Aldosterone in colonic potassium adaptation in rats

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ABSTRACT

The influence of adrenalectomy and administration of aldosterone on potassium secretion by colonic epithelium was studied in vivo in rats, particularly in relation to potassium adaptation (induced by feeding a potassium-rich diet) and the response to acute i.v. administration of a potassium load. Adrenalectomy (rats maintained on dexamethasone and saline) impaired the development of potassium adaptation or considerably reduced it if the rats had been previously adapted. The partial adaptation observed in the adrenalectomized rats may be related to the increased plasma potassium concentration developed when these rats received the potassium-rich diet.

Within 2 h of acute aldosterone administration, the response of the potassium secretion rate to acute potassium loading in adrenalectomized rats was significantly improved. When aldosterone (2 μg/day per 100 g body weight, given by osmotic minipump) was added to the replacement treatment, the plasma concentration of potassium was similar to that of the intact rats, and both potassium adaptation and the response to the acute potassium load were completely restored. Transepithelial potential difference and sodium transport were not stimulated, being similar to the values in intact rats. Considerable changes in potassium secretion induced by acute potassium loading did not significantly affect sodium transport.

The findings suggest that the sodium and potassium epithelial pathways are, to a large extent, independently influenced by aldosterone. Aldosterone appears to be essential for complete adaptation and, in a relatively low dose, can completely restore potassium adaptation and the response to acute potassium loads in adrenalectomized rats.


INTRODUCTION

The feeding of a potassium-rich diet results in adaptive changes in the kidneys so that when an acute potassium load is given, renal potassium excretion is more rapid than in rats on a normal diet (Silva, Brown & Epstein, 1977); a phenomenon referred to as potassium adaptation. It is now well-established that the mammalian colon also secretes potassium actively (Edmonds, 1967; Wills & Biagi, 1982; Foster, Hayslett & Binder, 1984; Ishida & Suzuki, 1987), and that this secretion is subject to a variety of influences (Smith & McCabe, 1984). One of these is potassium intake, potassium being secreted at an increased rate when the animal takes a potassium-rich diet (Fisher, Binder & Hayslett, 1976). Moreover, the administration of an acute potassium load results in a brisk rise of colonic potassium secretion (Bastl, Kliger, Binder & Hayslett, 1978), and this is considerably enhanced if the animal is taking a potassium-rich diet (Edmonds & Willis, 1988). Thus colonic epithelium behaves similarly to that of the kidney.

The plasma concentration of aldosterone is increased in animals taking a potassium-rich diet (Bojesen, 1966; Stanton & Giebisch, 1982). This, together with the observations showing that aldosterone, whether administered or derived from increased endogenous secretion (as in sodium-depleted animals), enhances colonic potassium secretion (Shields, Mulholland & Elmslie, 1966; Edmonds, 1967; Edmonds & Marriott, 1967), suggests that the hormone is important for potassium adaptation. Furthermore, adrenalectomized rats fed a potassium-rich diet fail to increase colonic potassium secretion to the extent found in intact rats, a defect which can be corrected by aldosterone administration (Foster, Jones, Hayslett & Binder, 1985; Martin, Oszi, Brocca et al. 1986). However, aldosterone also characteristically affects sodium transport, but sodium transport did not appear to be affected in rats on a potassium-rich diet (Fisher et al. 1976). The present study was undertaken to examine colonic potassium adaptation
further, particularly in regard to the response to the administration of acute potassium loads in adrenalectomized rats treated with aldosterone in relatively low dosage.

MATERIALS AND METHODS

Male albino rats (250–350 g) were fed with a standard pellet diet which contained 0·2 mmol/g potassium. The potassium-rich diet was made of similar pellets which had been prepared by preliminary soaking in 0·3 mol KCl/l and dried to their previous form. Their potassium content was about 0·7 mmol/g and the rats received this diet for 7 days before the experiments. The normal and adrenalectomized rats ate about 7 g/100 g body weight per day of this diet, an amount similar to that consumed when they were fed the standard diet. All rats had free access to drinking fluid, which in the case of the adrenalectomized rats was 0·9% (w/v) NaCl. Bilateral adrenalectomy was carried out through a midline posterior incision using methoxyfluorane inhalation anaesthesia. Rats subsequently received dexamethasone (Organon, Cambridge, U.K.; 1 μg/day per 100 g body weight) by i.m. injection. The rats recovered rapidly after adrenalectomy and ate normally. They were used for the perfusion experiments 3 days later, except for one experiment (group F) in which the animals had been adrenalectomized 10 days previously.

Full details of the methods for measurement of colonic ionic fluxes have been given previously (Edmonds, 1981; Edmonds & Mackenzie, 1987) and will be only briefly described here. The secretion and absorption studies were carried out under sodium pentobarbitone anaesthesia (6 mg/100 g body weight, injected i.p. well away from the distal colon). The abdomen was opened by a midline incision, then the distal (descending) colon was rinsed clean and a segment about 3 cm long cannulated. The method also allowed continuous measurement of the transepithelial electrical potential difference (p.d.) by means of bridges connecting to the lumen and the serosal surface of the segment of colon. For measurement of potassium secretion, the segment was perfused continuously with a solution containing NaCl (50 mmol/l) and mannitol (200 mmol/l) at 37 °C and a rate of 1 ml/min using a Watson–Marlow H.R. Flow Inducer. The concentration of sodium was chosen as being similar to that of faecal fluid in this part of the colon, and mannitol was added in sufficient concentration to render the solution isotonic. The object of the perfusion experiments was to measure potassium secretion rate, therefore no potassium was included. The potassium concentration in the effluent (due to secreted potassium) was very low so that back-diffusion of potassium was minimized. The solution was perfused for 15 min before collections began so that potassium secretion rate was steady, preliminary experiments having confirmed that this time sufficed. In the experiments in which sodium fluxes were measured, 0·5 ml of a solution of the same composition as the perfusion solution, but also containing 22Na (2 Bq/μmol sodium; Radiochemical Centre, Amersham, Bucks, U.K.) was instilled into the empty lumen. This was rinsed out and collected after 10 min of exposure. All animals had an i.v. polythene cannula implanted into the external jugular vein and brought out through the skin of the back of the neck. The cannula served for administering the potassium load and, in one study, was also used for giving aldosterone.

In one study (group D), aldosterone (Sigma Chemical Co. Ltd, Poole, Dorset, U.K.) was given i.v. by a constant-infusion pump over 20 min. The rats were in metabolic cages and anaesthesia was not necessary. About 1 h later, the colon segment was prepared and measurements of potassium secretion commenced at 1 h 40 min after completion of the aldosterone infusion. The long-term (72 h) infusions of aldosterone were given by means of osmotic minipumps (Alzet Corporation, Palo Alto, CA, U.S.A.) inserted into the peritoneal cavity through a small lateral incision. Kenyon, Saccoccio & Morris (1984) found that, using these minipumps, about 0·6 μg aldosterone/day per 100 g body weight was sufficient as replacement treatment for adrenalectomized rats. In previous experiments, we found that a dose rate of about 6 μg/day per 100 g body weight for 3 days produced a considerable rise of p.d. and stimulation of sodium transport with complete substitution of amiloride-sensitive sodium transport for the amiloride-insensitive sodium transport characteristically found in normal rats (Edmonds & Mackenzie, 1987). In the present studies, the object was to give sufficient aldosterone to stimulate the potassium transport system without, if possible, stimulating that of sodium. We therefore used aldosterone at two dose levels (2 and 4 μg/day per 100 g body weight) between these extremes. The minipumps also contained dexamethasone providing 1 μg/day per 100 g body weight. The acute potassium load was given i.v. by constant-infusion pump as a solution of KCl (120 mmol/l) and KHCO3 (30 mmol/l) at 270 μl/min for the first 10 min, and subsequently at 190 μl/min. No adverse effects were observed with this rate of potassium administration. Samples of venous blood were obtained from the inferior vena cava, the final sample being obtained just before the infusion was stopped at the end of the experiment.

Solutions were freshly prepared for each experiment. When amiloride was used, it was present in the perfusion solution at a concentration of 100 μmol/l.
Sodium and potassium concentrations were measured by flame photometry, and $^{22}\text{Na}$ by gamma counting. Flux results are expressed per cm² of mucosal area, obtained by measuring the length of the segment used on a standard glass tube after its removal at the end of the experiment. The basal preinfusion rate of potassium secretion was estimated from the 10 min (two 5-min collections) immediately preceding the infusion of the potassium load. The results are given as mean ± S.E.M. Significance was tested using two-tailed Student’s $t$-test.

RESULTS

Effect of the potassium-rich diet

The infusion of the acute potassium load produced a rise of potassium secretion rate which, in the normal rats (group A) during the period 10–20 min after beginning infusion, was nearly three times the basal preinfusion rate (Figs 1 and 2). The rats fed the potassium-rich diet (group B) had a basal preinfusion secretion rate of potassium which was about four times ($P<0.01$) that of the rats fed the standard diet, while during the i.v. infusion of potassium (10–20-min period), the secretion rate was about three times ($P<0.01$) as great.

The transepithelial p.d. was similar in these groups and was unaffected by the potassium infusion. A difference was, however, apparent when amiloride was also contained in the solution within the lumen. Amiloride, in the concentration used (100 μmol/l), blocks the sodium ion conductive pathway, but with little effect on the Na⁺-H⁺ electroneutral exchange system (Benos, 1982). Whereas the transepithelial p.d. of the rats on the standard diet did not change significantly when amiloride was present (Fig. 1), that of the rats on the potassium-rich diet fell by about 30% ($P<0.01$). Thus the potassium-rich diet had induced a state of partial sensitivity of the p.d. to amiloride by comparison with the complete sensitivity found in the epithelium of sodium-depleted rats (Will, Lebowitz & Hopfer, 1980; Edmonds, 1981). This suggests that the epithelium was under some degree of enhanced aldosterone action.

Adrenalectomy and potassium adaptation

All the rats used in these experiments received dexamethasone as glucocorticoid replacement as well as having 0.9% (w/v) NaCl as drinking fluid. When eating a normal diet, the adrenalectomized rats (group E) had a preinfusion secretion rate of potassium similar to that of normal animals, but the colonic response to the acute potassium load was much impaired (Fig. 2). When adrenalectomized rats were fed a potassium-rich diet (group F), although the colonic potassium secretion rate was increased significantly ($P<0.01$) it was still lower than that of intact rats taking this diet ($P<0.01$). The impairment of their adaptive response was particularly evident when these adrenalectomized rats were infused with the potassium load. The epithelial secretion rate of potassium (10–20-min period) rose by only 50% in contrast to the normal rats (group B) in which secretion rate doubled. A similar result was obtained in the rats (group G) which had been previously adapted to high potassium intake and then adrenalectomized. Thus potassium adaptation could not be sustained in the absence of the adrenals. No significant change of colonic p.d. occurred during the acute potassium infusion in any of the groups. The p.d. was similar in

![Figure 1](https://via.placeholder.com/150)

**Figure 1.** Secretion of potassium by the rat distal colon before and during i.v. infusion of a potassium load. The infusion was given from 0 to 20 min. Group A, four normal controls fed a standard diet. Group B, four normal rats fed the potassium-rich diet for 7 days before measurement of potassium secretion. Group C, five adrenalectomized rats fed a potassium-rich diet. Group D, four adrenalectomized rats fed the potassium-rich diet and which received 6 μg aldosterone/100 g body weight given i.v. over 20 min, beginning 2 h before secretion measurements. The transepithelial potential difference (p.d.) measured before and during potassium infusion (●) and 5 min after 100 μmol amiloride/l was added to the solution perfusing the lumen (○) is also shown. Values are means ± s.e.m.
the normal rats on the standard and potassium-rich diets (groups A and B) and the adrenalectomized rats on the standard diet (group E). The p.d. values in the adrenalectomized rats on the potassium-rich diet (groups F and G) were, however, significantly \( (P<0.01) \) greater than those of the adrenalectomized rats on the standard diet (group E).

Effect of administration of aldosterone

Administration of aldosterone improved the response to acute potassium infusion within 2 h (Fig. 1, group D). Although the basal preinfusion potassium secretion rate was not significantly increased, the secretion rate during the period 10–20 min after the beginning of the potassium infusion was significantly \( (P<0.05) \) greater in the treated (group D) compared with the untreated (group C) adrenalectomized rats. The p.d. was not significantly higher in the aldosterone-treated rats, nor did amiloride affect it. Changes in sodium transport can be shown by 4 h of administration of aldosterone (Edmonds & Mackenzie, 1987); the present findings indicate that the action of aldosterone on the potassium pathway is at least as fast and possibly faster than it is on the sodium pathway.

In the chronic experiments, a low dosage of aldosterone was used to see whether the defect in potassium adaptation could be corrected without significantly stimulating sodium transport. Aldosterone was given by osmotic minipump for 72 h preceding the colonic measurements (Fig. 3). With the lower dose rate of aldosterone (2 \( \mu \)g/day per 100 g body weight, group H), both basal secretion rate and the response to the potassium load were similar to those found in normal rats adapted to the potassium-rich diet. Moreover, the p.d. was not increased, and no significant change occurred during the potassium infusion. With the higher dose rate of aldosterone (4 \( \mu \)g/day per 100 g body weight, group I), the secretion rates during potassium infusion were significantly \( (P<0.01) \) greater, both when compared with the adrenalectomized rats treated with the lower rate of aldosterone infusion (group H) and the intact normal rats (group B). The relationship between the basal potassium secretion rate and that during potassium infusion was examined taking the data from all the adrenalectomized rats, including those treated and those not treated with aldosterone (Fig. 4). It is evident that there was a close relationship between the basal rate at which potassium was secreted and the rate which was developed during infusion.

Sodium fluxes were also measured (Table 1) in rats fed a potassium-rich diet, comparing groups of normal controls and adrenalectomized rats chronically infused with aldosterone (2 \( \mu \)g/day per 100 g body weight). There were no significant differences between these groups in any aspect of sodium transport. Moreover, the acute potassium load, although considerably stimulating potassium secretion, did not significantly affect sodium transport (Table 2).

Plasma potassium

In normal control rats, the plasma potassium concentration was similar whether they received the standard or potassium-rich diet (Table 3). In the adrenalectomized rats, on the other hand, the plasma concentration of potassium was markedly greater in those receiving the potassium-rich diet. Similarly, although the acute potassium infusion increased the plasma concentration of potassium in all groups, the level reached was significantly \( (P<0.05) \) greater in the adrenalectomized rats on the potassium-rich diet. When these animals were chronically treated with aldosterone, however, the plasma potassium level reached during infusion was no greater than that of the normal control rats.
Potassium secretion by the epithelium of the rat distal colon increases when rats are fed a potassium-rich diet, a change which may occur without any demonstrable increase of sodium transport (Fisher et al. 1976). That the sodium transport system undergoes some modification was, however, suggested in our experiments by the appearance of partial amiloride sensitivity of the p.d. in the rats fed a potassium-rich diet. Moreover, when the potassium supplement in the diet was very high (more than tenfold compared with threefold in our studies), complete amiloride sensitivity with an increased p.d. was observed (Budinger, Foster, Hayslett & Binder, 1986). Structural changes in the basolateral membrane, consistent with an increase of Na⁺-K⁺ ATPase, as well as an increase in conductance of the apical membrane of the epithelial cells, have been described in association with this enhanced potassium secretion (Kashgarian, Taylor, Binder & Hayslett, 1980; Sandle, Foster, Lewis et al. 1985).

Renal potassium adaptation is impaired by adrenalectomy with both the basal potassium secretion rate and the response to acutely administered potassium loads being reduced (Stanton, Klein-Robbenhaar, Wade et al. 1985). In the colon, the capacity to increase potassium secretion in response to a potassium-enriched diet is also impaired by adrenalectomy, a defect corrected by administration of aldosterone (Foster et al. 1985; Martin et al. 1986). Moreover, the results of the present study showed that adrenalectomy also considerably impairs the response to acutely administered potassium loads. There was, however, evidence of some degree of adaptation in the adrenalectomized rats, since both the basal rate of potassium secretion and that during potassium loading were enhanced by feeding the potassium-rich diet. The transepithelial p.d. was consistently higher in these adrenalectomized rats (compared with those fed the standard diet), but we have no satisfactory explanation for this at present. In these animals the plasma potassium concentration was considerably raised, suggesting the possibility that hyperkalaemia itself may have a mineralocorticoid-like effect on the colonic potassium secretory mechanism as proposed for renal collecting-duct epithelium (West, Sonnenberg, Veress & Halperin, 1987). When aldosterone was given, there was a rapid improvement in
TABLE 1. Sodium fluxes and potassium secretion rates measured in the distal colon of four normal and four adrenalectomized rats, the latter being treated with aldosterone (2 μg/day per 100 g body weight) and dexamethasone (1 μg/day per 100 g body weight) for 3 days by i.p. osmotic minipump. All rats were fed a potassium-rich diet. Values are means ± S.E.M.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sodium (nmol/min per cm²)</th>
<th>Potassium (nmol/min per cm²)</th>
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<tbody>
<tr>
<td></td>
<td>J_net</td>
<td>J_ms</td>
</tr>
<tr>
<td>Control</td>
<td>−159 ± 41</td>
<td>96 ± 11</td>
</tr>
<tr>
<td>Adrenalectomized</td>
<td>−154 ± 20</td>
<td>89 ± 13</td>
</tr>
</tbody>
</table>

J_net, net flux; J_ms, mucosal to serosal side flux (i.e. lumen to plasma); aJ_ms, active transcellular flux. The latter was estimated from the observed values of J_net, J_ms, and the transepithelial potential difference (Edmonds & Mackenzie, 1987). The negative sign indicates secretion. Fluxes were measured in duplicate in each animal using a solution of similar composition to the colon perfusion solution used in the other experiments, sodium concentration being 50 mmol/l.

TABLE 2. Effect of the acute i.v. potassium load on the sodium fluxes and potassium secretion of the distal colon in two normal and two adrenalectomized rats. The latter were treated with aldosterone (2 μg/day per 100 g body weight) and dexamethasone (1 μg/day per 100 g body weight). All rats were fed the potassium-rich diet. Values are means ± S.E.M.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sodium (nmol/min per cm²)</th>
<th>Potassium (nmol/min per cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>J_net</td>
<td>J_ms</td>
</tr>
<tr>
<td>Preinfusion</td>
<td>−114 ± 26</td>
<td>99 ± 25</td>
</tr>
<tr>
<td>During infusion</td>
<td>−124 ± 34</td>
<td>100 ± 29</td>
</tr>
</tbody>
</table>

J_net, net flux; J_ms, mucosal to serosal side flux; aJ_ms, active transcellular flux. The negative sign indicates secretion. Fluxes were measured in duplicate in each animal and the ‘during infusion’ measurements were over the period 10–30 min after beginning administration of the i.v. potassium load.

TABLE 3. Plasma potassium concentrations measured in various experimental situations in normal and adrenalectomized rats taking a standard or potassium-enriched diet or a potassium-enriched diet plus 2 μg aldosterone/day per 100 g body weight. Values are means ± S.E.M., the numbers in parentheses are the numbers of animals

<table>
<thead>
<tr>
<th>Plasma potassium concentration (mmol/l)</th>
<th>Control</th>
<th>Adrenalectomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preinfusion</td>
<td>End of infusion</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>4.8 ± 0.2 (4)</td>
<td>8.9 ± 0.3 (4)</td>
</tr>
<tr>
<td>Potassium-rich</td>
<td>4.6 ± 0.4 (4)</td>
<td>8.7 ± 0.6 (3)</td>
</tr>
<tr>
<td>Potassium-rich with aldosterone</td>
<td></td>
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</tbody>
</table>

All adrenalectomized rats were treated with dexamethasone and given 0.9% (w/v) NaCl to drink. The final blood sample was taken at the end of the experiment before the i.v. potassium infusion was stopped.

A potassium-rich diet increases aldosterone secretion, and plasma levels may be several-fold higher than those found in rats on an ordinary diet (Bojessen, 1966; Stanton & Giebisch, 1982). Consistent with this

potassium adaptation, with both the basal potassium secretion rate and the response to potassium loading being increased within 2 h of administration of aldosterone.

was the finding of partial amiloride sensitivity of the p.d., which became evident in our rats when fed a potassium-rich diet. However, in experiments on intact rats on a normal diet, aldosterone administration alone failed to produce the high potassium secretion rates found in rats on a potassium-rich diet (Foster et al. 1985; Edmonds & Willis, 1988), and similar observations have been made in respect of renal potassium adaptation (Stanton, Pan, Deetjen et al. 1987). In the present experiments, when adrenalectomized rats were fed a potassium-rich diet and received chronic administration of aldosterone at a rate of 2 µg/day per 100 g body weight, which is about three to four times that which has been found to be the maintenance dose rate of aldosterone (Kenyon et al. 1984), the potassium secretory mechanism was completely restored so that both the basal secretion rate and the response to acute potassium infusion, as well as plasma potassium concentrations were similar to those of intact rats fed the potassium-rich diet. This effect of normalizing potassium metabolism was achieved at a dose rate of aldosterone which did not demonstrably affect sodium transport. This is comparable with the situation in intact normal rats which also do not show any evidence of increased sodium absorption when fed a potassium-rich diet (Fisher et al. 1976; Budinger et al. 1986; Edmonds & Willis, 1988).

The secretion rate observed during the acute potassium infusion was closely related to the basal preinfusion secretion rate, suggesting that essentially similar potassium pathways were involved. However, the precise mechanism by which the increased secretion is produced during potassium infusion remains to be determined. It may be a consequence of a direct effect of the increased plasma potassium concentration or it may be produced by the release of other hormones, possibly adrenergic agents (Smith & McCabe 1986; Ishida & Suzuki, 1987). Sodium movement was altogether unaffected by the considerable changes of potassium secretion occurring during potassium loading. Thus in the normal and aldosterone-treated adrenalectomized rats (Table 2), potassium secretion was increased more than threefold during potassium infusion without producing any significant change of p.d., sodium absorption or of the estimated active transcellular sodium flux. The independence of aldosterone influence on sodium and potassium movements is also evident from the work of Bastl, Binder & Hayslett (1980) in which a relatively low dose of aldosterone was found to restore almost completely the depressed potassium secretion rate in the distal colon of adrenalectomized rats fed a normal diet, without having any significant effect on sodium absorption or p.d.

In conclusion, the sodium and potassium pathways in this epithelium appear, to a large extent, to be independent since considerable variations of potassium flux occurred (as induced by administration of acute potassium loads) without affecting sodium movements. The sodium and potassium pathways were also independently influenced by aldosterone, with the potassium pathway responding rapidly to aldosterone and, as shown by the chronic infusion experiments, being particularly sensitive to aldosterone so that a considerable effect on potassium secretion was produced at a dose level which had little or no action on sodium transport. Thus by administering an appropriate dose of aldosterone chronically, complete potassium adaptation without abnormal rise of plasma potassium concentration was achieved.

REFERENCES


