations in aldosterone-suppressed rats (26). This effect was reproducible, occurring in both experimental series where sodium was measured (series I and III). It is highly unlikely that the natriuresis reflected a difference in the sodium balance of the animals at the beginning of the experiment, because all rats were fed a standard rat chow for at least 1 wk before experimentation. Furthermore, animals were assigned at random to the control and aldosterone-treated groups. The rapid effect was also specific to sodium. Potassium and chloride excretion were unaffected, and there were no apparent differences in urinary pH. Given the rapid onset of the natriuresis, it seems likely that this effect is mediated by a nongenomic mechanism. Both the speed and nature of the response to aldosterone observed in this study contrast markedly with the classic genomic actions of aldosterone. Because this study was designed to detect rapid onset of action rather than the duration of response to aldosterone, we do not know how long the natriuresis would persist if aldosterone infusion continued. Genomic events would eventually lead to the activation of sodium retention mechanisms, so it is possible that under normal physiological conditions there may little net effect on longer term sodium balance. However, in the short term, aldosterone clearly has the potential to induce significant sodium loss.

Aldosterone’s main site of genomic action in the rat kidney is the collecting duct, although it also influences ion transport in the distal tubule and possibly the thick ascending limb. In the principal cells of the cortical collecting duct, it stimulates sodium reabsorption and potassium secretion by increasing the activity and number of ENaC and epithelial potassium channels in the apical membrane and Na⁺-K⁺-ATPase pumps in the basolateral membrane (22). In the intercalated cells of the inner stripe of the outer medulla, aldosterone stimulates hydrogen secretion by increasing the activity and number of H⁺-ATPase pumps in the apical membrane (22). Aldosterone also stimulates sodium reabsorption in the distal tubule by increasing the number of thiazide-sensitive NaCl cotransporters (NCC) in the apical membrane (18). The thick ascending limb is a major site of bicarbonate reabsorption that is driven by hydrogen secretion, mediated by both apical and basolateral NHE isoforms (12, 14). MRs are present in the thick ascending limb (33), but whereas chronic changes in plasma aldosterone have been shown to alter bicarbonate absorption (34), direct evidence of a genomic effect is still lacking in vivo.

Clearly, it is difficult to explain the changes in sodium handling induced by aldosterone in the present study in terms of the classic sites of genomic action. ENaC, Na⁺-K⁺-ATPase, and/or NCC activity or number would have to diminish to facilitate the observed natriuresis. Although we have no direct evidence to rule this out, it seems unlikely that this occurs. The lack of a simultaneous change in potassium excretion also suggests that this is not mediated by an inhibition of the classic collecting duct mechanisms.

Identification of the receptor that mediates aldosterone’s rapid, nongenomic actions would facilitate our understanding of the mechanisms underlying the physiological response that we report herein. However, the molecular identity of the putative membrane receptor for aldosterone is not yet known. Involvement of the intracellular MR, which mediates aldosterone’s genomic actions, has been proposed (23). However, MR knockout mice (MR⁻/⁻) still respond rapidly to hydrocortisone (16), suggesting that a second receptor mediates at least some nongenomic actions. Attempts to characterize the structure of this receptor have only been partially successful. A 50-kDa protein has been identified with a binding affinity of ~0.1 nM (5, 8), but beyond this, little more is known about the structure of the receptor.

In the absence of further information about the nongenomic receptor’s structure and location, we briefly discuss two possible alternative sites and mechanisms that could be involved in mediating this rapid natriuretic effect of aldosterone.
In addition to its well-established role in sodium and water reabsorption, there is now evidence that suggests that the inner medullary collecting duct (IMCD) can also secrete sodium, chloride, and water via a cAMP-dependent mechanism. Net salt secretion by the rat collecting duct was first demonstrated using microcatheterisation by Sonnenberg (31). This was subsequently confirmed in vitro using primary culture of IMCD cells (17) and isolated IMCD segments in which chloride secretion via the cAMP-dependent cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel was proposed as the driving force for paracellular sodium transport into the lumen (37). CFTR activation has also been shown to reduce sodium reabsorption by inhibiting ENaC (21). Our laboratory has reported recently (30) that aldosterone induces a rapid (within 4 min) increase in cAMP in isolated rat IMCD segments. CFTR is also activated by PKC phosphorylation (3). Aldosterone has been shown to induce a rapid increase in PKC in the renal M-1 cortical collecting duct cell line (15). Hence the natriuresis observed in the present study is consistent with CFTR activation. However, the concurrent modest increase in chloride excretion was not statistically significant and urine flow rate remained unaltered, so further evidence is required to establish whether cAMP- or PKC-mediated CFTR activation contributes to the natriuresis observed herein.

An alternative mechanism involves aldosterone-induced changes in NHE activity. Altered NHE activity is a common feature of the nongenomic actions of aldosterone in many cell types, including rat vascular smooth muscle cells (4), MDCK cells (11), and human distal colon (6). The NHE-3 isoform, which is located on the apical membrane in the proximal tubule, makes a significant contribution to sodium reabsorption. Activity of NHE-3 is acutely regulated, being inhibited by parathyroid hormone via cAMP and PKA and stimulated by angiotensin II through inhibition of cAMP and PKA (7). Aldosterone has been shown to rapidly stimulate cAMP generation in cultured human proximal tubule cells (20). However, we have been unable to demonstrate aldosterone-dependent stimulation of cAMP in isolated rat proximal tubule segments (28).

In contrast to the profound effects on urinary sodium excretion, aldosterone had no apparent effect on bicarbonate excretion and urinary pH. The kidney plays an important role in regulating systemic acid-base balance. The final stages in the acidification of urine occur in the collecting duct, with active secretion of hydrogen via vacuolar H+−ATPase in the outer medullary collecting duct (OMCD) (22) and reabsorption of bicarbonate in the terminal section of the IMCD (36). Nongenomic, aldosterone-induced electrogenic hydrogen secretion has been reported recently in murine OMCD. This effect was mediated by intracellular calcium and PKC (41). In the present in vivo study, aldosterone infusion did not appear to exert a rapid effect on urinary pH. However, we cannot discount the possibility that aldosterone induced rapid, nongenomic actions on renal tubular hydrogen and/or bicarbonate handling that were masked by buffering actions downstream.

In conclusion, this preliminary study has demonstrated that aldosterone induces a rapid increase in renal sodium excretion in vivo, in the absence of changes in urine flow rate and the excretion of potassium and chloride. The physiological significance of this novel natriuretic action remains to be determined. Clearly, this rapid response to aldosterone contrasts with its genomic antinatriuretic action. The specificity of the response to sodium suggests that it is associated with salt and volume homeostasis, rather than acid-base regulation. Although aldosterone has been shown to inhibit bicarbonate absorption in the medullary thick ascending limb in vitro (13), we did not observe any difference in urinary pH or bicarbonate excretion in vivo. The underlying mechanisms are unknown, but they could involve cAMP- or PKC-mediated activation of CFTR in the IMCD.

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