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TRANSPORT OF POTASSIUM BY THE COLON OF NORMAL AND SODIUM-DEPLETED RATS

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SUMMARY

1. Ascending and descending segments of colon of normal and Na-depleted rats were perfused with solutions of differing KCl concentration. Net K flux, electrical p.d. and, in some experiments, unidirectional K fluxes were measured.

2. Variation of luminal K concentration over the range 0–40 mM did not affect p.d. or K efflux rate.

3. K secretion rate fell about 30% when Na-free choline chloride solution was perfused.

4. Net flux was a linear function of the luminal K concentration, and fell as the latter increased. Na depletion increased K secretion rate and passive permeability of the mucosa to K. Adrenalectomy had the reverse effect. The luminal K concentration, associated with zero net K flux was much greater than expected if the colonic mucosa behaved passively with respect to K.

5. Unidirectional fluxes determined when 5 mM-KCl was in the lumen showed that the ratio influx/efflux was much less than predicted by Ussing's flux ratio equation.

6. It was concluded that K influx was due to simple diffusion and K efflux to diffusion and active transport, both processes being increased by Na depletion.

INTRODUCTION

Although there exists considerable information on the movement of K across cell membranes, there is relatively little on its transport across epithelia. K transport has been examined in the gall-bladder (Wheeler, 1963; Dietschy & Moore, 1964) and small intestine (Gilman, Koelle & Ritchie, 1963) but the epithelia of these structures do not appear to transport the ion actively and simple electrochemical considerations are adequate to explain the observed movements. In the stomach, however, K transport, although relatively small when compared with the movement of

other ions, does probably involve the active transport of K into the gut lumen (Harris & Edelman, 1960). In the kidney, where K transport across the renal tubular wall is probably the most important mechanism in the control of K homeostasis, the evidence is conflicting and it is still uncertain to what extent active and passive processes are involved (Oken & Solomon, 1963; Khuri, Goldstein, Maude, Edmonds & Solomon, 1963; Giebisch & Windhager, 1964).

Both in man and other animals, the K concentration in the stool water is very much higher than in the extracellular fluid so that there exists a considerable K gradient across the mucosal wall (Goiffon, Goiffon & Fron, 1961; Wrong, Metcalfe-Gibson, Morrison, Ng & Howard, 1965; Edmonds, 1967*a*). Previous experiments suggested that K was actively secreted into the lumen of the rat colon but the results were not completely conclusive (Edmonds, 1967*a*). In the present paper experiments are described which show that the colon mucosa can transport K ions to an extent greater than expected from the electrochemical gradient, indicating active transport of the ion.

The nomenclature used in this paper is as before (Edmonds, 1967*b*).

METHODS

Male albino rats weighing 300–350 g were used. Their diet and maintenance and the perfusion technique were as described previously (Edmonds, 1967*a*, *b*). On some rats adrenalectomy was performed in a single stage under ether anaesthesia, the rats being subsequently given 1% NaCl to drink but otherwise treated similarly to the rest. Perfusion solutions of varying K concentration were prepared from KCl and NaCl in quantities to give the desired K concentration while maintaining the solutions isosmotic with 150 mM-NaCl; subsequently perfusion solutions will be referred to only by their K concentration although all were isosmotic with 150 mM-NaCl. The solutions contained phenol red for measurement of water movement. Except where otherwise indicated, each perfusion was for a 30 min period and each solution perfused for two periods.

Determination of net flux. The net flux was determined from

$$J_n = (V_o[\mathrm{K}]_o - V_t[\mathrm{K}]_t)/bt \qquad (1)$$

where V = volume of solution circulating, [K] = luminal K concentration, b = length of colon segment (cm), t = time of perfusion (min). The subscripts, o and t refer to time. The sign of J_n indicates secretion or absorption in accordance with a previously discussed convention (Edmonds, 1967*b*).

In this calculation giving net flux/min it is assumed that the amount of K in the lumen changed linearly with time over the period of observation. In several preliminary experiments it was possible to show that this was true over a period of 1 hr (Fig. 1).

Tracer experiments. The application of methods used for estimating ionic fluxes in two compartment systems such as have been employed for measuring Na fluxes in the gut (Visscher, Varco, Carr, Dean & Erickson, 1944; Curran & Solomon, 1957) cannot be applied to a system in which there exists an intermediate compartment, until the latter has reached a steady state, i.e. until the amount of isotope in that compartment is constant during the period of observation. Only then will measurement of the rate of disappearance of tracer

from the labelled side or its appearance rate on the unlabelled side give the unidirectional flux. A large amount of K is present in the mucosal layer (Edmonds, 1967*b*) and so initial experiments were necessary to determine the time required for the specific activity of this K to reach a steady value when one or other side was exposed to ^{42}K. The time for the steady value to be reached was determined both when solutions of K concentration 5 mM and 40 mM containing ^{42}KCl (10 mμc/μmole K) were perfused, the solutions being circulated for 3 hr and small specimens of colon removed at hourly intervals with cutting cautery. This procedure involved trivial blood loss and especial care was taken not to damage the blood supply of the rest of the colon. The muscle coat was stripped from the mucosal layer and the latter rapidly rinsed several times in 150 mM-NaCl, blotted dry on filter paper (Whatman no. 42, 'ashless'), and the specific activity of its K determined after digestion in concentrated HNO_3.

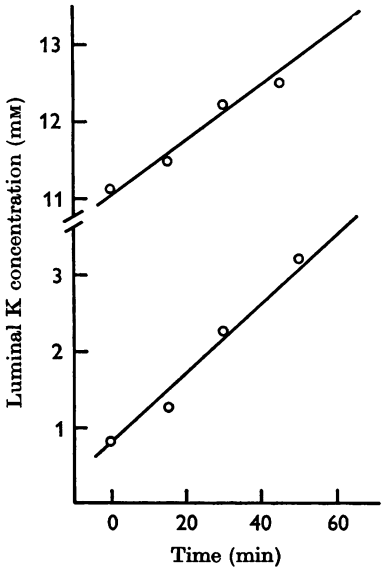

Fig. 1. Rise of luminal K concentration during perfusion of isotonic solutions of initial K concentration approximately 1 mM and 11 mM. The figure shows that over short periods the luminal K concentration rose linearly.

In estimating Na and Cl fluxes in the gut, the radioisotope has generally been placed in the lumen and the flux obtained from changes in the luminal fluid. In the present experiments the unidirectional fluxes were measured when the luminal K concentration was similar to that of the plasma but at this low concentration it was found in trial experiments that the change in the amount of ^{42}K in the lumen was too small to allow accurate observations. Accordingly, for the flux measurements, the ^{42}KCl was given instead to the rat, 24 hr being allowed for the isotope to equilibrate throughout the body K. Observation of the rate of its appearance in the lumen was then used to measure K efflux rate. Rats were each injected intraperitoneally with 30 $\mu c^{42}KCl$ in 150 mM-NaCl, 24 hr before use. The ascending and descending segments were studied individually, each being perfused for a total of 120 min, the circulating solution being removed every 30 min and a fresh solution substituted. At the end of 90 min the gut was rinsed out several times with the solution and the flux measurement made by circulating a known volume of solution through each segment for a further 30 min, observing the change of composition and the amount of ^{42}K entering the

lumen. The specific activity of the plasma K, S_p, was determined at the end of the experiment. The K efflux rate, J_o, was calculated from

$$J_o = -(^{42}K)_l/30bS_p, \quad (2)$$

where $(^{42}K_l)$ = the total amount of ^{42}K which appeared in the perfusate during the 30 min perfusion, b = length of colon perfused. J_o has a negative sign in accordance with a previously discussed convention (Edmonds, 1967*b*). J_n was determined from equation (1) and the K influx rate, J_i, from

$$J_i = J_n - J_o. \quad (3)$$

In calculating J_o from equation (2) it was assumed that loss of ^{42}K by backflux from the lumen during the 30 min perfusion was negligible. This was assumed correct since trial experiments in which perfusion was prolonged and samples taken every 15 min showed that over the first hour $(^{42}K_l)$ rose linearly with time.

^{42}K content of solutions was estimated in 0·2 ml. samples which were pipetted on to *A1* planchets each containing a disk of lens paper. These were dried in an oven and the radioactivity measured using an end-window G.M. counter (20th Century Electronics E.W. 2C). to an accuracy of ±3% (S.D., based on 10 replicates).

Tissue extraction, chemical methods and the measurement of potential difference (p.d.) across the gut wall were carried out as described previously (Edmonds, 1967*b*). Agar salt bridges were prepared with the same composition as the solutions under investigation to avoid contamination of the circulating solutions during the p.d. measurements.

Results are given as means ±1 S.E. of the mean.

RESULTS

Experiments with stable K

Variation in K secretion rate. Lengths of colon of about 7 cm, including some of the ascending and descending segments, were perfused with 150 mM-NaCl in four rats. Six perfusions of 30 min each were carried out consecutively in each rat to examine the variation in the amount of K secreted between one period and another. A coefficient of variation was obtained for each rat and the mean value for the four rats was 8·0%, S.D. ±2·9%. The mean rate of K secretion was calculated for each rat based on the total 180 min of perfusion to examine the variation between the rats. The coefficient of variation here was 32·5%, thus the variation in K secretion rate between rats is considerably greater than between repeated perfusions on the same rat.

Effect of luminal Na concentration on K secretion rate. It was previously shown that when the luminal Na concentration was reduced to about 25 mM, K secretion rate fell (Edmonds, 1967*b*). To examine the effect of removing Na entirely, the K secretion rate was compared when 155 mM-NaCl and 150 mM choline chloride were perfused through ascending and descending segments in four control and four Na-depleted rats (Table 1). In both segments of colon of all rats there was a moderate fall in the K secretion rate when Na was removed from the lumen, the fall being sig-

nificant ($P < 0{\cdot}05$) in all except the descending colon of the control rats. The p.d. also fell when the lumen was Na free.

K net flux. An important point to establish in defining the manner in which a substance crosses a membrane is to compare its distribution across the membrane at equilibrium with the distribution expected from thermodynamic considerations. When the concentration on one side is in equilibrium with that on the other, the unidirectional fluxes are equal and the net flux zero. With *in vivo* experiments the concentration of K on the serosal side of the colonic epithelium can be regarded as constant, being that of the extracellular fluid, while the K concentration in the lumen can be found by determining the concentration at which net flux is zero.

TABLE 1. Effect of presence or absence of Na in the colonic lumen on K secretion rate and transmucosal p.d. in four control and four Na-depleted rats. Results are given as mean ± 1 S.E.

		Ascending colon		Descending colon	
		P.d. (mV)	K secretion rate (n-mole/min/cm)	P.d. (mV)	K secretion rate (n-mole/min/cm)
Control	NaCl	7·9 ± 0·6	36 ± 4·2	9·4 ± 0·9	33 ± 6·4
	Choline Cl	0·9 ± 0·4	25 ± 4·5	1·4 ± 0·5	27 ± 3·6
Na-depleted	NaCl	14·8 ± 9·5	102 ± 8·7	29 ± 1·4 to 53 ± 5·2	101 ± 12
	Choline Cl	1·1 ± 0·4	70 ± 13	4·3 ± 1·1	75 ± 11

When 150 mM-NaCl was in the lumen the p.d. varied little over the length of the gut used in all observations except in the descending colon of the Na-depleted rats. A mean value for p.d. has therefore been given in all except in the latter case when the values at the proximal and distal ends are quoted.

The estimation in the present experiments was done by perfusing solutions of K concentrations, 0, 5, 10, 20 and 40 mM, through colon segments and determining the net flux in each case using equation (1). The 40 mM solution was perfused for one period only of 60 min since it was found in preliminary experiments that the change of K concentration was small and difficult to measure accurately over the shorter period. The most accurate determinations of K net flux were made when the luminal K concentration was low as the change in K concentration was relatively large. When the luminal K concentration was high, the small change of K concentration was difficult to measure precisely and, in addition, water absorption influenced the result of the calculation considerably and its measurement entailed relatively large error (Edmonds, 1967*b*).

In preliminary experiments, it was found that adrenalectomized rats did not survive long if both the ascending and descending segments were used, so in the present experiments only the ascending colon was studied in the adrenalectomized group.

Considering the ascending colon of the control rats first, when the

luminal K concentration was low, K was secreted, the net flux being negative (Fig. 2). As the luminal K concentration was increased K secretion diminished, so that when the 40 mM K solution was perfused the net flux was positive, K then being absorbed from the lumen. Net flux fell linearly in relation to the luminal K concentration over the range examined, and the critical luminal K concentration; that is, the concentration at which J_n was zero was given by the point of intersection of the plotted line with the abscissa.

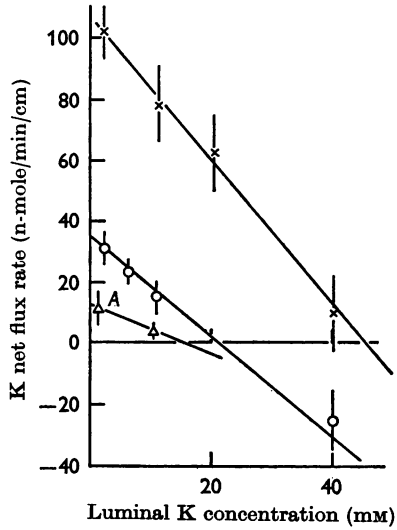

Fig. 2. Net flux rate of K determined for the ascending colon at different luminal K concentrations in nine control, four Na-depleted and six adrenalectomized (*A*) rats. All solutions except that of K concentration 40 mM were perfused for two periods each of 30 min. In the case of the 40 mM-K solution, a single perfusion of 60 min was carried out. Each result is given as a mean ±1 S.E.

With the descending colon and in both segments of colon of the Na-depleted rats, there also appeared to be a linear relationship between the K net flux and the luminal K concentration (Fig. 3). The slopes of the lines were similar in both the ascending and descending segments. After Na depletion, the slope was somewhat steeper in both segments. The most striking difference, however, between the control and Na-depleted state was in the rate of influx of K when there was no K in the lumen, this value J_n^0 being much greater in the Na-depleted rats. The critical luminal K concentration was greater after Na depletion but appeared to be similar in both the ascending and descending segments.

The observations on the adrenalectomized rats were limited as survival time under anaesthetic was relatively short. It was, however, easily

possible to carry out four perfusions on each rat. Consequently, since only two points were obtained, it was not possible in this group to confirm the linear relationship shown in the others. The line drawn through the two points was less steep than that of the control rats and much less so than that observed with the Na-depleted rats. However, the flux J_n^0 was only about half that observed in the control animals, so that the estimated luminal K concentration for zero net flux was about 15 mM.

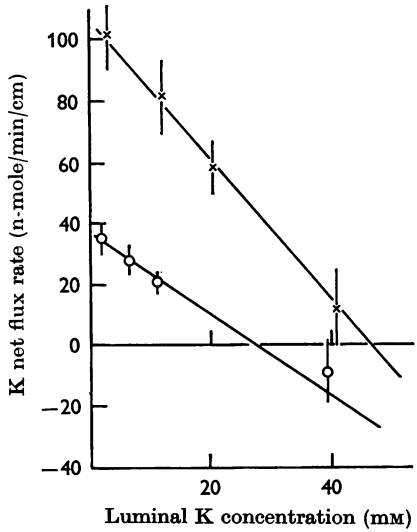

Fig. 3. Net flux rate of K determined for the descending colon at different luminal K concentrations in nine control and four Na-depleted rats. The method used was similar to that for Fig. 2. The symbols are as in Fig. 2 and each result is given as a mean $\pm$ 1 S.E.

The p.d. across the colon was measured in all these experiments (Table 2). The p.d. profile showed the same general picture as already observed (Edmonds, 1967*a*, *b*). There was little variation over both segments of the colon in control rats. After Na depletion, although the p.d. was increased in the ascending colon, there was little variation along the length of the segment but in the descending colon the p.d. rose considerably from the proximal to the distal end. The adrenalectomized rats also showed little variation along the length of the ascending colon and the mean p.d. did not differ significantly from that observed in the control rats.

If the colonic mucosa were behaving in relationship to K simply as a charged barrier allowing diffusion yet not actively transporting K ions, the luminal K concentration at which the net flux would be zero could be calculated from the K concentration on the serosal side of the mucosa and from the p.d., since the net flux would be zero when the electrochemical

TABLE 2. Electrical p.d. and the observed and calculated critical luminal K concentration in control, Na-depleted and adrenalectomized rats. Results are given as mean ± 1 S.E.

		Ascending colon			Descending colon		
			Critical K concentration (mM)			Critical K concentration (mM)	
	No. of rats	P.d. (mV)	Calculated	Observed	P.d. (mV)	Calculated	Observed
Control	9	8·9 ± 0·7	6·4	21	10·2 ± 0·9	6·7	32
Na-depleted	4	14·8 ± 0·5	7·5	45	29 ± 1·4 to 53 ± 5·2	13–32	50
Adrenalectomized	6	7·9 ± 0·9	6·9	14	—	—	—

Where there was little variation of p.d. over the length of the gut segment, the mean p.d. has been used in the Nernst equation to obtain the calculated critical luminal K concentration. In the case of the descending colon of the Na-depleted rats this was not so, however, and so the calculation has been made using the p.d. measurement at each end. In the calculation the mean plasma K was used; for the control group this was 4·6 mM; for the Na-depleted 4·3 mM, and for the adrenalectomized rats 5·1 mM.

potential of K was the same on both sides of the mucosa. The Nernst equation could be applied:

$$[K]_l = [K]_s \exp. (\Delta VF/RT), \quad (4)$$

where $[K]_l$ is the equilibrium luminal K concentration, $[K]_s$ the [K] concentration on the serosal side, ΔV the transmucosal p.d. and F, R and T have their usual significance. The activity coefficients have been omitted here as the plasma and luminal solution were of approximately equal ionic strength.

TABLE 3. Mucosal K content and specific activity determined in normal rats during and after perfusion of solutions of 5 mM and 40 mM-KCl for 3 hr. Results are given as mean ±1 S.E.

Luminal K concentration (mM)	Specific activity of mucosal K S_m (counts/min/μmole)		S_m/S_l	Mucosal K content (μmole/mg dry wt.)
	1st hour	3rd hour		
5	186±22	218±15	0·02±0·004	0·36±0·03
40	1250±111	1144±143	0·13±0·02	0·40±0·02

The perfusion solutions contained NaCl to render them isotonic with 150 mM-NaCl. Three rats were used for each K concentration. One mucosal specimen from ascending and one from descending colon were removed at the times stated. S_l refers to the specific activity of the luminal K.

In Table 2 the equilibrium luminal K concentrations calculated in this way have been compared with the critical luminal K concentrations obtained from the experiments. In all cases the observed values were considerably greater than expected from a simple passive distribution.

Experiments with ^{42}K

Mucosal K. The experiments were carried out on three rats, and as the ascending and descending colon gave similar results they have been treated together. There was no change in the specific activity of the mucosal K (S_m) after the first hour, indicating that the steady state had been reached (Table 3). The ratio S_m/S_l was low when the 5 mM-K solution was perfused, but was considerably higher when 40 mM-K solution was perfused. The K content of the mucosa was not influenced significantly by the K concentration of the luminal solution.

Unidirectional fluxes. In the control state, K influx was considerably less than efflux both in the ascending and descending colon (Table 4). A similar result was obtained in the Na-depleted rats although the difference was even more obvious, the K influx rate being slightly greater than in the controls but the K efflux rate being about 3 times as great.

The p.d. across the colon wall was measured in all experiments, and as found previously (Edmonds, 1967*a*, *b*) Na depletion elevated the p.d.,

TABLE 4. Unidirectional transmucosal K fluxes measured in the ascending and descending colons of four control and four Na-depleted rats when the gut lumen contained a solution of KCl concentration 5 mM rendered isotonic by NaCl. Results are given as mean ± 1 S.E.

	Colon segment	K influx rate J_i (n-mole/min/cm)	K efflux rate J_o (n-mole/min/cm)	P.d. (mV)	J_i/J_o observed	J_i/J_o calculated
Control	Ascending	6·7 ± 2·7	33 ± 3·1	9·1 ± 1·4	0·21 ± 0·03	0·78 ± 0·06
	Descending	5·3 ± 2·0	31 ± 2·2	10·9 ± 1·1	0·17 ± 0·03	0·73 ± 0·02
Na-depleted	Ascending	9·2 ± 3·0	101 ± 8·1	13·4 ± 1·1	0·09 ± 0·03	0·68 ± 0·04
	Descending	10·1 ± 2·2	97 ± 7·9	22 ± 1·7 to 43 ± 3·9	0·1 ± 0·03	0·22 ± 0·02 to 0·48 ± 0·08

Plasma K concentration (mean for all rats) was 4·6 ± 0·2 mM. The calculated value of J_i/J_o was obtained using Ussing's (1949) flux ratio equation as described in the text.

especially in the descending colon. Ussing (1949) has derived an equation to describe the flux ratio when ions move independently across a membrane under the influence of electro-chemical gradient only. Applying to the present situation, it can be stated as

$$\frac{J_i}{J_o} = \frac{\gamma_l [\mathrm{K}]_l}{\gamma_s [\mathrm{K}]_s} \text{exp. } (\Delta VF/RT), \tag{5}$$

where γ_l and γ_s refer to the activity coefficients of the luminal and serosal side solutions respectively and the other symbols are as for equation (4). Since the luminal solution had an ionic composition like that of the plasma and e.c.f. then $\gamma_l = \gamma_s$. The plasma K concentration can be substituted for $[\mathrm{K}]_l$, and as $[\mathrm{K}]_s$ and the p.d. are known, then the expected flux ratios can be calculated.

Comparison of the calculated with the observed values (Table 4) indicated that in all the experiments the observed ratio J_i/J_o was much less than expected if the colonic mucosa were behaving as a simple passive membrane. The discrepancy was most evident in the control state and in the ascending colon of the Na-depleted rats. But even with the descending colon of the latter group, where the observed p.d.s were high, the flux ratio was still not accounted for by electrochemical gradient alone. One possible explanation of the inconsistency between the predictions of Ussing's (1949) equation and the observations was that K was being actively transported from the e.c.f. into the lumen of the colon. Ussing's equation is not, however, entirely unequivocal and other possibilities have to be considered. Solvent drag cannot account for the present findings since the net flow of water was from the lumen to the e.c.f. as the luminal Na concentration was always high. The effect of this flow would cause a deviation from Ussing's equation in a way opposite to that observed. The presence of exchange diffusion also offers no explanation of the observed deviation since it tends to displace the flux ratio towards 1·0, whereas the opposite was the case here.

Interaction between tracer and non-tracer species of the ion, the so-called 'single file' diffusion effect (Hodgkin & Keynes, 1955), is a further source of deviation between observations and the predictions of the flux ratio equation. If this were of importance in the present experiments the flux ratio would be given by

$$\frac{J_i}{J_o} = \left[\frac{\gamma_l [\mathrm{K}]_l}{\gamma_s [\mathrm{K}]_s} \text{exp. } (\Delta VF) \right]^{n+1}, \tag{6}$$

where n = the number of single file positions in the pore, and other symbols have the meanings previously assigned. When $J_i/J_o = 1{\cdot}0$ the above equation deviates little from that of Ussing's and so the 'single file'

effect can be examined by comparing calculated and observed flux ratios at different values of J_i/J_o (Sjodin, 1965). The experiments described earlier showed that K net flux in the colon was zero in the control rats when the luminal K concentration was 25–30 mM and hence when this solution was perfused $J_i/J_o = 1{\cdot}0$. Yet the flux ratio expected from Ussing's equation was 3·8–4·5 (calculated using $[K]_s = 4{\cdot}6$ mM and a p.d. of 10 mV). Thus a similar relationship between the calculated and the observed flux ratio existed here as when 5 mM-K solution was perfused. This result indicated that there was little interaction between the ions flowing in opposite directions across the tissue and that deviation from Ussing's equation on this account would not be expected.

TABLE 5. Effect of luminal K concentration on K efflux rate in normal rats. Results are given as mean ± 1 S.E.

Luminal K concentration (mM)	Ascending colon (n-mole/min/cm)	Descending colon (n-mole/min/cm)
5	30·6 ± 4·8	40·6 ± 7·5
40	28·6 ± 6·2	39·8 ± 8·3

Variation of J_o with luminal K concentration. Four rats received ^{42}KCl by intraperitoneal injection 24 hr before use. The experiments were essentially similar to those carried out for measuring unidirectional flux except that here the object was to compare the value of J_o when 5 mM-K was circulating with that when 40 mM-K was circulating. Each solution was perfused for 1 hr to allow the steady state to be reached and J_o calculated from the S_p and the ^{42}K influx during the periods 60–90 and 90–120 min (Table 5). The K efflux rate was slightly reduced both in the ascending and descending colon when the higher K concentration was in the lumen. There was, however, considerable variability in the results and the differences did not prove to be significant.

DISCUSSION

The relatively high K content of stools compared with ileostomy fluid (Field, Dailey, Boyd & Swell, 1954; Sammons, 1961) and the rise of K concentration in fluid placed in the colon to levels much above that in the blood (D'Agostino, Leadbetter & Schwartz, 1953) suggest that K is secreted by the colonic mucosa. In the present experiments the finding that the critical luminal K concentration was much greater than expected from the observed p.d. and that the unidirectional fluxes were not explicable in terms of passive processes alone indicated unequivocally that the rat colonic mucosa actively transported K from the e.c.f. into the gut lumen.

The value of K net flux was linearly related to the luminal K concentration over the range examined, and since K efflux was constant J_i must have been directly proportional to the luminal K concentration. The observed behaviour was thus consistent with the K influx being due to simple diffusion. There was no evidence that exchange diffusion was significant in K movements. The present findings therefore suggested that K efflux had simply two components—active transport and passive diffusion—while K influx was due to diffusion alone.

The passive permeability coefficient of the mucosa for K was calculated on the following basis. The efflux, J_o, was constant over the range studied and hence was given by J_n^0. Using equation (3) and the data of Figs. 2 and 3 the K influx rate could therefore be obtained for any luminal K concentration and so the K passive permeability coefficient, P_K, calculated. This working does, however, ignore the effect of p.d., and since in the experiments its polarity was such as to reduce the passive flow from lumen to

TABLE 6. Active and passive components of K efflux in normal and Na-depleted rats

	Ascending colon (n-mole/min/cm)		Descending colon (n-mole/min/cm)	
	Active	Passive	Active	Passive
Control	24	10	29	7
Na-depleted	90	18	63	40

Values were calculated as described in text from data of Figs. 2 and 3 when luminal Na concentration was 145–150 mM.

plasma the values of P_K would be underestimated. The error can be corrected for on the basis of Ussing's derivation of the flux ratio equation (Ussing, 1949). When this was done, P_K for the ascending colon of normal rats was $2{\cdot}0 \times 10^{-3}$ cm³/min/cm. Comparison of these values with those of Na permeability (Curran & Schwartz, 1960; Edmonds, 1967*b*) showed that they were of similar magnitude. After Na depletion, however, P_K for the ascending colon was $3{\cdot}1 \times 10^{-3}$ cm³/min/cm, and for the descending, $4{\cdot}2 \times 10^{-3}$ cm³/min/cm. Thus it appeared that this procedure increased mucosal permeability to the passive flow of K ions in contrast to the decrease induced in Na permeability (Edmonds, 1967*b*).

Clapp, Rector & Seldin (1962) in renal micropuncture experiments on rats found that the p.d. across the distal tubular wall was increased by Na depletion and suggested that this change was responsible for the increased K secretion although they were unable to produce conclusive quantitative evidence. The question must now be considered whether the increased colonic K secretion observed in Na depletion was explicable in this way. Using the permeability coefficient obtained above and the observed p.d. the passive diffusion component could be calculated, and when subtracted

from the total efflux the active component obtained (Table 6). The calculation suggested that the increase of p.d. and the permeability change were not adequate to account for the rise of secretion rate in Na depletion and that active transport must therefore have been increased. There was in this estimation, however, the implicit assumption that the permeability coefficient calculated from K influx rate was valid for movement of K in the opposite direction.

That there is a relationship between Na and K transport has been shown in several tissues (e.g. Harris & Maizels, 1951; Hodgkin, 1958; Koefoed-Johnsen & Ussing, 1958; Essig & Leaf, 1963), and it has been suggested that in some cases there may be a definite stoicheiometric relationship (e.g. Harris, 1954; Glynn, 1956). When 150 mM-NaCl was in the colonic lumen of normal rats the rate of active Na absorption was about 250 n-mole/min/cm (Edmonds, 1967*b*), whereas the active K transport rate in the opposite direction was little more than 10 % of this value. Moreover, changes in the luminal Na concentration produced large variations in Na absorption (Curran & Schwartz, 1960; Edmonds, 1967*b*) but little change in K secretion. Even when the luminal Na concentration was zero, although K secretion was reduced, it still continued at a fairly high rate. There appeared thus to be some dependence of K secretion on the luminal Na content but no stoicheiometric relationship was evident in the present experiments.

The active transport of K requires energy expenditure by the colonic mucosa which must be increased when K secretion is stimulated by Na depletion. The question arises whether colonic K secretion serves the organism in some way. That it does so is suggested by the findings of the experiments in which the amount of unabsorbable anion in the gut was increased by giving rats a cation exchange resin (Edmonds, 1967*a*). In normal rats this resulted in a disproportionate stool Na loss, the Na/(Na + K) ratio being considerably greater in the stool water of rats taking resin than in rats not on resin, an effect evidently due to inadequate colonic K secretion. When rats were Na-depleted very little Na was lost in the stool, but, as shown by the present work, K secretion increased considerably under these conditions. Thus it appears that when there is unabsorbable anion in the gut, if the K secretion rate is low, then there will be a large loss of Na as obligatory counter-ion. Gut secretion of K therefore plays an important role in Na conservation.

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