Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 397–401, January 1989
Physiological Sciences

Aldosterone stimulates K secretion across mammalian colon independent of Na absorption

(epithelial transport/K absorption/intestine/guinea pig)

GERHARD RECHKEMMER* AND DAN R. HALM†

Department of Physiology and Biophysics, University of Alabama at Birmingham, University Station, Birmingham, AL 35294

Communicated by Gerhard Giebisch, July 5, 1988 (received for review August 4, 1987)

ABSTRACT **K transport across guinea pig (*Cavia porcellus*) distal colon was measured *in vitro* using isotopically determined unidirectional fluxes. Aldosterone stimulated electrogenic Na absorption, as measured by amiloride-sensitive short-circuit current (I_{sc}), and reduced net K absorption from +2.5 ± 0.2 μEq/cm² per hr to +0.8 ± 0.3 μEq/cm² per hr (mean ± SEM). Amiloride addition to the mucosal solution did not enhance net K absorption, as expected if inhibiting active Na absorption would reduce active K secretion as in the distal nephron. The amiloride-insensitive I_{sc} was −1.0 ± 0.2 μEq/cm² per hr (mean ± SEM) and was inhibited by mucosal addition of Ba, a K channel blocker. Addition of bumetanide to the serosal solution also inhibited this negative I_{sc}, and K transport returned to the control level of net absorption. Thus, the amiloride-insensitive, negative I_{sc} is consistent with active K secretion stimulated by aldosterone. This stimulation of an active K secretory pathway by aldosterone occurred without altering the active K absorption pathway that also is present. These results indicate that the aldosterone-stimulated K secretory pathway operates independently of the amiloride-sensitive Na absorption pathway, which also is stimulated by aldosterone.**

Mammalian colon functions primarily to absorb Na and Cl, which drives reabsorption of fluid, conserving salt and water. K secretion also occurs so that as luminal Na concentration falls, the K concentration increases (1, 2). In the distal colon of many mammals, the mechanism of active Na absorption is electrogenic, producing a lumen-negative, transepithelial electrical potential difference (3–5). Absorption of Na from the lumen occurs by entry into the epithelial cells via apical membrane Na channels and subsequent extrusion by the Na/K pump across the basolateral membrane into the interstitium. Addition of the diuretic amiloride to the lumen blocks Na entry through the apical membrane channels, thereby inhibiting absorption and reducing the transepithelial electrical potential toward zero.

K transport across the colonic epithelium includes active absorptive and active secretory pathways such that either net K absorption or net K secretion is possible, depending on the balance between the two active transport processes (6–8). Active, electrogenic K secretion is stimulated in rabbit and guinea pig distal colons by epinephrine (8, 9). The mechanism of this secretion involves active uptake across the basolateral membrane via the Na/K pump and subsequent exit into the lumen via an apical membrane K conductance. Na entry across the basolateral membrane via a loop-diuretic-sensitive cotransport allows the Na/K pump to continue extrusion of Na and uptake of K. Addition of loop-diuretics inhibits K secretion and results in a large net K absorption because active K absorption continues. A common feature of Na absorption and K secretion is the dependence on the basolateral membrane Na/K pump. Na absorption, however, occurs through Na influx across the apical membrane, whereas K secretion relies on Na entry across the basolateral membrane.

The mineralocorticoid aldosterone stimulates Na absorption across colonic epithelia (4, 10) as observed in distal renal epithelia (11). Stimulation of K secretion across colon also is observed together with increased Na absorption when plasma aldosterone is elevated (1, 12). High levels of plasma aldosterone were obtained in these studies of colonic transport by chronic changes in salt intake or by *in vivo* infusion of aldosterone. The stimulation of K secretion, therefore, may have resulted from the *in vivo* actions of other hormones affected by chronic changes in salt and water balance (1). To minimize the influence of secondary factors, the studies reported here were conducted with *in vitro* addition of aldosterone. The results demonstrate that aldosterone directly stimulates K secretion across a mammalian colon and that the secretion continues after inhibition of Na absorption.

METHODS

Distal colon was obtained from male guinea pigs (*Cavia porcellus*) (300–600 g) after decapitation. All studies were performed by using standard Ussing-type chambers in which mucosal sheets of tissue were mounted after the muscularis externa had been removed by blunt dissection. The chamber aperture gave an exposed surface area of 0.64 cm². Bathing solutions were circulated by gas lift through water-jacketed reservoirs that were maintained at 37°C. The standard Ringer solution contained (in mM) 145 Na, 125 Cl, 5 K, 1.2 Ca, 1.2 Mg, 25 HCO_3, 4.2 PO_4, and 10 glucose. The solution pH was maintained at 7.4 by continuous bubbling with a gas mixture of 95% O_2/5% CO_2. Penicillin (4 units/ml) and streptomycin (6 μg/ml) were added to the bathing solution in some experiments to extend viability during the incubation with aldosterone. These antibiotics did not appear to alter the results obtained.

Each tissue chamber was connected to an automatic voltage clamp that allowed continuous measurement of short-circuit (I_{sc}) and compensation for solution resistance. The transepithelial electrical potential difference was measured by two calomel cells connected to the chambers by Ringer/agar bridges. The I_{sc} is referred to as positive when current flows across the tissue from mucosal side to serosal side. Tissue conductance (G_t) was measured by recording the current resulting from short-duration, square bipolar voltage pulses (5–10 mV) imposed across the tissue.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: I_{sc}, short-circuit current; G_t, tissue conductance; J_{ms}, mucosa-to-serosa flux; J_{sm}, serosa-to-mucosa flux; J_{net}, net flux.

*Present address: Department of Physiology, School of Veterinary Medicine, Bischofsholer Damm 15, D-300 Hannover 1, F.R.G.
†To whom reprint requests should be addressed.

Unidirectional tracer fluxes were measured by a sample-and-replace procedure as described (8). The length of time between successive samples was 10 min. The isotopes ^{42}K and ^{36}Cl were obtained from New England Nuclear and ICN, respectively. A correction for the decay of ^{42}K during the time of counting was performed before calculation of unidirectional fluxes.

Drugs were added in small volumes from concentrated stock solutions. Amiloride was provided by Merck Sharp & Dohme, and bumetanide was provided by Hoffmann–La Roche. All other chemicals were obtained from Sigma or Aldrich.

RESULTS

The distal colon of the guinea pig absorbs Na via an electrogenic, amiloride-sensitive mechanism (5). The size of the amiloride-sensitive I_{sc}, therefore, can be used as a measure of Na absorption rate. Indomethacin (1 μM) was added to both bathing solutions to suppress the variable rate of spontaneous Cl secretion that also can contribute to the size of the I_{sc} (8, 9). Fig. 1 shows the time course of the increase in I_{sc} after addition of aldosterone (1 μM) to the bath.‡ This increase in I_{sc} was paralleled by an increase in net Na absorption measured isotopically (data not shown) similar to that observed when guinea pigs were fed a low Na diet (5). By 4 hr after aldosterone addition, the I_{sc} was near maximal, although a slow increase continued for the next 2–3 hr. Inhibition of Na absorption with amiloride addition to the mucosal solution (0.1 mM) reversed the orientation of I_{sc} from $+4.98 \pm 0.20$ μEq/cm^2 per hr to -1.02 ± 0.23 μEq/cm^2 per hr (mean ± SEM, $n = 5$). The negative I_{sc} is consistent with either electrogenic cation secretion or anion absorption. Mucosal addition of Ba^{2+} (5 mM), a blocker of K conductance (8, 13), reduced this negative I_{sc} toward zero. Control tissues had a stable I_{sc}, over a 5- to 6-hr period, which decreased to near zero with mucosal amiloride and increased slightly with Ba. The large amiloride-sensitive I_{sc} indicates that aldosterone stimulated electrogenic Na absorption, whereas the large Ba^{2+}-sensitive negative I_{sc} present in treated tissues suggests that aldosterone also stimulated electrogenic K secretion.

Measurement of unidirectional K fluxes (Table 1) indicated that net K absorption occurred across the distal colon in the control condition, as reported previously (9). After 6 hr of aldosterone treatment, net K absorption decreased by a factor of 3, whereas I_{sc} increased. The decrease in net absorption was composed of a proportionally equal decrease in the J^K_{ms} and increase in the J^K_{sm}. A decrease in active absorption or an increase in active secretion could account for this change in net K flux. In paired tissues serving as time controls, the K fluxes were unchanged after 6 hr, whereas the increase in I_{sc} was only 15% of that observed in the tissues receiving aldosterone. Addition of amiloride (0.1 mM) to the mucosal solution rapidly inhibited Na absorption, as indicated by the decrease in I_{sc} (see Fig. 1), without a large change in K transport (Fig. 2). The small increase in J^K_{sm} and decrease in J^K_{ms} that occurred after amiloride addition may have resulted from continued action of aldosterone on K transport. In the presence of amiloride, 6.5 hr after aldosterone addition, net K transport was not significantly different from zero, with J^K_{sm} 3-fold higher than initial values, and I_{sc} was negative (Table 1). In control tissues, amiloride-insensitive I_{sc} was not significantly different from zero and

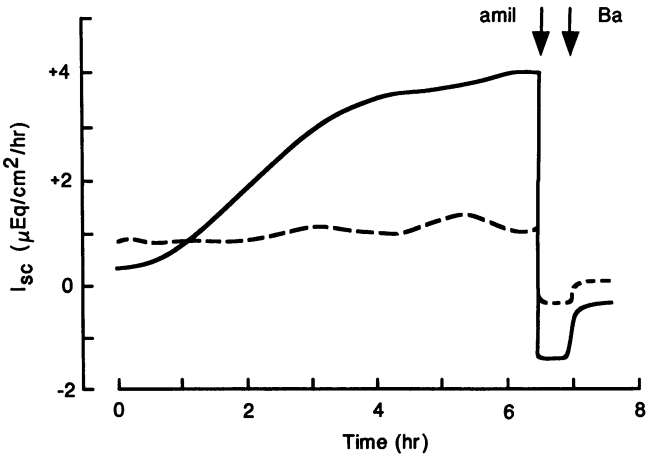

FIG. 1. Aldosterone stimulates I_{sc}. I_{sc} values from a representative pair of tissues are shown. Solid line, aldosterone (1 μM) at time zero; dashed line, untreated. Amiloride (amil; 0.1 mM) and Ba^{2+} (5 mM) were added to the mucosal solution.

J^K_{sm} was small. The Ba^{2+} sensitivity of the aldosterone-stimulated negative I_{sc} together with the high J^K_{sm} are consistent with electrogenic K secretion that persists after inhibition of electrogenic Na absorption.

The loop-diuretic bumetanide, which inhibits K secretion in distal colon from guinea pig (9) and rabbit (8), inhibited the amiloride-insensitive negative I_{sc} and restored net K absorption to control levels (Table 1). The increase in J^K_{net} was identical to the increase in I_{sc}, further supporting the notion that K secretion was responsible for producing the negative I_{sc}. Net K absorption after bumetanide addition is similar in control and treated tissues, suggesting that aldosterone did not alter net K transport by inhibiting active K absorption but rather acted by stimulating active secretion.§ Bumetanide (0.1 mM) added to the serosal solution during ongoing electrogenic Na absorption (in the absence of amiloride) decreased J^K_{sm} and increased J^K_{ms}, producing a large net K absorption (Table 2). An increase in I_{sc} also occurred, consistent with inhibition of electrogenic K secretion. This action of bumetanide on K fluxes and I_{sc} (Table 2) is identical to that observed when Na absorption was inhibited by amiloride (Table 1), suggesting that inhibiting Na entry across the basolateral membrane via a bumetanide-sensitive cotransporter is sufficient to inhibit active K secretion. In addition, the amiloride-sensitive I_{sc} was identical in the presence and absence of bumetanide, supporting the notion that Na absorption is unaltered by inhibition of electrogenic K secretion.

Sensitivity to loop-diuretics is a characteristic of the epinephrine-stimulated K secretory process observed in guinea pig (9) and rabbit distal colons (8). Stimulation of K secretion by epinephrine is similar to that induced by aldosterone (Table 1), with a decrease in net K absorption due to an increase in J^K_{sm} and a decrease in J^K_{ms}. As in rabbit distal colon (8), this stimulation by epinephrine can be inhibited with β-adrenergic antagonists; however, neither propranolol (β-adrenergic antagonist) nor phentolamine (α-adrenergic antagonist) altered the size of the amiloride-insensitive negative I_{sc} observed in aldosterone-treated tissues (data not shown). This suggests that aldosterone did not act on K transport by stimulating the release of epinephrine from enteric nerve cells, enteroendocrine cells, or other cells in the

‡A complete dose–response for aldosterone was not performed, but the results illustrated in Figs. 1 and 2 and Table 1 were equivalent when either 0.01 μM or 1 μM aldosterone was used. The higher concentration was used routinely to avoid possible degradation of the steroid.

§An increase or decrease in active K absorption, as measured by J^K_{net} after bumetanide, of <20% would not have been detected with these experiments. Thus, any change in active K absorption produced by aldosterone must be small.

Table 1. Response to aldosterone

	J^K_{ms}	J^K_{sm}	J^K_{net}	I_{sc}	G_t
Time control					
Initial	2.62 ± 0.11	0.25 ± 0.04	+2.37 ± 0.15*	+0.62 ± 0.37	5.59 ± 0.62
6 hr	2.45 ± 0.24	0.32 ± 0.07	+2.14 ± 0.30*	+1.32 ± 0.51	4.59 ± 0.53
Amiloride	2.33 ± 0.25	0.39 ± 0.09	+1.95 ± 0.33*	+0.14 ± 0.25	4.58 ± 0.52
Bumetanide	2.32 ± 0.22	0.27 ± 0.04	+2.05 ± 0.25*	+0.50 ± 0.21	4.81 ± 0.48
Treated					
Initial	2.82 ± 0.09	0.31 ± 0.07	+2.51 ± 0.16*	+0.58 ± 0.24	6.69 ± 1.19
Aldosterone	1.48 ± 0.16†	0.67 ± 0.14†	+0.80 ± 0.28*†	+4.98 ± 0.20*†	7.27 ± 0.67†
Amiloride	1.32 ± 0.16†	0.91 ± 0.16†	+0.41 ± 0.31†	−1.02 ± 0.23*†	6.59 ± 0.75†
Bumetanide	2.09 ± 0.23	0.31 ± 0.06	+1.78 ± 0.29*	+0.45 ± 0.11*	5.30 ± 0.71
Δ aldosterone	−1.34 ± 0.14*†	+0.37 ± 0.09*†	−1.71 ± 0.19*†	+4.40 ± 0.23*†	+0.58 ± 0.65
Δ amiloride	−0.16 ± 0.02*	+0.24 ± 0.06*†	−0.39 ± 0.04*†	−6.00 ± 0.14*†	−0.68 ± 0.25*
Δ bumetanide	+0.77 ± 0.17*†	−0.60 ± 0.11*†	+1.37 ± 0.17*†	+1.47 ± 0.25*†	−1.29 ± 0.26*†

Values are means ± SEM of paired experiments from five colons; two tissues were used to determine the unidirectional flux for each colon and three consecutive 10-min flux periods were obtained for each condition. Indomethacin (1.0 μM) was present during all measurements. The time course of amiloride (0.1 mM, mucosal) and bumetanide (0.1 mM, serosal) addition can be seen in Fig. 2. Flux (J) and I_{sc} were measured as μEq/cm² per hr. G_t was measured as mS/cm². J^K_{ms} is mucosa-to-serosa K flux; J^K_{sm} is serosa-to-mucosa K flux; J^K_{net} is net K flux calculated from the paired unidirectional fluxes.
*Values of J_{net}, I_{sc}, and Δ that are significantly different from zero ($P \leq 0.05$), as determined by a two-tailed Student's t test.
†Values of J, I_{sc}, G_t, and Δ from aldosterone-treated tissues that are significantly different from the untreated tissues ($P \leq 0.05$).

lamina propria and submucosa. Addition of epinephrine (1 μM), in the presence of amiloride, produced identical values of J^K_{net} in control and aldosterone-treated tissues and I_{sc} was −2.26 ± 0.08 μEq/cm² per hr and −2.52 ± 0.22 μEq/cm² per hr, respectively (mean ± SEM, n = 6). This nonadditive effect suggests that aldosterone and epinephrine act on the same transport pathway for K, with epinephrine stimulation producing the maximal transport rate through this pathway.

Responsiveness to Cl secretagogues was examined to determine if aldosterone also had potentiated Cl secretion. J^{Cl}_{net} was not significantly different from zero in either control or aldosterone-treated tissues (incubation with aldosterone was similar to Fig. 1). Epinephrine (1 μM) did not change J^{Cl}_{net} in either group (amiloride present, 0.1 mM), but subsequent addition of prostaglandin E_2 (1 μM) stimulated Cl secretion equally in control and aldosterone-treated groups. Concurrently, prostaglandin E_2 stimulated equivalent rates of net K secretion in the two groups, such that the I_{sc} was the sum of Cl secretion and K secretion (J^{Cl}_{net} = −4.18 ± 0.62 μEq/cm² per hr, J^K_{net} = −1.35 ± 0.11 μEq/cm² per hr, and I_{sc} = +2.48 ± 0.26; mean ± SEM, n = 6). These findings indicate that aldosterone did not augment secretagogue-dependent Cl and K transport.

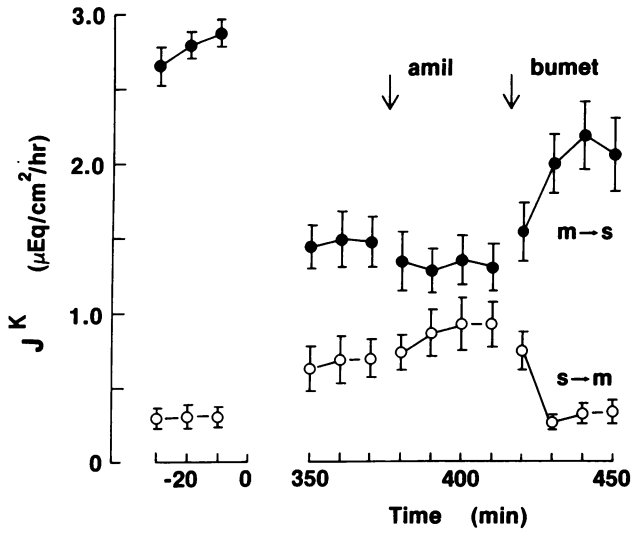

FIG. 2. Response of K transport to aldosterone. Unidirectional K fluxes (J^K_{ms}, J^K_{sm}) are the average values from five colons (Table 1). Aldosterone (1 μM) was added to the serosal solution at zero time after the initial flux measurements. Amiloride (amil; 0.1 mM) was added to the mucosal solution and bumetanide (bumet; 0.1 mM) was added to the serosal solution.

DISCUSSION

Aldosterone stimulation of K secretion has been inferred from studies of animals with elevated plasma aldosterone due to low Na diets, high K diets, or infusion of aldosterone (1, 7, 12, 14–16). The observed changes in K transport due to these chronic procedures may have resulted from activation of secondary regulatory pathways operating *in vivo* rather than as a result of aldosterone. The stimulation presented here was conducted *in vitro* so that secondary actions of aldosterone, such as those affecting whole body fluid balance, would not be encountered.¶ A potential source of secondary effects remaining with the *in vitro* approach is the enteroendocrine cells (17) and cells in the lamina propria, such as neurons and lymphocytes (18–20). The inability of adrenergic blockers to inhibit the aldosterone response strongly suggests that aldosterone did not act on a second cell type to release epinephrine and thereby indirectly stimulate K secretion via an adrenergic pathway (8, 9). The results in Table 1, therefore, demonstrate that the changes in K transport, apparent within 6 hr of aldosterone addition, are consistent with a direct action of the mineralocorticoid on the colonic epithelium.

The model for electrogenic Na absorption is shown in the upper portion of Fig. 3. K secretion stimulated by aldosterone and epinephrine involves the transport processes shown in the lower portion of Fig. 3 (8, 21). In this pathway, K is actively taken into the cells by the basolateral Na/K pump and exits through an apical membrane K conductance. Na entry via the basolateral cotransporter allows for continued turnover of the Na/K pump and results in cycling of Na

¶The *in vitro* stimulation by aldosterone of rabbit distal colon (10) did not produce net K secretion, but a change may have been obscured by the smaller K fluxes in rabbit distal colon.

Table 2. Inhibition of K secretion

	J^K_{ms}	J^K_{sm}	J^K_{net}	I_{sc}	G_t
Aldosterone	1.12 ± 0.24	0.79 ± 0.11	+0.33 ± 0.13	+6.18 ± 0.77*	6.93 ± 0.87
Bumetanide	1.44 ± 0.33	0.29 ± 0.04	+1.15 ± 0.30*	+7.31 ± 0.76*	6.16 ± 0.84
Amiloride	1.35 ± 0.34	0.33 ± 0.06	+1.03 ± 0.29*	+0.25 ± 0.05*	3.98 ± 0.67
Δ bumetanide	+0.32 ± 0.11*	−0.49 ± 0.08*	+0.82 ± 0.18*	+1.14 ± 0.19*	−0.77 ± 0.13*†
Δ amiloride	−0.09 ± 0.02*	+0.03 ± 0.03‡	−0.12 ± 0.02*‡	−7.07 ± 0.72*	−2.18 ± 0.28*‡

Experiments (n = 5) were conducted as described in the legend to Table 1. Paired results were obtained from tissues with amiloride addition preceding bumetanide addition; the values after aldosterone from these two groups were not significantly different ($P \leq 0.05$).

*Values of J_{net}, I_{sc}, and Δ significantly different from zero ($P \leq 0.05$).

†Changes induced by bumetanide were compared to the paired tissues with amiloride present; significant differences ($P \leq 0.05$) are indicated.

‡Changes induced by amiloride were compared to the paired tissues with bumetanide absent; significant differences ($P \leq 0.05$) are indicated.

across the basolateral membrane. The amiloride-insensitive negative I_{sc} results from conductive K exit across the apical membrane and possibly conductive Cl exit across the basolateral membrane (8). The illustration of Na absorption and K secretion in separate cell types is made only to stress the functional independence of these two transport pathways—that is, inhibition of Na absorption with amiloride did not reduce K secretion (Table 1), and inhibition of K secretion with bumetanide did not alter Na absorption (Table 2). Insensitivity of K secretion to inhibition by amiloride also has been reported in studies with chronic changes in aldosterone (1, 7). The presence of all of the illustrated transport processes in a single cell type is possible but would require a regulatory mechanism to produce the observed functional separation.

The presence of two active transport pathways for K complicates the study of regulation, because both are possible targets of hormones such as aldosterone. In the guinea pig distal colon, the active absorptive process dominates under basal *in vitro* conditions producing net absorption. The reduction of net K absorption induced by aldosterone could have resulted from stimulating the active K secretory pathway or inhibiting the active K absorptive pathway. Three findings support the notion that only active K secretion was stimulated. (*i*) The large negative I_{sc}, uncovered after amiloride addition, was observed only in aldosterone-treated tissues. This Ba^{2+}-sensitive negative current is consistent with electrogenic K secretion. (*ii*) I_{sc} and J^K_{net} were altered equally by bumetanide (Table 1), suggesting that the negative I_{sc} was a result of electrogenic K secretion. (*iii*) J^K_{net} after inhibition of the negative I_{sc} was not significantly different in control and aldosterone-treated tissues, suggesting that the active absorptive capacity for K was unchanged by aldosterone addition. Previous studies of K transport from chronically treated animals also indicated that active K absorption was not altered by elevated plasma aldosterone (15, 16). These three results support the model for K transport shown in Fig. 3 and indicate that at least one transport element involved in secretion was activated by aldosterone—in the apical membrane possibly the K conductance or in the basolateral membrane either the Na/K/2Cl cotransport or the Na/K pump.

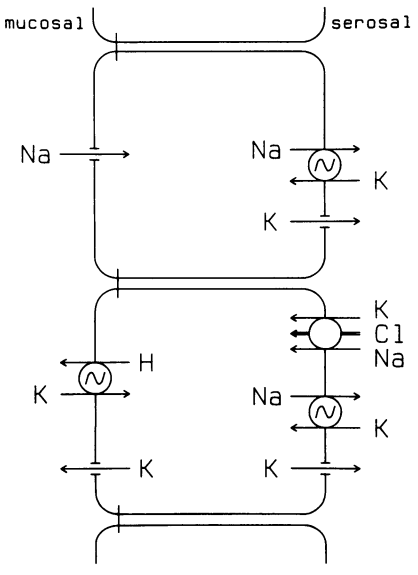

FIG. 3. Cellular model for Na and K transport.

Aldosterone stimulation of the guinea pig colon involves increased Na absorption and K secretion, and a single site of action possibly could account for both of these changes. The mode of action for aldosterone has been studied extensively in renal epithelia (11). Initially, aldosterone stimulates Na absorption by opening Na channels in the apical membrane (see Fig. 3) so that Na entry into epithelial cells increases. Later in the response, the number of basolateral membrane Na/K pumps increases (22). In the distal nephron, stimulation of Na absorption is accompanied by K secretion (23). Coupling between K secretion and Na absorption is indicated by the dependence of K secretion on the rate of Na absorption (24, 25); amiloride inhibits Na absorption and K secretion solely by blocking apical membrane Na conductance (26). Amiloride-sensitive K secretion also was observed in turtle colon (27). Coupling between Na absorption and K secretion presumably occurs via the basolateral membrane Na/K exchange pump in these epithelial cells. Reduction of apical membrane Na entry with amiloride blockade would restrict turnover of the pump and limit uptake of K into the cell. K secretion in guinea pig distal colon, however, is strictly dependent on the activity of a loop-diuretic-sensitive uptake process in the basolateral membrane. Inhibition of this cotransport with bumetanide eliminates active K secretion during ongoing Na absorption or after inhibition of this absorption with amiloride. Sensitivity to bumetanide presumably results from restricting the supply of cellular Na available for turnover of the basolateral Na/K pump, the driving force for K secretion. The rate of K secretion appears to be sensitive only to decreases in cell Na resulting from reduced Na entry across the basolateral membrane. In addition, bumetanide did not alter the rate of amiloride-sensitive Na absorption, suggesting further that the K secretory process and the Na absorptive pathway are functionally independent. This independence could be accounted for by a segregation of the Na absorptive pathway and the K secretory pathway to separate cell types or by a single cell type with a set of regulatory constraints that define K secretion solely by the

rate of Na entry via the basolateral cotransporter. Thus, the activation of apical membrane Na channels by aldosterone would not account for the increase in K secretion, but an increased number of basolateral membrane Na/K pumps as in toad bladder (22) could increase K secretion if basolateral Na entry also increased. An additional site of action for aldosterone remains a possibility for the stimulation of K secretion.

The apparent transport mechanism for aldosterone-stimulated and epinephrine-stimulated K secretion is identical, as noted above (see Fig. 3). This similarity suggests that aldosterone and epinephrine act on the same transport pathway in the colonic epithelium. Further support for this notion is obtained from the similar rate of K secretion after epinephrine stimulation in control and aldosterone-treated tissues. This identical limiting value is consistent with an intrinsic maximal rate for the transport pathway producing K secretion. The site of activation may be similar for the two agonists because aldosterone did not augment the epinephrine-stimulated K secretion; however, the site of action for aldosterone and epinephrine stimulation cannot be determined from the present experiments. The implications for salt balance of aldosterone acting on a K transport pathway functionally separate from the Na absorption pathway are not immediately apparent, but the potential for independent modulation of Na absorption and K secretion is clear.

We thank Ellis Bynum for technical assistance in performing the long experiments necessary to observe the response to aldosterone and Ray Frizzell for valuable discussions and for reading the manuscript. This work was supported by National Institutes of Arthritis, Diabetes, Digestive and Kidney Diseases (Grants DK31091 and DK39007). G.R. was supported by Deutsche Forschungsgemeinschaft (Grant Re592-2).

1. Turnheim, K., Plass, H., Grasl, M., Krivanek, P. & Wiener, H. (1986) *Am. J. Physiol.* **250,** F235–F245.
2. Rechkemmer, G., Krause, M., Becker, G. & von Engelhardt, W. (1987) *Dtsch. Tieraerztl. Wochenschr.* **94,** 12–15.
3. Frizzell, R. A., Koch, M. J. & Schultz, S. G. (1976) *J. Membr. Biol.* **27,** 297–316.
4. Will, P. C., Cortright, R. N., DeLisle, R. C., Douglas, J. G. & Hopfer, U. (1985) *Am. J. Physiol.* **248,** G124–G132.
5. Clauss, W., Durr, J. & Rechkemmer, G. (1985) *Am. J. Physiol.* **248,** G176–G183.
6. McCabe, R., Cooke, H. J. & Sullivan, L. P. (1982) *Am. J. Physiol.* **242,** C81–C86.
7. Foster, E. S., Hayslett, J. P. & Binder, H. J. (1984) *Am. J. Physiol.* **246,**G611–G617.
8. Halm, D. R. & Frizzell, R. A. (1986) *Am. J. Physiol.* **251,** C252–C267.
9. Rechkemmer, G., Halm, D. R. & Frizzell, R. A. (1986) *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **45,** 748 (abstr.).
10. Frizzell, R. A. & Schultz, S. G. (1978) *J. Membr. Biol.* **39,** 1–26.
11. Garty, H. (1986) *J. Membr. Biol.* **90,** 193–205.
12. Foster, E. S., Jones, W. J., Hayslett, J. P. & Binder, H. J. (1985) *Gastroenterology* **88,** 41–46.
13. Latorre, R. & Miller, C. (1983) *J. Membr. Biol.* **71,** 11–30.
14. Halevy, J., Budinger, M. E., Hayslett, J. P. & Binder, H. J. (1986) *Gastroenterology* **91,** 1227–1233.
15. Tannen, R. L., Marino, R. & Dawson, D. C. (1986) *Am. J. Physiol.* **250,** F483–F487.
16. Foster, E. S., Sandle, G. I., Hayslett, J. P. & Binder, H. J. (1986) *Am. J. Physiol.* **251,** G619–G626.
17. Chang, W. W. L. & Leblond, C. P. (1971) *Am. J. Anat.* **131,** 73–100.
18. Tapper, E. J. (1983) *Am. J. Physiol.* **244,** G457–G468.
19. Bridges, R. J., Rack, M., Rummel, W. & Schreiner, J. (1986) *J. Physiol.* **376,** 531–542.
20. Kagnoff, M. F. (1987) in *Physiology of the Gastrointestinal Tract,* ed. Johnson, L. R. (Raven, New York), 2nd Ed., pp. 1699–1728.
21. McCabe, R. D., Smith, P. L. & Sullivan, L. P. (1984) *Am. J. Physiol.* **246,** G594–G602.
22. Geering, K., Girardet, M., Bron, C., Kraehenbuhl, J.-P. & Rossier, B. C. (1982) *J. Biol. Chem.* **257,** 10338–10343.
23. Giebisch, G. & Stanton, B. (1979) *Annu. Rev. Physiol.* **41,** 241–256.
24. O'Neil, R. G. & Helman, S. I. (1977) *Am. J. Physiol.* **233,** F544–F558.
25. Stokes, J. B., Lee, I. & Williams, A. (1981) *Am. J. Physiol.* **241,** F395–F402.
26. Koeppen, B. M., Biagi, B. A. & Giebisch, G. H. (1983) *Am. J. Physiol.* **244,** F35–F47.
27. Halm, D. R. & Dawson, D. C. (1984) *Am. J. Physiol.* **246,** C315–C322.