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Alimentary tract and pancreas

Electrophysiology of the human colon: evidence of segmental heterogeneity

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SUMMARY The electrical properties of epithelial cell membranes in human descending and ascending colon were studied using microelectrodes and the Na channel blocker amiloride. Under control (pre-amiloride) conditions, the transepithelial electrical measurements in the two colonic segments were similar. The mucosal addition of 0·1 mM amiloride to descending colon totally abolished the transepithelial voltage (V_t) and short-circuit current (Isc), and significantly increased the total tissue resistance (R_t) by 19% ($p<0·005$). Intracellular recordings in descending colon obtained with microelectrodes revealed that the transepithelial effects of amiloride reflected hyperpolarisation of the apical membrane and a significant increase in apical membrane resistance, changes which were consistent with amiloride-blockade of apical Na channels and complete inhibition of electrogenic Na transport. An appreciable amiloride-insensitive conductance was also present in the apical membrane of the descending colon. In contrast, the mucosal addition of 0·1 mM amiloride to ascending colon decreased V_t by only 30% ($p<0·02$) and Isc by 43% ($p<0·05$), but had no significant effect on R_t. These results indicate that (i) electrogenic Na transport accounts totally for Isc in human descending colon *in vitro*, but only partly for Isc in human ascending colon, suggesting that Na transport in ascending colon is mediated primarily by electroneutral processes, and (ii) the apical membrane of human descending colon contains an amiloride-sensitive conductance for Na in parallel with an amiloride-insensitive conductance, which may transport K.

Segmental differences in the colonic absorption of Na and water have been shown in a variety of species, including man.[1–7] Perfusion studies in human colon indicate that Na and water are absorbed mainly in the ascending and transverse colon,[4 5] while little or no electrolyte and water absorption occurs in the rectum.[5 8] Dialysis studies have provided similar results, with a gradual decrease in Na absorption between the transverse colon and the rectum.[6] Although recent *in vitro* studies have established segmental differences in Na transport processes in rabbit[7 9 10] and rat[11–13] colon, similar studies have not been done in human colon. Those *in vitro* studies that have been carried out on human colonic epithelium have concentrated exclusively on the descending colon,[14–17] and confirmed that active (electrogenic) Na absorption accounts for the high (20–50 mV) transmucosal potential difference observed *in vivo*.[18–20] This potential difference is abolished by the mucosal addition of amiloride,[16] which blocks Na channels in the apical membrane of the surface epithelial (Na transporting) cells.[17] In the present study we have used this property of amiloride to compare the magnitude of electrogenic Na transport in human ascending and descending colon. The results suggest that different mechanisms for Na transport may operate in the ascending and descending segments of the colon in man.

In addition, we have investigated the electrophysiology of human descending colon in more detail using intracellular microelectrodes and amiloride. Our findings are consistent with a cellular model for Na and K transport which is similar to that proposed for rabbit descending colon.[21]

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Methods

PATIENTS

Tissues were obtained from 11 patients (age 33–84

years) undergoing resection of the ascending or descending colon for carcinoma or diverticular disease. In patients with carcinoma, tissue was obtained at least 12 cm from the edge of the tumour. Segments of colon were placed immediately into oxygenated NaCl-Ringer solution at 37°C before transporting to the laboratory. The epithelial layer was dissected free by opening the colon as a flat sheet, rinsing the luminal surface, and then removing serosal muscle and fat using a razor blade with the aid of a stereoscopic microscope, while the tissue was bathed in oxygenated Ringer solution. The isolated epithelium was then mounted between Ussing-type chambers modified to minimise edge damage, and allow temperature regulation and microelectrode impalements from the luminal (apical) side.[22] Dissection and mounting of the tissue was usually completed within 10–15 minutes after removal from the patient. The pH and temperature of the bathing solutions were maintained at 7·4 and 37°C respectively, while being continuously stirred and gassed with 95% O_2–5% CO_2. Tissue surface area was 1·0 cm.^{2}

Tissues were normally bathed with a NaCl–Ringer solution containing (in mmol/l): Na 136·2; K 7·0; Cl 121; Ca 2·0; Mg 1·2; HCO_3 25; H_2PO_4 1·2; SO_4 1·2; and glucose 10·0. This solution was identical to that used in previous studies in rabbit[21] and rat[23] descending colon and contained a slightly higher concentration of K than normally found in human plasma. In preliminary experiments, however, this solution and a similar solution containing K 5·2 mmol/l gave identical transepithelial and microelectrode results, and therefore the solution containing K 7·0 mmol/l was used throughout (see also ref.[17]).

Transepithelial voltage (V_t) was monitored with lM KCl–4% agar bridges placed 5 mm on either side of the tissue, and attached to 3M KCl half-cells. Current pulses were passed across the epithelium *via* Ag-AgCl electrodes located at the back of each chamber. Glass fibre filled microelectrodes (tip diameter <0·5 μm) were prepared with a horizontal pipette puller (Industrial Science Associates, Ridgewood, NY), filled with 0·5 M KCl, and had tip resistances of 40–100MΩ in NaCl-Ringer solution. Cell impalements were carried out from the apical side of the tissue, and microelectodes were positioned with an accuracy of 1 μm using a manually operated hydraulic microdrive (Trent Wells, Southgate, CA). Membrane voltages were measured within ±0·1 mV with a high impedance electrometer (WP Instruments, New Haven, CT, Model 750), and microelectrodes were referenced to the serosal solution such that basolateral membrane voltage (V_{bl}) was monitored directly.

Current pulses were passed using an Anapulse stimulator and stimulus isolation unit (WP Instruments, New Haven, CT, Models 302–T and 305, respectively). Measurements of voltage and current were recorded on a dual-beam oscilloscope (Tektronix, Beaverton, OR, Model D12), and a high frequency response chart recorder (Gould, Cleveland, OH, Model 2200). Apical membrane voltage (V_a) was calculated as $V_a = V_t - V_{bl}$, and the ratio of the changes in apical (ΔV_a) and basolateral (ΔV_{bl}) membrane voltages in response to the current pulse was used to calculate the resistances ratio, α (α=ratio of the apical to basolateral membrane resistances, R_a/R_{bl}). Total tissue resistance (R_t) and α were corrected for series resistance of the bathing solution, as described previously.[10] Amiloride (a gift of Merck, Sharp and Dohme Research Laboratories, West Point, PA) was added to the mucosal bath to a concentration of 0·1 mM by adding aliquots from a 10 mM stock solution.

IMPALEMENT CRITERIA

In all tissues, three to five successful impalements were done before and after the addition of amiloride, and average values of transepithelial and microelectrode measurements were calculated for each tissue before obtaining mean values for the group. Impalements were judged to be acceptable if they met the following criteria: (i) V_{bl} reached a steady value within 10 seconds, (ii) V_{bl} and α remained stable throughout the impalement (generally 30–75 seconds), (iii) the microelectrode tip resistance was unchanged by the impalement, and (iv) the microelectrode recorded the baseline voltage (V_t) upon withdrawal.[21 24] Owing to the limited number of tissues, impalement damage could not be assessed by comparing impalements from the mucosal side with those from the serosal side. Consequently, we cannot completely exclude the possibility of some impalement damage to the apical membrane, and the values of membrane voltages and conductances should be taken as estimates.

Results are expressed as mean ± SEM, and statistical comparisons were undertaken using Student's *t* test for paired or unpaired data as appropriate.[25]

Results

COMPARISON OF TRANSEPITHELIAL MEASUREMENTS IN DESCENDING AND ASCENDING COLON

Table 1 presents values of V_t, Isc and R_t obtained in 13 tissues from the descending colon, and four tissues from the ascending colon. Under control (pre-amiloride) conditions, there were no significant differences in the transepithelial parameters be-

Table 1 *Comparison of transepithelial measurements and the effects of 0·1 mM amiloride in ascending and descending colon*

	V_t (mV)	Isc ($\mu A/cm^2$)	R_t ($\Omega.cm^2$)
Ascending (n=4)			
Pre-amiloride	−10±3	88±31	124±5
Postamiloride	−7±3	50±21	139±3
p*	<0·02	<0·05	NS
Descending (n=13)			
Pre-amiloride	−14±2	97±11	138±10
Postamiloride	−1±1	7±8	164±14
p*	<0·001	<0·001	<0·005

Results are expressed as mean±SEM. Tissues were bathed in NaCl-Ringer solution. Pre- and postamiloride measurements were obtained when values of V_t (transepithelial voltage, mucosal surface negative), Isc (short-circuit current) and R_t (total resistance) were constant. n is the number of tissues studied (from two subjects for ascending colon and nine subjects for descending colon).
*difference between pre- and postamiloride values.

tween the two colonic segments. Transepithelial values for human proximal colon have not been reported previously, but V_t in the descending colon (−14±2 mV) was similar to the mean values reported in other studies.[14 15 17] R_t in the descending colon (138±10 $\Omega.cm^2$) was higher than the previously reported value of 96$\Omega.cm^2$[15]; this difference may reflect (i) our chamber design, which minimised edge damage, or (ii) differences in membrane area due to variations in the degree of tissue stretch, as other investigators[15] have reported values of Isc which were approximately twice that observed in the present study (97±11 $\mu A/cm^2$), or (iii) possible differences between transport rates.

Despite the similarities between the basal transepithelial results in the descending and ascending colon, the two groups of tissues exhibited different responses to the mucosal addition of amiloride (Table 1). In the descending colon, amiloride completely abolished V_t and Isc (postamiloride values of V_t and Isc were not significantly different from zero; $p>0·3$ and $p>0·4$, respectively) and significantly increased R_t by 19% ($p<0·005$). These changes indicate that electrogenic Na transport was entirely responsible for the potential difference across this colonic segment. In contrast, the addition of amiloride to ascending colon decreased V_t by 30% ($p<0·02$) and Isc by 43% ($p<0·05$), but there was no significant change in R_t. Amiloride induced decreases in V_t and Isc in the descending colon (13±2 mV and 90±12 $\mu A/cm^2$, respectively) were significantly greater than those in the ascending colon (3±1 mV, $p<0·05$ and 38±12 $\mu A/cm^2$, $p<0·05$, respectively). These data indicate that the ascending colon is only partially responsive to amiloride – that is, electrogenic Na transport accounts for less than half of the short circuit current and the remainder reflects the transport of other ions.

Transepithelial measurements obtained in descending colon after the addition of amiloride were used to calculate the transepithelial electromotive force (EMF) and the shunt resistance ($R_s=1/G_s$), which is assumed to represent a lumped resistance provided by the paracellular pathway – that is, intercellular tight junction and the lateral interspace,[21 26 27] and any conductance in parallel cell types.[21] According to the simple equivalent circuit shown in Figure 1 (see ref.[21]), the Na transport process can be modelled as a battery (E_{Na}=the transepithelial EMF) in series with the resistive pathway for Na ($R_{Na}=1/G_{Na}$). These are arranged in parallel with R_s. V_t can therefore be described by the equation:

$$V_t = \frac{E_{Na}.G_{Na}}{G_{Na}+G_s}$$

where $E_{Na}.G_{Na}$=Isc (the short circuit current) and $G_{Na}+G_s=G_t$ (the total conductance). By further substitution, $G_t=E_{Na}^{-1}$ (Isc)$+G_s$. It should be noted that the plot of G_t and Isc was linear (Fig. 2), consistent with the assumption that amiloride altered only one circuit parameter – that is, G_{Na}.

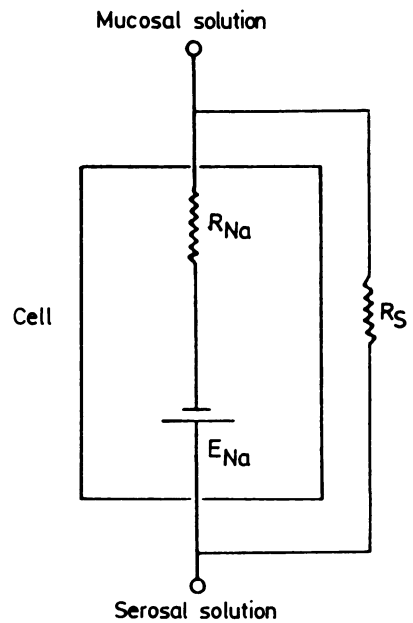

Fig. 1 *Simple equivalent circuit describing Na transport: R_{Na}=resistance of the Na transport pathway; R_s=shunt resistance; E_{Na}=the transepithelial EMF or Na battery.*

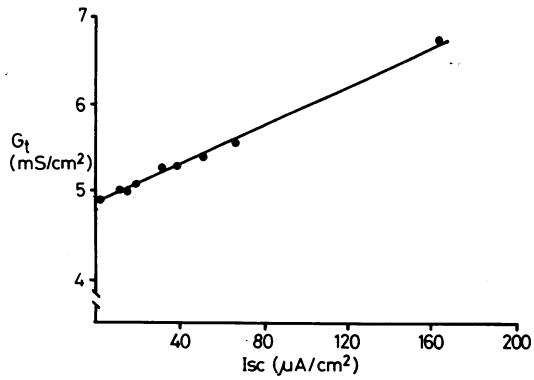

Fig. 2 *Typical experiment showing the effect of amiloride on total tissue conductance (G_t) and short-circuit current (Isc) in human descending colon. Values of G_t and Isc were obtained before (uppermost data point) and at five second intervals after the addition of amiloride to the mucosal solution (final concentration 0·1 mM). For this tissue, linear regression analysis revealed E_{Na} (slope^{-1})=85 mV and G_s (G_t intercept)=4·9 mS/cm² (r=0·998).*

This plot gives an inverse slope of E_{Na} and a G_t intercept equal to G_s. Using this approach, the mean values of E_{Na} and G_s were 82±15 mV and 5·2±0·4 mS/cm² (R_s=197±15 Ω.cm²), respectively (n=6).

MICROELECTRODE MEASUREMENTS IN DESCENDING COLON

Table 2 presents values of V_{bl}, V_a and α (=R_a/R_{bl}) obtained during successful impalements in six tissues from the descending colon. Under control conditions, the values of V_t and R_t were similar to those reported in Table 1. V_{bl} (−37±4 mV) and V_a (20±3 mV) were lower than reported for rat distal colon (V_{bl} ≃−50 mV; V_a≃47 mV, refs[25 28]) and rabbit descending colon (V_{bl}≃−52 mV; V_a≃32 mV, refs[21 29]). The addition of amiloride completely depolarised the epithelium (which mainly reflected hyperpolarisation of the apical membrane (ΔV_a=13±4 mV) as there was no significant change in V_{bl}), and increased R_t by 20% ($p<0·01$) and α by 100% ($p<0·01$). These changes are generally consistent with amiloride blockade of Na conductive channels in the apical membrane.

Table 2 *Effect of 0·1 mM amiloride on microelectrode measurements in descending colon*

	V_t (mV)	R_t (Ω.cm²)	V_{bl} (mV)	V_a (mV)	α
Pre-amiloride	−17±2	157±10	−37±4	20±3	2·0±0·9
Post-amiloride	1±2	189±13	−32±2	33±2	4·0±1·9
p*	<0·005	<0·01	NS	<0·025	<0·01

Results are expressed as mean±SEM. Tissues were bathed with NaCl-Ringer solution. Pre- and postamiloride measurements were obtained when transepithelial measurements were constant. V_t=transepithelial voltage (mucosal surface negative); R_t=total resistance; V_{bl}=basolateral membrane voltage (negative with respect to serosa); V_a=apical membrane voltage (positive with respect to cell interior); α=membrane resistance ratio (calculated as $\Delta V_a/\Delta V_{bl}$; see Methods). Six tissues were studied.
*difference between pre- and postamiloride values.

Discussion

COMPARISON OF TRANSEPITHELIAL ELECTRICAL PROPERTIES OF DESCENDING AND ASCENDING COLON

The transepithelial electrical measurements obtained in human descending colon in the present study agree closely with those reported previously.[14 15 17] Basal electrical measurements in human ascending colon, reported here for the first time. were similar to those in the descending segment. The most striking difference between tissues from the two sites, however, was in their response to amiloride. In descending colon, mucosal addition of amiloride resulted in complete transepithelial depolarisation and a significant decrease in total tissue conductance (ΔG_t 1·1±0·3 mS/cm², $p<0·005$). These changes are consistent with amiloride blockade of apical Na channels, and show that electrogenic Na transport accounts for all[15] or almost all[14 30] of the observed short circuit current in human descending colon. It should be noted, however, that Rask-Madsen and Hjelt[16] found that 75% of net Na absorption across human descending colon persisted in the presence of amiloride. Recent studies by Sellin and DeSoignie[31] in human descending colon have shown similar rates of net Na and Cl absorption under short circuit conditions with net Na absorption almost three times greater than the short circuit current; 0·1 mM amiloride decreased the short circuit current by 80% but inhibited net Na absorption by only 50%. These studies and those of Rask-Madsen and Hjelt suggest that other amiloride insensitive or electroneutral Na transport processes may also operate in this epithelium.

In contrast with the descending colon, the addition of amiloride to ascending colon produced a significant but limited (30%) decrease in transepithelial voltage with a smaller and statistically insignificant increase in total tissue resistance. The relative insensitivity of the ascending colon to amiloride indicates that amiloride sensitive electrogenic Na transport is not the main source of the short circuit current (and hence the transepithelial voltage) in this segment. Although *in vitro* studies

have shown that human transverse and descending colon have similar rates of net Na and Cl absorption and short circuit currents, only 30% of the short circuit current in the transverse colon was amiloride-sensitive.[31] It is possible that varying degrees of amiloride sensitivity are partly related to variations in Na balance and circulating aldosterone levels between different patients. It seems likely, however, that the difference in amiloride sensitivity that we have shown between the descending and ascending colon reflects true regional differences in amiloride sensitive Na transport rather than drug induced or technical artifact, as none of the patients had received corticosteroids, diuretics, or cardiac glycosides before surgery, and care was taken to avoid traumatised areas of resected colon. Although additional studies are required to establish the nature of possible electroneutral Na transport processes it is clear that amiloride sensitive electrogenic Na transport is present in all parts of the human colon and is more marked in the descending segment.

MICROELECTRODE AND AMILORIDE STUDIES IN DESCENDING COLON

The basal intracellular electrical properties of human descending colon are qualitatively similar to those found in rabbit descending colon[21] – that is, apical membrane voltage (positive with respect to cell interior) is appreciably lower than the basolateral membrane voltage (negative with respect to serosal solution). The electrical basis for the basolateral membrane voltage in human descending colon is unclear, but it may reflect a K diffusion potential across the basolateral membrane, as it does in rabbit descending colon;[21] both colonic epithelia possess ouabain sensitive Na,K-ATPase activity in the basolateral membrane which is assumed to mediate cellular K uptake and maintain a high intracellular K concentration.

The addition of amiloride to descending colon resulted in marked hyperpolarisation of the apical membrane (ΔV_a 13±4mV, $p<0.025$) without a significant change in basolateral membrane voltage, and a 100% increase ($p<0.01$) in the membrane resistance ratio (α). These changes reflect amiloride inhibition of apical Na channels and a decrease in apical membrane conductance, and provide the cellular basis for the decreases in transepithelial voltage and total tissue conductance outlined above.

Pre- and postamiloride microelectrode data were used to obtain estimates of individual membrane conductances as previously described for other amiloride sensitive epithelia.[21 24] A number of assumptions have been made in resolving total tissue conductance (G_t) into its apical (G_a), basolateral (G_{bl}) and shunt (G_s) components, and the values are preliminary. First, the method assumes that amiloride selectively decreases G_a without changing G_{bl} and G_s. Human colon was therefore modelled as a simple equivalent circuit, where R_a and R_{bl} were series resistors arranged in parallel with the shunt resistance (R_s), and membrane conductances were calculated by solving the simultaneous equations:

$G_t' = G_s + G_{bl}\ (1+\alpha')^{-1}$ and $G_t'' = G_s + G_{bl}\ (1+\alpha'')^{-1}$

where $G_t = 1/R_t$, $G_s = 1/R_s$ and $G_{bl} = 1/R_{bl}$, and superscripts (′) and (″) denote values before and after the addition of amiloride. If amiloride changes only one circuit parameter—that is, G_{Na} and therefore G_a, as suggested by the data in Figure 2, the drug should increase V_{bl}. The reason for our failure to detect a rise in V_{bl} in the present study is unclear, but it may be related to the necessity to obtain pre- and postamiloride values of V_{bl} from different cells. Second, it is assumed that the ratio of the changes in apical and basolateral membrane voltages that occur in response to the transepithelial current pulse is equal to the membrane resistance ratio ($\alpha = G_{bl}/G_a$). In relatively 'leaky' (low resistance) epithelia this assumption may lead to underestimation of α[32 33] and a degree of error when calculating membrane conductances. Despite these limitations, as an initial step in resolving the membrane properties of this epithelium, we have calculated the inidividual membrane conductances, which are presented in Table 3. These results indicate that amiloride blockade of apical Na channels resulted in a 50% decrease in the apical membrane conductance (G_a). An appreciable apical membrane conductance remained in the presence of amiloride (3·0±0·8 mS/cm^2), however, which could reflect conductive channels for ions other than Na (*vide infra*).

Our previous current fluctuation studies have shown the presence of Na channels in the apical membrane of the human descending colon.[17] If amiloride sensitive Na channels form the main conductive pathway in this membrane, amiloride should, in theory, decrease G_a almost to zero and increase α to an infinitely large value. The postamiloride values of G_a (3·0±0·8 mS/cm^2) and α

Table 3 *Membrane conductances in descending colon*

	G_a (mS/cm^2)	G_{bl} (mS/cm^2)	G_s (mS/cm^2)
Pre-amiloride	6·1±1·4	9·2±3·2	3·3±0·4
Postamiloride	3·0±0·8	–	–
p*	<0·02		

Results are expressed as mean±SEM. Tissues were bathed in NaCl-Ringer solution. G_a, G_{bl} and G_s=apical, basolateral and shunt conductances, respectively. Six tissues were studied.
*Difference between pre- and postamiloride value.

(4·0±1·9) suggest, however, the presence of an appreciable apical conductance, even after the blockade of apical Na channels. Although part of this amiloride insensitive conductance may reflect a small degree of impalement damage or distributed resistance effects, several observations suggest that it mainly represents an apical conductance to another ion(s) – for example, K. First, human descending colon exhibits net K secretion under short circuit conditions, indicating the presence of an active (transcellular) K secretory process.[15 30] Second, our previous current fluctuation and microelectrode studies in human descending colon have shown a K conductance in the apical membrane which may be mediated by K channels; a serosally directed K gradient across the colon produced a Lorentzian component in the power density spectrum which resembled signals from apical K channels in rabbit colon.[17]

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