Control of Sodium and Potassium Transport in the Cortical Collecting Duct of the Rat

Effects of Bradykinin, Vasopressin, and Deoxycorticosterone

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Abstract

Several factors interact to maintain precise control of electrolyte transport in the mammalian cortical collecting duct. We have studied the effects of deoxycorticosterone, arginine vasopressin, and bradykinin on net transepithelial sodium and potassium transport in isolated, perfused rat cortical collecting ducts. Chronic administration of deoxycorticosterone to rats increased both sodium absorption and potassium secretion above very low basal levels. Consequently, deoxycorticosterone-treated rats were used for all remaining studies. Arginine vasopressin (10^{-10} M in the bath) caused a sustained fourfold increase in net sodium absorption and a sustained threefold increase in net potassium secretion. Bradykinin (10^{-9} M in the bath) caused a reversible 40–50% inhibition of net sodium absorption without affecting net potassium transport or the transepithelial potential difference. In the perfusate, up to 10^{-6} M bradykinin had no effect. We conclude: (*a*) As in rabbits, chronic deoxycorticosterone administration to rats increases sodium absorption and potassium secretion in cortical collecting ducts perfused in vitro. (*b*) Arginine vasopressin causes a reversible increase in net potassium secretion and net sodium absorption. (*c*) Bradykinin in the peritubular bathing solution reversibly inhibits net sodium absorption, possibly by affecting an electroneutral sodium transport pathway.

Introduction

It is generally recognized that the cortical collecting duct plays a major role in the fine control of renal sodium excretion, and thus in the regulation of extracellular fluid volume. The cortical collecting duct is also an important site of control of renal potassium transport. Factors that may influence electrolyte transport in this segment include adrenal steroids, vasopressin, and kinins (1). Of these three agents, least is known about the role of kinins.

Kinins are generated in the kidney by the action of the enzyme kallikrein on the protein substrate, kininogen. Many studies in intact animals have indicated that kinins are natriuretic (2–5). However, it is unclear whether natriuresis results from the hemodynamic effects of kinins or from a direct renal tubular action on sodium transport. Several lines of evidence point to the cortical collecting duct as a possible site of kinin action on sodium transport. First, both kallikrein (6–8) and kininogen (9) have been localized to the collecting duct system. Second, high-affinity binding sites for bradykinin have recently been localized to the cortical and outer medullary collecting ducts (10). Third, kinins have a marked inhibitory effect on vasopressin-stimulated water permeability in the isolated, perfused cortical collecting duct of the rabbit (11). The primary purpose of the present study, therefore, was to assess whether bradykinin directly affects net sodium transport in the cortical collecting duct of the rat using the isolated, perfused tubule technique. In addition, because little is known about the actions of mineralocorticoids and vasopressin on the rat cortical collecting duct, we have also studied the effects of chronic deoxycorticosterone administration and in vitro vasopressin on sodium and potassium transport.

The results show that bradykinin in the peritubular bathing solution, but not in the lumen, directly inhibits net sodium absorption. Bradykinin, however, has no demonstrable effect on net potassium transport or transepithelial potential difference, which indicates that it probably affects an electroneutral sodium transport pathway. In addition, both deoxycorticosterone administration in vivo and arginine vasopressin in vitro markedly enhance sodium absorption and potassium secretion in isolated rat cortical collecting ducts.

Methods

Pathogen-free male Sprague-Dawley rats weighing 65–100 g (Small Animal Breeding Facility, National Institutes of Health, Bethesda, MD) were injected with deoxycorticosterone pivalate (5 mg i.m., Percorten pivalate suspension, Ciba) 7–12 d before experiments. This is a depot preparation, which gives a sustained release of the hormone for at least 4 wk. Untreated rats served as controls. The rats were isolated in closed cages and received autoclaved food (National Institutes of Health-03, Ziegler Brothers, Inc., Gardners, PA) and bedding. These procedures make possible the dissection of single nephron segments from rat kidneys without enzymatic treatment of the tissue (12).

Both kidneys were removed rapidly from decapitated rats and coronal slices were prepared. Cortical collecting ducts were dissected at 17°C from corticomedullary rays stripped from the slices. The dissection solution contained (in mM) NaCl, 118; $NaHCO_3$, 25; K_2HPO_4, 2.0; $MgSO_4$, 1.2; calcium lactate, 2.0; sodium citrate, 1.0; L-alanine, 6.0; and glucose, 5.5. The dissection solution was gassed with 95% O_2 and 5% CO_2 before and during the dissection.

Tubules were mounted on concentric pipets as described previously (13). The perfusion, bath, and dissection solutions were identical (see description above). Two modifications of the perfusion technique were introduced. First, Dow-Corning 200 dielectric fluid (Dow Corning Corp., Midland, MI) was used instead of Sylgard 184 (Dow Corning Corp.) in the guard pipet at the collecting end. This material, like Sylgard 184, effectively prevents leaks between the bath and the tubule-holding pipet at the collection end, but because of its lower density, it has a lesser tendency to constrict the end of the tubule and allows steady flow even at very low perfusion rates (we thank Dr. J. Bourdeau, Northwestern University, Evanston, IL, for suggesting this approach). Second, a continuously-flowing bath exchange system with a gas-liquid mixer was used just before the input to the bath chamber. The mixer

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Table I. Effect of Deoxycorticosterone (DOC), Arginine Vasopressin (AVP), and Bradykinin (BK) on Sodium and Potassium Transport

Group	Pre-treatment	Number of tubules	Hormone in bath	Time*	Collection rate	Sodium flux	Potassium flux	Rate of fluid transport‡	Transepithelial potential difference
				min	*nl/min*	*pmol/mm/min*	*pmol/mm/min*	*nl/mm/min*	*mV*
A	None	3	None	30–50	0.95±0.13	0.2±0.2	−0.1±0.1	−0.01±0.04	−0.8±0.3
B	DOC	8	None	30–50	0.82±0.12	14.7±3.3	−2.0±0.6	−0.04±0.03	−4.1±1.4
			None	50–80	0.81±0.25	15.2±2.5	−1.0±0.5§	−0.03±0.03	−3.3±1.9
C	DOC	6	None	30–50	0.82±0.07	13.8±2.4	−2.1±1.2	−0.05±0.05	−3.6±1.3
			BK	50–80	0.85±0.12	7.2±1.6§	−1.5±0.9	−0.04±0.04	−2.1±0.6
D	DOC	6	None	30–60	0.87±0.08	12.5±2.7	−5.1±2.5	−0.01±0.02	−10.7±3.4
			AVP	60–90	0.97±0.04	58.0±11.3§	−16.6±6.2§	0.26±0.04§	−26.6±5.8§
			None	90–120	0.95±0.08	27.7±6.6‖	−7.3±3.9‖	0.09±0.02‖	−13.6±3.4‖
E	DOC	6	AVP	30–60	0.85±0.10	51.0±8.3	−12.0±5.2	0.24±0.05	−24.5±6.7
			AVP + BK	60–90	0.91±0.09	31.2±6.7§	−9.6±3.4	0.18±0.06§	−22.1±5.9
			AVP	90–120	0.80±0.07	45.3±7.5‖	−6.2±1.6	0.23±0.05‖	−21.6±5.5

* Time after warming to 37°C. ‡ Fluid absorption was measured in four tubules in group B and five in group C. In each time period, 2–4 collections were made. The mean sodium concentration in all perfusate determinations was 146.3±0.5 meq/liter, and the mean potassium concentration was 4.01±0.04 meq/liter (n = 36). Values are means±SE. § $P < 0.05$; 2nd period vs. 1st period. ‖ $P < 0.05$; 3rd period vs. 2nd period.

was a three-way stopcock (K-75, Pharmaseal, Inc., Toa Alta, PR) modified so that all three ports were opened to a central chamber. Separate streams of gas (95% O_2/5% CO_2) and bathing solution entered the mixer and formed an output consisting of short, alternating boluses of gas and equilibrated bath solution that flowed at 0.4 ml/min. In addition, the perfusion chamber was suffused with 95% O_2/5% CO_2 throughout the experiments. In control experiments in which a pH microelectrode was positioned in the bath at the site normally occupied by the tubule, it was shown that the bath solution was maintained at pH 7.44–7.46.

After mounting, the tubules were warmed to 37°C and then equilibrated for 20–30 min while establishing a steady perfusion rate of ~1 nl/mm per min. The lengths of the perfused segments ranged from 0.4 to 0.9 mm with a mean of 0.58 mm. Flow rates were determined by timing the filling of calibrated 8–18-nl constriction pipettes. 2–4 collections were made for each experimental condition.

The collected fluid and perfusate were analyzed for sodium and potassium by helium glow photometry (Aminco Instrument Co., Silver Spring, MD; no longer commercially available). Each 8–18-nl sample of collected fluid or perfusate was mixed under mineral oil with 357 nl of diluent containing 30 mM cesium nitrate and 5 mM monobasic ammonium phosphate. Two 10–13-nl aliquots of the diluted sample were taken for assay. Each measurement of collected fluid was followed immediately by a measurement of the perfusate with which it is compared in the flux calculations (see below). Differences of 2 meq/liter in sodium concentration and 0.2 meq/liter in potassium concentration could be distinguished. ^{14}C-inulin (New England Nuclear, Boston, MA) was added to the perfusate (20 μCi/ml) for measurement of fluid absorption. A 228-nl aliquot was removed from the diluted collected fluid or perfusate samples and mixed with Aquasol (New England Nuclear) for measurement of radioactivity by liquid scintillation counting (Searle, model 6872, Searle Analytical Inc., Des Plaines, IL).

The perfusion rate (V_o) was calculated from $V_o = V_L (X_L/X_o)$, where V_L is the collection rate, X_o is the activity (cpm) of ^{14}C in the perfusate, and X_L is the activity of ^{14}C in the collected fluid. The rate of fluid absorption (J_v) was calculated as $J_v = (V_o - V_L)/L$, where L is the tubule length. It was assumed that $V_o = V_L$ when vasopressin was absent from the bath and ^{14}C-inulin was absent from the perfusate. The rate of sodium or potassium transport (J_i) was calculated as $J_i = (C_oV_o - C_LV_L)/L$, where C_o is the ion concentration in the perfusion fluid, and C_L is the ion concentration in the collected fluid. The transepithelial potential difference was measured as previously described (14).

Bradykinin (Peninsula Laboratories, Belmont, CA) or arginine vasopressin (Sigma Chemical Co., St. Louis, MO) were introduced into the bath chamber via the bath exchange system. Bradykinin and the kininase inhibitor captopril (E. R. Squibb Inc., Princeton, NJ) were added to the perfusate in some experiments. To test for possible loss of bradykinin from the perfusate (e.g., by adsorption to the glass pipettes), perfusate containing 10^{-9} M bradykinin was passed through the perfusion system via the exchange pipette, collected from the drain, and bradykinin was determined by radioimmunoassay. The bradykinin was recovered completely (105.2±2.6% [SE], n = 4).

Differences between means were tested for statistical significance using the t test for paired data. A P value < 0.05 was considered statistically significant.

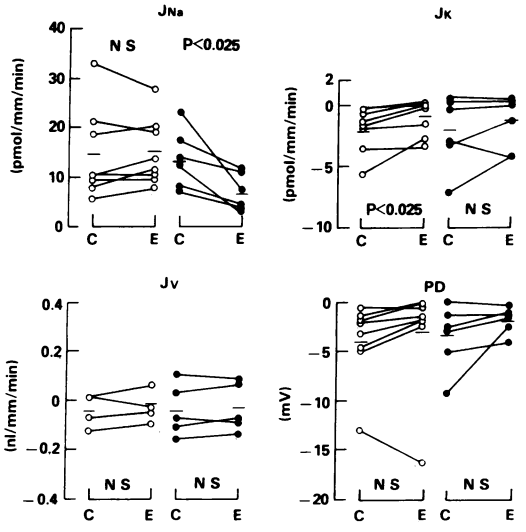

Figure 1. Effect of 10^{-9} M bradykinin in the bath on cortical collecting ducts from deoxycorticosterone-treated rats (closed circles). J_{Na}, net sodium flux; J_K, net potassium flux; J_V, rate of fluid transport; PD, transepithelial potential difference (lumen with respect to bath). Negative flux indicates net secretion; positive flux, net absorption. C, control period; E, experimental period. Open circles indicate time control experiments with no added bradykinin (Table I, group B). Horizontal bars indicate mean values. Statistical comparisons were by paired t test.

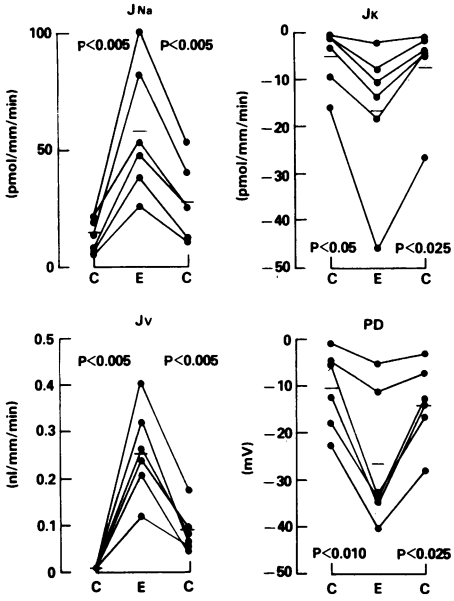

Figure 2. Effect of 10^{-10} M arginine vasopressin in the bath on cortical collecting ducts from deoxycorticosterone-treated rats. Terminology and abbreviations are the same as for Fig. 1.

Results

Basal transport (Table I, group A). In untreated rats, the transepithelial potential difference, the rates of sodium and potassium transport, and rate of fluid absorption were not significantly different from zero.

Effect of deoxycorticosterone (Table I, group B). When deoxycorticosterone was administered to rats, significant rates of net sodium absorption (14.7±3.3 pmol/mm per min) and net potassium secretion (−2.0±0.6) were observed. The transepithelial potential difference was lumen negative (−4.1±1.4 mV). Fluid transport was not significantly different from zero. To serve as time controls for later experiments (see Fig. 1), measurements were extended for ~30 min beyond the initial collections. There was no change in net sodium transport, fluid transport, or potential difference. However, the rate of net potassium secretion decreased significantly with time ($P < 0.025$).

Effect of bath bradykinin on tubules from deoxycorticosterone-treated rats (Table I, group C; Fig. 1). Bradykinin, 10^{-9} M in the bath, significantly decreased net sodium absorption from 13.8±2.4 pmol/mm per min to 7.2±1.6. However, there was no significant change in net potassium secretion or potential difference. There was no demonstrable fluid transport before or after bradykinin addition.

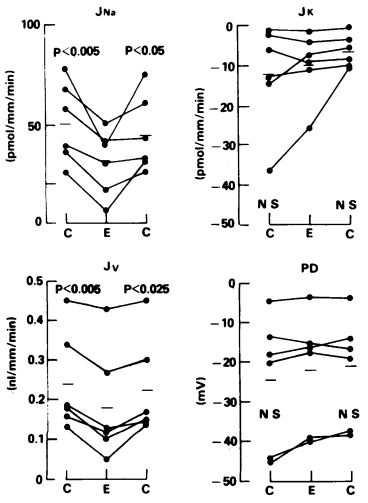

Figure 3. Effect on 10^{-9} M bradykinin in the bath in presence of arginine vasopressin. Vasopressin (10^{-10} M) was present in bath throughout the experiments. Cortical collecting ducts were dissected from deoxycorticosterone-treated rats. Terminology and abbreviations are the same as for Fig. 1.

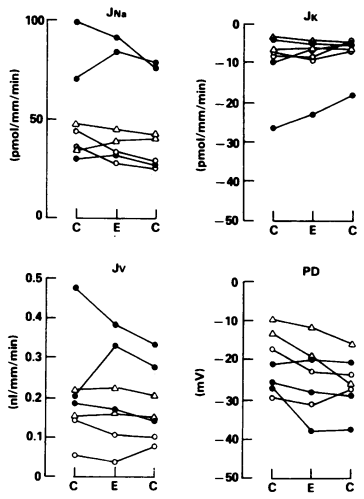

Figure 4. Effect of luminal bradykinin on cortical collecting ducts from deoxycorticosterone-treated rats. Vasopressin (10^{-10} M) was present in the bath throughout the experiments. Open circles, 10^{-9} M bradykinin; closed circles, 10^{-7} M bradykinin; triangles, 10^{-6} M bradykinin plus 10^{-4} M captopril. Abbreviations are the same as for Fig. 1.

Effect of arginine vasopressin on cortical collecting ducts from deoxycorticosterone-treated rats (Table I, group D; Fig. 2). Vasopressin, 10^{-10} M in the bath, caused a striking increase in net sodium absorption from a control level of 12.5±2.7 pmol/mm per min to 58.0±11.3. This increase in sodium absorption was associated with the appearance of a significant rate of spontaneous fluid absorption ($P < 0.005$ vs. control), which was undoubtedly facilitated by the marked increase in osmotic water permeability caused by vasopressin in this segment (15). Vasopressin also caused a marked enhancement of the lumen-negative potential difference, from a control level of −10.7±3.4 mV to −26.6±5.8 mV ($P < 0.01$), and caused a marked increase in net potassium secretion from a control level of −5.1±2.5 pmol/mm per min to −16.6±6.2 ($P < 0.05$). All effects of vasopressin were reversible (Fig. 2).

Effect of bradykinin in the presence of vasopressin (Table I, group E; Fig. 3). With vasopressin (10^{-10} M) in the bath, bradykinin, 10^{-9} M in the bath, caused a substantial decrease in net sodium absorption from 51.0±8.3 pmol/mm per min with vasopressin alone to 31.2±6.7 with vasopressin plus bradykinin in the bath. Concomitantly, a significant decrease in the rate of fluid absorption was observed. The inhibition of net sodium and fluid absorption were reversed when bradykinin was removed from the bath. Despite causing a large inhibition of net sodium transport, bradykinin had no significant effect on either transepithelial potential difference or potassium transport.

Effect of luminal bradykinin (Fig. 4). Bradykinin in the luminal perfusate at 10^{-9} or 10^{-7} M, as well as 10^{-6} M bradykinin together with 10^{-4} M captopril (added to inhibit kininase activity if present in the lumen), had no effect on sodium or potassium transport.

Discussion

The objective of this study was to determine the effects of deoxycorticosterone, arginine vasopressin, and bradykinin on sodium and potassium transport in rat cortical collecting ducts. Use of isolated, perfused tubules permits evaluation of the direct effects of these agents. Tubules from rats (12) rather

than rabbits were used to facilitate comparison with in vivo data. The choice of bradykinin rather than lysyl-bradykinin was based on the evidence (16) that rat renal kallikrein forms bradykinin and not lysyl-bradykinin, which is the predominant kinin formed in man (17).

Basal transport rates and the effect of deoxycorticosterone

In agreement with previous observations (15, 18), we found that isolated, perfused cortical collecting ducts from untreated rats have transepithelial potential differences that are close to zero, and exhibit little if any net sodium transport (Table I, group A). In addition, we found no potassium transport. These results were surprising in view of the substantial rates of active sodium absorption and potassium secretion observed in cortical collecting ducts from untreated rabbits (19–21). This difference could be genetically determined, or simply due to a lower potassium-to-sodium ratio in the rat chow. Consistent with the latter is the fact that rabbits on a low potassium-high sodium diet show a marked reduction in transepithelial potential difference and in sodium and potassium transport in their cortical collecting ducts perfused in vitro (19–21).

We observed that chronic administration of deoxycorticosterone causes an increase in sodium absorption and potassium secretion in rat cortical collecting ducts (Table I, group B). However, the transport rates were considerably lower than in tubules from similarly treated rabbits (20, 21). The response to in vivo deoxycorticosterone is thought to be a direct mineralocorticoid effect (21).

Effect of arginine vasopressin

Arginine vasopressin added to the bath caused a sustained increase in both the transepithelial potential difference and the rate of net sodium absorption, which is consistent with prior observations (15, 18). These results contrast with observations in rabbit cortical collecting ducts in which there is only a transient stimulation of potential difference and sodium transport (19, 22). The transience of the vasopressin effect has been attributed to prostaglandins (22), which are synthesized by the collecting duct cells in response to vasopressin and directly inhibit sodium transport (23, 24). Therefore, the lack of a secondary decrease in sodium absorption after vasopressin in the rat could be due to an inability of the cells of the rat cortical collecting duct to synthesize prostaglandins in response to vasopressin or, alternatively, to an ineffectiveness of prostaglandins in inhibiting transport.

An important new finding in the present studies was that vasopressin directly increases the rate of net potassium secretion in rat cortical collecting ducts. This is in contrast to the rabbit cortical collecting duct, where vasopressin did not affect potassium transport (22). Stimulation of potassium secretion by vasopressin has also been observed in the rat distal tubule (25, 26), the late portion of which is morphologically similar to the cortical collecting duct (27). The physiological significance of the stimulation of potassium secretion by vasopressin in the distal tubule and collecting duct may lie in the need to maintain potassium excretion during antidiuresis when slower volume flow rates would tend to limit the rate of potassium secretion (25).

Effect of bradykinin

Bradykinin added to the bath caused a 40–50% inhibition of net sodium absorption without affecting net potassium transport or the transepithelial potential difference.[1] This response was seen in deoxycorticosterone-treated rats with (Table I, group E) or without (Table I, group C) vasopressin in the bath. Bradykinin had no effect when added to the lumen (Fig. 4).

The present view of sodium transport in the cortical collecting duct is that sodium is absorbed via an electrogenic mechanism (29, 30). Therefore, it was anticipated that a change in sodium transport in response to bradykinin would be associated with a change in the transepithelial potential difference. However, bradykinin inhibited net sodium absorption without affecting the potential difference (Figs. 1 and 3). Furthermore, bradykinin did not significantly change net potassium transport, a finding that is consistent with the unaltered voltage. These results are compatible with the hypothesis that bradykinin affects an electroneutral pathway for sodium transport.

The preponderance of kallikrein in the apical aspect of distal nephron cells (31) and the appearance of kinins in urine has raised the possibility that kinins act on the apical surface of renal tubular cells. However, our results and those of Schuster et al. (11) have demonstrated effects of kinins only when they were in contact with the basolateral membrane. Similar results were obtained in the mammalian colon (32, 33), which has many epithelial characteristics in common with the cortical collecting duct.

The observation that kinins affect sodium transport (present study) and osmotic water permeability (11) at relatively low concentrations is consistent with a receptor-mediated mechanism. In support of this hypothesis, specific, high-affinity kinin binding sites have been detected in isolated rabbit cortical collecting ducts (10).

If the inhibition of net sodium transport by peritubular kinins plays a physiologically significant role in vivo, a source of interstitial kinin must be present. Kallikrein has been identified in the basolateral membrane-rich fraction of kidney homogenates (34), and a recent immuno-electron microscopic study has shown that a small fraction of the cellular kallikrein in connecting tubule cells is associated with the basolateral surface (35). In addition, both immunoreactive kallikrein and kininogen have been measured in rat renal lymph (36). Thus, both kallikrein and kininogen may be available to the interstitium to form kinins.

Based on the observed inhibitory effect of bradykinin on cortical collecting duct sodium absorption, we propose that the renal kallikrein-kinin system may play an important role in the regulation of renal sodium excretion and, consequently, in the control of extracellular fluid volume. To have such a role, bradykinin must not only affect sodium transport, but its interstitial levels must respond in an appropriate manner to changes in extracellular fluid volume. There are presently no direct data on the latter point. Nevertheless, the hypothesis that extracellular fluid volume expansion results in a kinin-mediated inhibition of sodium absorption in the cortical collecting duct has considerable appeal, particularly in view of the absence of a kinin effect on potassium transport. For example, the natriuretic states associated with mineralocorticoid

1. In a recent abstract, it was reported that lysyl-bradykinin does not affect lumen-to-bath ^{22}Na flux in rabbit cortical collecting ducts (28). This finding does not necessarily conflict with ours, since there are many technical differences between the two studies, including the species of animal studied.

escape (37), and chronic vasopressin and water administration (38, 39), both of which occur without major concomitant changes in potassium excretion (37, 39), may be mediated in part by bradykinin.

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