Regulation of Active Sodium and Potassium Transport in the Distal Colon of the Rat

Role of the Aldosterone and Glucocorticoid Receptors

Steven G. Turnamian and Henry J. Binder
Department of Internal Medicine, Yale University, New Haven, Connecticut 06510

Abstract

To determine whether mineralocorticosteroids and glucocorticosteroids have specific effects on colonic electrolyte transport, we compared the effect of aldosterone and RU 28362, a glucocorticoid receptor-specific agonist that does not bind to the aldosterone receptor, on unidirectional Na, Cl, and K fluxes across isolated mucosa of the rat distal colon. Continuous infusion of aldosterone for 7 d produced changes in four specific transport processes: induction of both active electrogenic, amiloride-sensitive sodium absorption and active electrogenic potassium secretion, enhancement of active electroneutral potassium absorption, and inhibition of electroneutral Na-Cl absorption, the predominant transport process in this epithelium. In contrast, continuous infusion of RU 28362 for 1–11 d produced a sustained increase in electroneutral Na-Cl absorption. This glucocorticoid receptor-specific agonist did not induce electrogenic sodium absorption nor affect either potassium absorption or secretion. These studies demonstrate that aldosterone (i.e., mineralocorticoid) and glucocorticoid receptors modulate separate and specific changes in active sodium and potassium transport. These results suggest that other glucocorticoids (e.g., dexamethasone, methylprednisolone) are not glucocorticoid receptor-specific and that their effects on electrogenic sodium absorption and potassium transport most likely represent the binding of these agonists to the aldosterone receptor.

Introduction

Dietary sodium depletion results in significant changes in electrolyte transport in the distal colon of the rat (1–4). The primary effect seen in this model of secondary hyperaldosteronism is an induction of active amiloride-sensitive sodium transport and active electrogenic potassium secretion which are the changes usually observed in other aldosterone-responsive epithelia (1, 3). However, dietary sodium depletion also affects electroneutral sodium and potassium absorption in the rat distal colon: electroneutral Na-Cl absorption is inhibited and electroneutral potassium absorption is stimulated (3, 5). Recent studies with continuous infusion of aldosterone have confirmed that the changes in sodium and chloride transport

observed in dietary sodium depletion are due to aldosterone (6); similar studies have not yet been performed for potassium transport.

Synthetic glucocorticoids (e.g., dexamethasone, methylprednisolone) also produce substantial changes in both sodium and potassium movement in the mammalian distal colon (1, 3, 4, 7–12). Although both glucocorticoid and aldosterone (i.e., mineralocorticoid) receptors have been identified in the cytosol of colonic epithelial cells (13–17), there has been considerable controversy whether separate and specific changes in ion transport are mediated by the activation of these glucocorticoid and mineralocorticoid receptors. Experiments with dexamethasone and methylprednisolone reveal that many (but not all) of the changes in electrolyte transport produced by these glucocorticoids are similar to those observed in dietary sodium depletion and after aldosterone infusion (1, 3, 7, 18). However, in the absence of crossover binding of one corticosteroid to the opposite cystolic receptor, it is not known whether glucocorticoids and aldosterone produce distinct and unique changes in sodium and potassium transport.

Resolution of this question has been long hampered by the failure to appreciate, until recently, that most "pure" synthetic glucocorticoids (i.e., dexamethasone, methylprednisolone) also bind to the aldosterone receptor at doses that have been frequently employed in these experiments. The recent synthesis by Roussel UCLAF, a French pharmaceutical company, of a family of "ultrapure" glucocorticoids has provided an opportunity to delineate this problem in better detail (19). 11β, 17β-Dihydroxy-6-methyl-17α-(1-propynyl) androsta-1,4,6-triene-3-one (RU 28362)[1] is such an ultrapure synthetic glucocorticoid, and has high affinity only for the glucocorticoid (not the aldosterone) receptor. In recent studies with this and related synthetic ultrapure glucocorticoids in adrenalectomized rats, Bastl (20) has concluded that these glucocorticoid receptor-specific agonists regulate basal sodium transport which in the rat distal colon is predominantly electroneutral sodium absorption. Since higher doses of dexamethasone, but not of the glucocorticoid receptor-specific agonist, induced amiloride-sensitive, electrogenic sodium absorption, Bastl (20) speculated that, whenever glucocorticoids appear to stimulate electrogenic sodium absorption, it may be due to crossover binding of the glucocorticoid (i.e., dexamethasone, but not RU 28362) to the aldosterone receptor. Bastl based these conclusions on in vivo luminal perfusion studies that were performed

soon after adrenalectomy. Thus, these experiments were limited by an inability to assess directly the effect of ultrapure glucocorticoids on active sodium and potassium transport processes, and by the possible confounding issue of endogenous steroid release after anesthesia and surgery (21). This previous study did not address the question of the mechanism by which glucocorticoids affect electrolyte transport in the colon of animals with intact adrenal glands. As a result, these present studies were designed to evaluate and compare the effect of continuous infusion of aldosterone and RU 28362 for 1–11 d on unidirectional and net sodium, chloride, and potassium fluxes that were performed across isolated distal colonic mucosa of nonadrenalectomized rats under voltage-clamp conditions. These results establish that aldosterone and glucocorticoid receptors mediate specific and distinct effects on active electrogenic and electroneutral sodium absorption as well as on active potassium absorptive and secretory processes.

Methods

Nonfasting Sprague-Dawley rats weighing between 250 and 300 g were used in all experiments. All animals received a standard diet (Prolab 3000 Formula, Agway, Syracuse, NY). The aldosterone and RU 28362 animals received aldosterone or RU 28362, respectively, via subcutaneously implanted minipumps (Alza Corp., Palo Alto, CA) that were filled with a concentration calculated to deliver the specific steroid at the rate of 70 μg per 100 g body wt per day. This dose of aldosterone was selected because in other studies it produced plasma aldosterone levels similar to those observed in dietary sodium depletion (22).

The colon was removed during anesthesia, placed on a glass pipette, and stripped of its serosa and part of the muscularis. Two pieces, each measuring 2.3 cm in length, were obtained from each colon beginning immediately cephalad to the lymph node located at the pelvic brim. The mucosa was mounted in Lucite chambers with internal surface area of 1.13 cm^2 and bathed in Ringer's solution that contained (in millimolar): Na 140, K 5.2, Ca 1.2, Mg 1.2, Cl 119.8, HCO$_3$ 25, HPO$_4$ 5.2, glucose 10 mM (pH 7.4). Short-circuit current

(I_{sc}), potential difference (PD), and conductance (G) were determined as previously described (3). Unidirectional ^{22}Na, ^{36}Cl, and ^{42}K fluxes were performed under voltage-clamp conditions, as described in prior studies (3), and net fluxes were calculated by pairing tissues on the basis of G that were within 10%.

In the ^{22}Na and ^{36}Cl studies there was a 15-min equilibration period, whereas in the ^{42}K experiments this period was 55 min. Positive values represent net absorption, and negative ones, net secretion. The results are presented as the mean of two 15-min periods; 10 μM amiloride or 1.0 mM ouabain was added to the mucosa or serosal bathing solution, respectively. After a 12-min equilibrium period, two additional 15-min flux periods were determined.

Aldosterone, amiloride, and ouabain were purchased from Sigma-Aldrich Co., St. Louis, MO; ^{42}K and ^{36}Cl were purchased from New England Nuclear, Boston, MA; and ^{22}Na was purchased from Amersham Corp., Arlington Heights, IL. RU 28362 was kindly provided by Roussel UCLAF, Romainville, France.

Results

Sodium and chloride transport. Table I presents the results of unidirectional and net sodium and chloride fluxes in both the control group and the 1-d and 7-d steroid-infused groups. In the control group, net sodium absorption was equal to net chloride absorption and was significantly greater than the I_{sc}. Since the diuretic amiloride affects sodium absorption in normal and hyperaldosterone rats differently, the effect of 10 μM amiloride on ion transport was also determined. Fig. 1 presents the results of 10 μM amiloride on $J_{net}{}^{Na}$ and I_{sc} in the several experimental groups. As previously presented, amiloride did not alter net Na absorption (Fig. 1 *A*), net Cl absorption (data not shown), or I_{sc} (Fig. 1 *B*). These results are similar to those previously reported in the distal colon of normal rats (23) and are consistent with electroneutral Na-Cl absorption as the predominant sodium absorptive process in this epithelium.

The 1-d steroid-infused group comprised animals that received infusion of either aldosterone or an equivalent amount

Table I. Unidirectional and Net Sodium and Chloride Fluxes in Control, 1-d Steroid-infused and 7-d Steroid-infused Groups

	n	Sodium fluxes			Chloride fluxes			I_{sc}	G
		J_{ms}	J_{sm}	J_{net}	J_{ms}	J_{sm}	J_{net}		
		$\mu eq/h \cdot cm^2$			$\mu eq/h \cdot cm^2$			$\mu eq/h \cdot cm^2$	mS/cm^2
A. Control	6	9.7±0.7	4.9±0.7	4.9±0.5	12.9±0.4	8.4±0.7	4.5±0.7	0.9±0.2	8.0±0.8
B. *1-d steroid infusion*									
Aldosterone	5	12.9±0.3	3.2±0.7	9.6±0.7	17.5±0.2	8.9±0.8	8.5±0.9	2.8±0.6	7.1±0.6
$P*$		<0.02	NS	<0.001	<0.001	NS	<0.01	<0.02	NS
RU 28362	6	15.2±1.1	3.7±0.3	11.5±1.0	19.9±1.6	8.7±0.7	11.2±1.6	0.6±0.1‡	7.7±0.8
$P*$		<0.005	NS	<0.001	<0.005	NS	<0.005	NS	NS
C. *7-d steroid infusion*									
Aldosterone	5	11.5±0.3	4.8±0.8	6.7±0.7	9.5±0.5	8.3±1.2	1.2±1.2	6.8±1.2	9.3±1.0
$P*$		NS	NS	NS	<0.001	NS	<0.05	<0.001	NS
RU 28362	7	16.8±0.5‡	4.7±0.5‡	12.1±0.8‡	26.7±1.5‡	13.4±1.1§	13.3±1.4§	0.7±0.2§	5.6±0.7
$P*$		<0.001	NS	<0.001	<0.001	<0.005	<0.001	NS	<0.05

Values are mean±SE. All animals were fed regular diet. The aldosterone and the RU 28362 animals received continuous infusion of either aldosterone or RU 28362, respectively, at 70 μg/100 g body wt per day for either 1 or 7 d. Unidirectional Na and Cl fluxes were determined with ^{22}Na and ^{36}Cl under short circuit conditions. n, number of tissue pairs. * Compared with control group. $^{\ddagger}P$ < 0.005 compared with aldosterone group. $^{\S}P$ < 0.05 compared with aldosterone group.
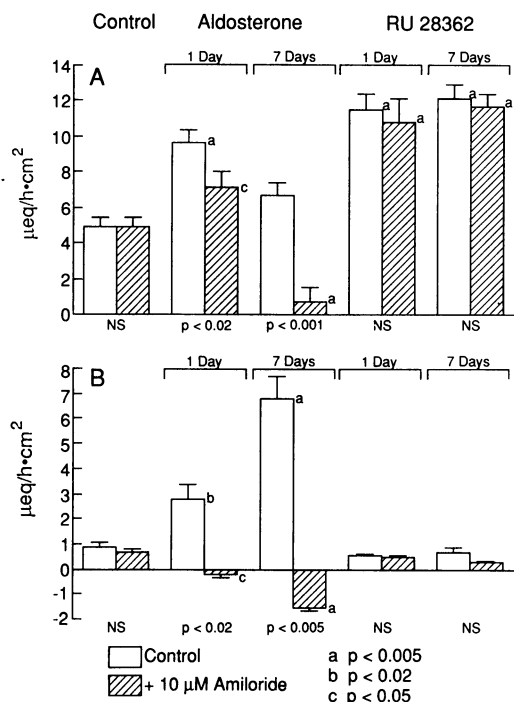
Figure 1. Effect of 10 μM amiloride on (A) J_{net}^{Na} and (B) I_{sc} in normal, 1- and 7-d aldosterone and RU 28362-infused groups. The number of tissue pairs studied is provided in the legend to Table I. The open and hatched bars represent the mean of two 15-min flux periods before and after, respectively, the addition of 10 μM amiloride to the mucosal bathing solution. The probability values shown in the figure compare the pre- and post-amiloride results. The symbols indicate comparison with their respective control group: (a) $P < 0.005$ compared with the control group; (b) $P < 0.02$ compared with the control group; (c) $P < 0.05$ compared with the control group.

of RU 28362. A significant increase in net sodium and net chloride absorption, as a result of a stimulation of mucosal to serosal fluxes, was observed in both 1-d steroid-infused groups (Table I B). There was no significant change in J_{sm}^{Na} or J_{sm}^{Cl} in either of the two experimental groups compared with the control group, and conductances were similar in the experimental and the control groups. The I_{sc} in the 1-d aldosterone-infused group was significantly increased compared with the control group (2.8 ± 0.6 vs. 0.9 ± 0.2 μeq/h · cm^2). In contrast, the I_{sc} in the 1-d RU 28362-infused group was identical to that of the control group. The addition of 10 μM amiloride to the 1-d aldosterone group resulted in a parallel reduction of both J_{ms}^{Na} and J_{net}^{Na} and I_{sc} (Fig. 1). In addition, the amiloride-insensitive component of J_{net}^{Na} in the 1-d aldosterone group was significantly greater than that in the control group (7.2 ± 0.9 vs. 4.9 ± 0.4 μeq/h · cm^2; $P < 0.05$). In contrast, 10 μM amiloride had no effect on any parameter of ion transport in the RU 28362 group.

Table I B also presents the results of ion transport in those animals that had received a 7-d infusion of either aldosterone or RU 28362. Although net sodium absorption in the aldosterone group was slightly but not significantly increased compared with the control group, the I_{sc} in the aldosterone group, as has been previously reported (3), was substantially and significantly increased to 6.8 ± 0.9 μeq/h · cm^2 compared with the control group. In contrast, net chloride absorption in the 7-d

aldosterone-infused group was significantly reduced compared with the control group as a result of a decrease in J_{ms}^{Cl}. Also, 10 μM amiloride produced substantial changes in ion transport in the 7-d aldosterone group; amiloride reduced J_{net}^{Na} to zero and inhibited I_{sc} (Fig. 1).[2]

Infusion of RU 28362 for 7 d resulted in significantly higher rates of net sodium and chloride absorption (12.1 ± 0.8 and 13.3 ± 1.4 μeq/h · cm^2, respectively) compared with the control group. This stimulation was predominantly the result of substantial enhancement of both J_{ms}^{Na} and J_{ms}^{Cl}. I_{sc} was similar in the 7-d RU 28362 and the control groups. The G was, however, significantly lower in the RU 28362 group (5.6 ± 0.7 mS/cm^2) than that of the control group (8.0 ± 0.8 mS/cm^2). Finally, amiloride had no effect on unidirectional or net Na absorption or I_{sc} in the 7-d RU 28362 group. As a result, the amiloride-insensitive component of J_{net}^{Na} was significantly greater in the RU 28362 group (11.7 ± 0.7 meq/h · cm^2) than in both the aldosterone and the control groups. These results demonstrate that the long term effects of aldosterone and RU 28362 on sodium and chloride transport in the rat distal colon differ both qualitatively and quantitatively.

The effect of RU 28362 on sodium and chloride transport with time is illustrated in Fig. 2. Infusion of RU 28362 for 1, 3, 7, and 11 d resulted in substantial stimulation of both J_{net}^{Na} and J_{net}^{Cl} compared with the control group; however, the rate of net sodium and chloride absorption observed after 3, 7, and 11 d of RU 28362 infusion was not significantly greater than that observed after 1 d of steroid infusion. These results indicate that stimulation of electroneutral Na-Cl absorption by RU 28362 is rapid and is not time dependent.

Potassium transport. Table II provides the results of unidirectional and net potassium fluxes in control, 7-d aldosterone-infused, and 7-d RU 28362-infused groups. In the control group net potassium absorption was 0.41 ± 0.8 μeq/h · cm^2) which is similar to that previously reported by this laboratory (3, 5). Aldosterone infused for 7 d resulted in induction of active potassium secretion (-0.49 ± 0.08 μeq/h · cm^2) as a result of a significant increase in J_{sm}^{K}. This effect of long-term aldosterone infusion on potassium transport in the distal colon of the rat is similar to that previously reported for prolonged dietary Na depletion (5). In contrast, a 7-d infusion of RU 28362 had no effect on unidirectional or net potassium fluxes and indicates that this glucocorticoid receptor-specific agonist did not alter potassium transport in the distal colon of the rat.

Previous in vitro studies of potassium transport in the rat distal colon have established that dietary sodium depletion not only induces active potassium secretion but also stimulates active K absorption (1, 5, 24). This stimulation of active K absorption can be demonstrated when the K secretory process in inhibited by one or more experimental maneuvers (e.g., removal of Na from the serosal bathing solution, or the addition of either ouabain or bumetanide to the serosal bathing solution [24]). To determine whether aldosterone or RU 28362 also induced active K absorption unidirectional ^{42}K

---

2. These results are virtually identical to previous studies of Na and Cl transport in both dietary Na-depleted animals and those that had received continuous infusion of aldosterone (3, 6) and have been interpreted to indicate that aldosterone both induces amiloride-sensitive electrogenic Na absorption and inhibits electroneutral Na-Cl absorption.
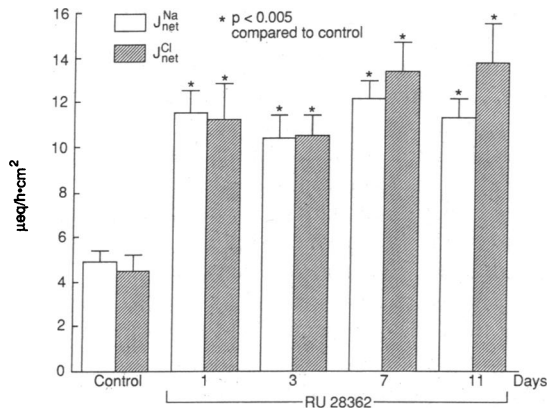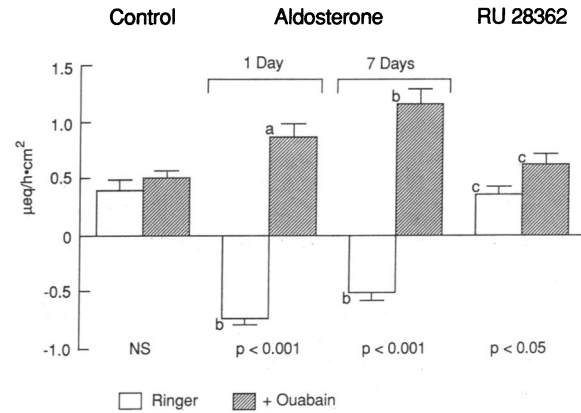
Figure 2. Net Na and Cl transport in control group and the experimental groups infused with RU 28362 for 1, 3, 7, and 11 d. The number of tissue pairs studied in each group was 6, 6, 6, 7, and 5, respectively.

Figure 3. Net potassium transport in control, 1- and 7-d aldosterone-infused and 7-d RU 28362-infused groups. The number of tissue pairs is provided in the legend to Table II. Open and hatched bars represent the mean of two 15-min flux periods before and after, respectively, the addition of 1 mM ouabain to the serosal bathing solution. The probability values shown in the figure compare the pre- and post-ouabain results. The symbols indicate comparison with their respective control groups: (a) $P < 0.025$ compared with the control group; (b) $P < 0.001$ compared with the control group; (c) NS (not significant) compared with the control group.

fluxes were performed in the presence of 1 mM ouabain in the serosal bathing media. Fig. 3 demonstrates that 1 mM ouabain did not alter J_{net}^{K} in the control group ($0.05 < P < 0.10$) although there was a small but statistical significant decrease in J_{sm}^{K}. In contrast, in the 7-d aldosterone group, serosal ouabain not only inhibited net K secretion but resulted in a substantial increase of the rate of net K absorption (1.16 ± 0.14 $\mu eq/h \cdot cm^2$). J_{net}^{K} in the aldosterone animals after the addition of serosal ouabain was greater than that observed in the control group (0.52 ± 0.06 $\mu eq/h \cdot cm^2$). In contrast, K transport in the RU 28362 group after ouabain addition was identical to that observed in the control group. In the 1-d aldosterone group, both active potassium secretion (-0.72 ± 0.06 $\mu eq/h \cdot cm^2$) and, in the presence of serosal ouabain, active K absorption (0.88 ± 0.12 $\mu eq/h \cdot cm^2$) were observed. The rates of these two potassium transport processes were not significantly different than that in the 7-d aldosterone group.

Discussion

Present concepts of the regulation of electrolyte transport by corticosteroids have evolved substantially over recent years (1). It is now well accepted that aldosterone stimulates active amiloride-sensitive sodium absorption and active potassium secretion in the distal colon of rat and rabbit (3-5). Glucocor-

ticosteroids have similar, but not identical effects on electrolyte transport in the mammalian colon (1, 7-12), and considerable uncertainty exists regarding the exact role of aldosterone and glucocorticoids in the regulation of colonic ion transport. The demonstration that both specific mineralocorticoid and glucocorticoid cytosolic receptors are present in the rat and rabbit colon is consistent with the interpretation that each cytosolic steroid receptor mediates specific ion transport processes (13-16). However, to date no study has convincingly demonstrated which corticosteroid receptor is specifically responsible for each of the several previously identified corticosteroid-induced changes in sodium and potassium transport.

Recently a series of compounds has been synthesized by the French pharmaceutical company, Roussel UCLAF, which are well suited to identify the specific role of the two corticosteroid receptors (19). Binding studies with glucocorticoid receptor-specific agonists, designated RU 26988 and RU 28362, have demonstrated these agonists bind with high affinity to the glucocorticoid receptor, do not displace the binding of radiolabeled aldosterone from the aldosterone receptor, and are

Table II. Unidirectional and Net Potassium Fluxes in Control, 7-d Aldosterone-infused, and 7-d RU 28362-infused Groups

	n	J_{ms}	J_{sm}	J_{net}	I_{sc}	G
		$\mu eq/h \cdot cm^2$				mS/cm^2
Control	6	0.83±0.07	0.42±0.04	0.41±0.08	1.1±0.2	8.0±0.7
Aldosterone	8	0.81±0.06	1.30±0.10	−0.49±0.08	5.0±0.3	13.1±1.2
P*		NS	<0.001	<0.001	NS	NS
RU 28362	7	0.97±0.12	0.61±0.08	0.36±0.08	0.9±0.2	7.9±0.9
P*		NS	NS	NS	NS	NS

Values are mean±SE. Unidirectional potassium fluxes were determined with ^{42}K. Positive values represent net absorption, and negative ones, net secretion. See the legend to Table I for additional details. * Compared with control group.

not displaced from the glucocorticoid receptor by aldosterone (16, 19). These compounds, therefore, permit investigation of the specific role of the glucocorticoid receptor in mediating changes in colonic ion transport.

Although four studies of colonic epithelial function have been reported to date with these agonists (16, 18, 20, 25), none have identified the active electrolyte transport changes that occur when glucocorticoids are administered to nonadrenalectomized animals. In studies of colonic electrolyte movement in adrenalectomized rats in vivo, Bastl (20) has suggested that the glucocorticoid receptor regulated basal electroneutral sodium absorption. The major limitations of this study are that in vivo studies are not ideal to establish the presence of active potassium secretion and that these synthetic glucocorticoid receptor-specific agonists were administered as pulses during the initial 26-h period after general anesthesia for surgical adrenalectomy. Halevy et al. (25) reported that RU 28362 infused into rats for 24 h increased amiloride-insensitive I_{sc} which may represent either active chloride secretion or amiloride-resistant, electrogenic sodium transport. The former has been shown to be stimulated by dexamethasone and methylprednisolone in rat distal colon (26) and rat ileum (27), respectively, and the latter was recently described in the rabbit cecum (28). Unfortunately, neither ion flux measurements nor ion replacement studies were performed to establish the basis for this increase in I_{sc}. Electrophysiologic studies compared the effects of RU 28362, dexamethasone, and secondary hyperaldosteronism in the rat distal colon and concluded that the two steroid receptors mediate changes in sodium and potassium transport that differ both qualitatively and quantitatively and that dexamethasone activates both types of receptors (18). Two limitations of this study were the absence of isotopic sodium and potassium flux measurements and the use of very large amounts of corticosteroids (approximately 10 times the estimated K_m of the glucorticoid receptor and the amount used in the other studies [20, 25] and in the present study).

Continuous infusion of aldosterone via implanted Alzet osmotic minipumps produce identical changes in sodium and chloride transport as dietary sodium depletion (6 and Table I). Long-term 7-d infusion of aldosterone resulted in both stimulation of electrogenic amiloride-sensitive sodium absorption and inhibition of electroneutral Na-Cl absorption which is the primary sodium transport system in normal animals. These studies further demonstrate that infusion of aldosterone produced identical changes in potassium transport compared to those that are observed in dietary sodium depleted animals: both 1- and 7-d infusion of aldosterone resulted in active potassium secretion (Table II). When aldosterone-stimulated potassium secretion was inhibited by the addition of 1 mM serosal ouabain, electroneutral potassium absorption was also enhanced (Fig. 3). The rate of the potassium absorptive process in the presence of ouabain in the aldosterone-infused animals was significantly greater than that observed in the control animals and, therefore, indicates that aldosterone not only induced active potassium secretion but also stimulated active electroneutral potassium absorption.

Aldosterone infused for 1 d produced a modest (though significant) stimulation of electroneutral Na-Cl absorption, in addition to its induction of electrogenic sodium absorption. We suggest that this transient enhancement of electroneutral Na-Cl absorption is a result of the binding of aldosterone to the

glucocorticoid receptor since RU 28362 did not inhibit electroneutral Na-Cl absorption at any time up to 11 d (Fig. 2) and experiments with both aldosterone (3) and sodium repletion (29) indicate that inhibition of electroneutral Na-Cl absorption requires exposure to aldosterone for at least 48–72 h. We speculate that the stimulation of electroneutral Na-Cl absorption by aldosterone at 24 h is secondary to its binding to the glucocorticoid receptor[3] but that at latter time points its inhibition which mediated by the aldosterone receptor is dominant over its enhancement by the glucocorticoid receptor.

The glucocorticoid receptor-specific agonist RU 28362 resulted in stimulation of electroneutral Na-Cl absorption which was observed as early as 24 h after its infusion (Fig. 2). Although aldosterone both induced electrogenic sodium absorption and inhibited electroneutral Na-Cl absorption, there was no evidence of either induction of electrogenic sodium transport or inhibition of electroneutral Na-Cl absorption even after 11 d of infusion of RU 28362 (Fig. 2). Studies of potassium transport also did not reveal any effect of RU 28362 on either potassium absorption or potassium secretion (Fig. 3). These results are in marked contrast to the changes in sodium and potassium transport produced by aldosterone and indicate that the two corticosteroid receptors in the distal colon produce highly specific changes in electrolyte transport. This distinct separation of the action of RU 28362 and aldosterone on ion transport in this epithelia indicates that RU 28362 is a specific glucocorticoid receptor agonist and, as a consequence, implies that the changes in potassium and electrogenic sodium transport mediated by aldosterone are mediated solely as a result of aldosterone's binding to the mineralocorticoid receptor. Thus, the mineralocorticoid receptor mediates very specific changes in sodium and potassium transport in the rat distal colon while the glucocorticoid receptor mediates other sodium (but not potassium) transport processes.

The efficacy of corticosteroids in the therapy of inflammatory bowel disease has been recognized for 40 years. Originally, the usefulness of corticosteroids in these clinical conditions was assumed solely the result of their anti–inflammatory effect. Newer understanding of the role of corticosteroids in the regulation of colonic electrolyte transport has raised the possibility that the antidiarrheal action of these steroids in inflammatory bowel disease may also be related to their proabsorptive effect on electrolyte movement (1, 29). The results of this present study together with the recent demonstration that sodium and chloride are actively absorbed throughout the normal human colon predominantly by electroneutral transport mechanisms (30–32) may have important therapeutic implications for inflammatory bowel disease. An ultrapure glucocorticoid receptor-specific agonist such as RU 28362 may provide greater efficacy with fewer side effects than the presently used "glucocorticoids" which manifest significant mineralocorticoid agonist activity.

---

3. Since general anesthesia and abdominal surgery can result in elevation of plasma corticosterone levels (21), it is possible that the increase in electroneutral Na-Cl absorption observed after 24 h of aldosterone infusion is a result of elevated endogenous corticosteroid levels and not of aldosterone. This possibility is unlikely since in animals subjected to considerably greater stress than the implantation of a subcutaneous minipump, plasma corticosterone levels had returned to normal within 14 h (21).

Acknowledgments

References

1. Sandle, G. I., and H. J. Binder. 1987. Corticosteroids and intestinal ion transport. *Gastroenterology*. 93:188–196.

2. Edmonds, C. 1967. Transport of sodium and secretion of potassium and bicarbonate by the colon of normal and sodium depleted rats. *J. Physiol. (Lond.)*. 193:589–602.

3. Foster, E. S., T. W. Zimmerman, J. P. Hayslett, and H. Binder. 1983. Corticosteroid alteration of active electrolyte transport in rat distal colon. *Am. J. Physiol.* 245:G688–G675.

4. Will, P. C., J. L. Lebowitz, and U. Hopfer. 1980. Induction of amiloride sensitive sodium transport in the rat colon by mineralocorticoids. *Am. J. Physiol.* 238:F261–F268.

5. Foster, E. S., J. P. Hayslett, and H. J. Binder. 1984. Mechanism of active potassium absorption and secretion in the rat colon. *Am. J. Physiol.* 246:G611–G617.

6. Halvey, J., M. E. Budinger, J. P. Hayslett, and H. J. Binder. 1986. Role of aldosterone in the regulation of sodium and chloride transport in the distal colon of sodium-depleted rats. *Gastroenterology*. 91:1227–1233.

7. Binder, H. J. 1978. Effect of dexamethasone on electrolyte transport in the large intestine of the rat. *Gastroenterology*. 75:212–217.

8. Charney, A. N., M. D. Kinsey, L. Myers, R. A. Giannella, and R. E. Gots. 1975. Na^+-K^+-activated adenosine triphosphatase and intestinal electrolyte transport: effects of adrenal steroids. *J. Clin. Invest.* 56:653–660.

9. Charney, A. N., J. Wallach, S. Ceccarelli, M. Donowitz, and C. L. Costenbader. 1981. Effects of spironolactone and amiloride on corticosteroid-induced changes in colonic function. *Am. J. Physiol.* 241:G300–G305.

10. Perrone, R. D., and S. L. Jenks. 1984. Suppression of coupled Na-Cl absorption by aldosterone and dexamethasone in rat distal colon in vitro. *Am. J. Physiol.* 246:F787–F793.

11. Will, P. C., R. N. Cartright, R. C. DeLisle, J. G. Douglas, and U. Hopfer. 1985. Regulation of amiloride-sensitive electrogenic sodium transport in the rat colon by steroid hormones. *Am. J. Physiol.* 248:G124–G132.

12. Jorkasky, D., M. Cox, and G. M. Feldman. 1985. Differential effects of aldosterone and dexamethasone on rat colon in vitro. *Am. J. Physiol.* 248:G424–G431.

13. Marusic, E. T., J. P. Hayslett, and H. J. Binder. 1981. Corticosteroid-binding studies in cytosol of colonic mucosa of the rat. *Am. J. Physiol.* 240:G417–G423.

14. Binder, H. J., A. White, D. Whiting, and J. Hayslett. 1986.

Demonstration of specific high affinity receptors for aldosterone in cytosol of rat colon. *Endocrinology* 118:628–631.

15. Marver, D. 1984. Assessment of mineralocorticoid activity in the rabbit colon. *Am. J. Physiol.* 246:F437–F446.

16. Bastl, C. P., C. A. Barnett, T. J. Schmidt, and G. Litwack. 1984. Glucocorticoid stimulation of sodium absorption in colon epithelia is mediated by corticosteroid 1B receptor. *J. Biol. Chem.* 259:1186–1195.

17. Schulman, G., A. Miller, G. Litwack, and C. Bastl. 1986. Characterization of the unactivated and activated aldosterone receptor. *J. Biol. Chem.* 261:12102–12108.

18. Binder, H. J., F. McGlone, and G. I. Sandle. 1989. Effects of corticosteroid hormones on the electrophysiology of the rat distal colon: implications for Na and K transport. *J. Physiol. (Lond.)*. 410:425–441.

19. Teutsch, G., G. Costerousse, R. Deraedt, J. Benzoni, M. Fortin, and D. Philibert. 1981. 17-alkynyl-11,17Dihydroxyandrostane derivatives: A new class of potent glucocorticoids. *Steroids*. 38:651–665.

20. Bastl, C. P. 1987. Regulation of cation transport by low doses of glucocorticoids in in vivo adrenalectomized rat colon. *J. Clin. Invest.* 80:348–356.

21. Fromm, M., W. Oelkers, and U. Hegel. 1983. Time course of aldosterone and corticosterone plasma levels, in rats during general anesthesia and abdominal surgery. *Pfluegers Arch. Eur. J. Physiol.* 399:249–254.

22. Martin, R. S., W. J. Jones, J. P. Hayslett. 1983. Animal model to study the effect of adrenal hormones on epithelial function. *Kidney Int.* 24:386–391.

23. Binder, H. J., E. Foster, M. E. Budinger, and J. P. Hayslett. 1987. Mechanism of electroneutral sodium-chloride absorption in distal colon of the rat. *Gastroenterology*. 93:449–455.

24. Sweiry, J., and H. J. Binder. 1989. Characterization of aldosterone-induced potassium secretion in rat distal colon. *J. Clin. Invest.* 83:844–851.

25. Halevy, J., E. L. Boulpaep, M. E. Budinger, H. J. Binder, and U. P. Hayslett. 1988. Glucocorticoids have a different action than aldosterone on target tissue. *Am. J. Physiol.* 254:F153–F158.

26. Bridges, R. J., W. Rummel, and P. Wollenberg. 1984. Effects of vasopressin on electrolyte transport across isolated colon from normal and dexamethasone-treated rats. *J. Physiol. (Lond.)*. 355:11–23.

27. Marane, W. G., Y. H. Tai, R. A. Decker, E. C. Boedecker, A. N. Charney, and M. Donowitz. 1981. Methylprednisolone stimulation of guarylate cyclase activity in rat small intestinal mucosa: possible role in electrolyte transport. *Gastroenterology*. 81:90–100.

28. Sellin, J. H., H. Oyarzabal, and E. J. Cragoe. 1988. Electrogenic sodium absorption in rabbit cecum in vitro. *J. Clin. Invest.* 81:1275–1283.

29. Sandle, G. I., J. P. Hayslett, and H. J. Binder. 1986. The effect of glucocorticoids on rectal transport in normal subjects and patients with ulcerative colitis. *Gut.* 27:309–316.

30. Sandle, G. I., N. K. Wills, W. Alles, and H. Binder. 1986. Electrophysiology of the human colon: evidence of segmental heterogeneity. *Gut.* 27:999–1005.

31. Hubel, K. A., K. Renquist, and S. Shirazi. 1987. Ion transport in human cecum, transverse colon, and sigmoid colon in vitro. *Gastroenterology.* 92:501–507.

32. Sellin, J. H., and R. DeSoignie. 1987. Ion transport in human colon in vitro. *Gastroenterology.* 93:441–448.