Review

Salt and water absorption in the human colon: a modern appraisal

Introduction

The past 20 years have seen many advances in all aspects of colonic physiology, and the unrelenting appearance of new information is daunting to clinicians and scientists alike. Nevertheless, we should not lose sight of the fact that the main function of the human colon is to absorb about 90% of the 1.5–2 litres of ileal effluent which passes daily through the ileocaecal valve.[1 2] In mammalian species, the key determinant of colonic water absorption is the rate of Na^+ absorption. We now know that Na^+ transport processes are not distributed uniformly throughout the human colon, a concept which has important clinical implications. This review provides an update on the basic mechanisms underlying salt and water transport in the human colon in health and disease, and highlights several interesting areas for future research.

General description of Na^+ absorptive processes

The human colon has a nominal mucosal surface area of about 2000 cm^2,[3] but in reality the total absorptive area is even greater because colonic crypt cells are capable of absorption as well as secretion.[4] Although it is well established that the rates of colonic salt (Na^+ plus Cl^-) and water absorption are directly related,[5] it is only recently that we have begun to appreciate the array of Na^+ absorptive processes present in human colon. These show considerable intrinsic segmental heterogeneity.[6–10] This explains, at least in part, why the colon's capacity for sodium and water absorption in vivo is greater in the proximal (ascending) segment than in the distal (descending and sigmoid colon/rectum) segment.[11–15] Several different active (transcellular) Na^+ absorptive processes exist in human colon. It will become clear that segmental differences in the distribution and regulation of these processes play an important role in colonic Na^+ salvage during periods of salt deprivation, in the presence of mucosal inflammation, and after surgical resection.

ELECTROGENIC Na^+ ABSORPTION

Electrogenic Na^+ absorption is present throughout the human colon.[6 7 10] The hallmark of this process is the presence of Na^+ channels located predominantly in the apical membrane of surface colonocytes,[6 16] through which Na^+ ions diffuse into the cell along a favourable electrochemical gradient. This gradient reflects the low intracellular Na^+ concentration (<15 mM) and the negative intracellular electrical potential difference.[6 16] Active extrusion of Na^+ ions across the basolateral membrane is mediated by the ouabain sensitive electrogenic Na^+ pump (Na^+,K^+-ATPase). Each pump cycle results in the extrusion of three Na^+ ions in exchange for the basolateral uptake of two K^+ ions, resulting in the net transfer of one positively charged (Na^+) ion across the basolateral membrane (fig 1). As the potential difference across the basolateral membrane (negatively charged with respect to the serosal surface) exceeds that across the apical membrane (negatively charged with respect to the luminal surface), a substantial lumen negative transmucosal potential difference (25–45 mV) is normally present in healthy human colon in vivo and in vitro, which largely reflects electrogenic Na^+ transport.[6 7 10 15 17 18]

An outstanding feature of the classic electrogenic Na^+ absorptive process in "tight" (high electrical resistance) epithelia is its extreme sensitivity to micromolar concentrations of the pyrazine diuretic, amiloride.[19] In general, apical addition of amiloride produces Na^+ channel blockade, inhibition of electrogenic Na^+ absorption, and a reduction or abolition of the transepithelial potential difference. In the human colon, however, the nature and distribution of apical Na^+ conductances, and their responses to amiloride, are more complex. Thus, under in vitro conditions, addition of 0.1–1.0 mM amiloride to distal colon decreases the potential difference by 61–94% and the short-circuit current (an indicator of net transcellular ionic flow when the potential difference is electrically "clamped" to zero) by 76–93%, whereas in proximal colon the electrical changes are minimal.[6 7 20] Furthermore, 1 μM aldosterone stimulates the amiloride sensitive short-circuit current in isolated human distal colon after five hours, but has no effect in human proximal colon despite the presence of aldosterone receptors in this segment.[10 21] The speed of action of aldosterone in human distal colon is consistent with receptor mediated induction of one or more of the three Na^+ channel subunits (designated α, β and γ, see below)[22–24] or an additional channel regulatory protein, the activation of "latent" apical Na^+ channels, or a combination of these possibilities.

Recent progress in defining the structure–function relations of epithelial Na^+ channels is likely to provide new insights into the nature and regulation of Na^+ channels in human colon. The primary structure of the aldosterone induced, amiloride sensitive Na^+ channel in rat distal colonic epithelium has been established by expression cloning.[22–24] Coexpression studies have shown that all three homologous subunits (designated α-, β- and γ-rENaC) are required to produce maximal amiloride sensitive Na^+

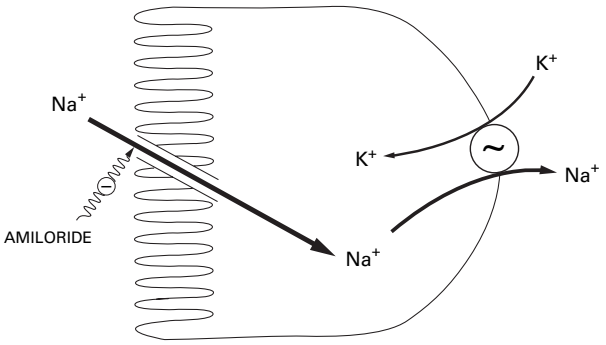

Figure 1 Proposed cellular model of electrogenic Na^+ absorption in human colon. This process is located predominantly in surface colonocytes.[6 16] Apical Na^+ entry is passive, channel mediated, and inhibited by amiloride. Basolateral Na^+ extrusion is mediated by Na^+,K^+-ATPase (the electrogenic "Na^+ pump").

currents in *Xenopus laevis* oocytes, even though the α-rENaC subunit alone is capable of functioning as an amiloride sensitive Na^+ conductor.[24] Equivalent Na^+ channel subunits (designated α-, β- and γ-hENaC) in human kidney and lung (another aldosterone responsive epithelium) have predicted protein sequences which are highly homologous (83–85% identical) to the corresponding subunits in rat distal colon.[25–27] The equivalent human colonic α-subunit clone has recently been isolated from a human distal colonic cDNA library,[28] shown to function as an amiloride sensitive Na^+ channel when expressed in *Xenopus* oocytes,[28] and has an almost identical sequence to human lung α-hENaC (GI Sandle, unpublished data). Although the human colonic β- and γ-subunit clones have yet to be isolated and sequenced, they are not expected to differ significantly (except, perhaps, in their level of tissue expression) from the corresponding clones in human kidney and lung. Nevertheless, either or both of the human colonic Na^+ channel β- and γ-subunits may be important from the standpoint of aldosterone regulated electrogenic Na^+ transport, as aldosterone increases the expression of both the β-subunit and the γ-subunit in rat distal colon.[29]

There seems little doubt that net Na^+ absorption in each region of the human colon has a variable component which is electrogenic but *amiloride insensitive*, and this seems to be most noticeable in the proximal colon.[7–10] In molecular terms, the precise explanations for the segmental differences in amiloride sensitivity and aldosterone responsiveness seen in human colon are presently unclear. Apical Na^+ channels in the proximal colon may differ fundamentally from those in the distal colon in terms of their ability to bind amiloride, which might reflect a post-translational modification of the Na^+ channel protein. However, recent studies using rat lingual circumvillate papillae have shown that a single gene accounts for the Na^+ channel α-subunit and two alternatively spliced variants, one of which exhibits amiloride binding but is incapable of generating amiloride sensitive currents in *Xenopus* oocytes.[30] These findings suggest that the amiloride binding site of the α-subunit is separate and distinct from that part of the subunit which constitutes the channel pore. Thus, different α-subunit isoforms may exist in different regions of the human colon, providing a variety of heteromeric Na^+ channel structures with a range of amiloride sensitivities. In the case of the proximal colon, one or more of these Na^+ channel structures may function as a Na^+ conductance, but have negligible affinity for amiloride. A further possibility is that the apical Na^+ conductance in human proximal colon reflects a population of amiloride insensitive non-selective cation channels, as seems to be the case in rabbit caecum.[31 32] It is not difficult to foresee that strategies combining molecular biology and electrophysiology will eventually identify the cellular basis for the variability of basal and aldosterone induced, amiloride sensitive electrogenic Na^+ transport between different regions of the human colon.

ELECTRONEUTRAL NaCl ABSORPTION

Studies in isolated sheets of human sigmoid colonic and rectal mucosa have shown that 1 mM amiloride applied apically, decreases the short-circuit current to a far greater extent than net Na^+ absorption, which suggests that a substantial fraction of net Na^+ absorption is mediated by a process (or processes) other than amiloride sensitive electrogenic Na^+ transport.[20] It is also clear from other studies that net Na^+ absorption exceeds the short-circuit current, and there is considerable net Cl^- absorption, in the proximal, transverse and distal colonic segments.[9] These findings suggest that an electroneutral Cl^- dependent Na^+ absorptive process is present in all segments of the colon, with the exception of the caecum. In the caecum, net Na^+ absorption equates with the amiloride insensitive short-circuit current and net Cl^- transport is zero,[8] features consistent with amiloride insensitive electrogenic Na^+ transport, which may be mediated by apical non-selective cation channels.[32]

Although electroneutral NaCl absorption has been studied most extensively in rat distal colon, there is good reason to believe that the key components of this process are also present in human colon. In rat distal colon, basal net Na^+ absorption is electroneutral, Cl^- dependent, and inhibited by 1 mM amiloride (a concentration which inhibits apical Na^+–H^+ exchange).[33 34] Furthermore, net Cl^- absorption and net Na^+ absorption are equal and probably regulated by intracellular pH, as both are inhibited by acetazolamide, a carbonic anhydrase inhibitor that reduces endogenous HCO_3^- production.[33 34] Thus, it is now generally accepted that electroneutral NaCl absorption in rat distal colon reflects dual Na^+–H^+:Cl^-–HCO_3^- exchanges operating in parallel in the apical membrane.[35] Studies performed in human colon have been fewer and perhaps less stringent than those performed in rat distal colon. Nevertheless, removal of Na^+ from human proximal and distal colon in vitro decreases the unidirectional Cl^- flux from mucosa to serosa and abolishes net Cl^- absorption, a response consistent with apical Na^+ coupled Cl^- uptake.[9] Theophylline, a cAMP mediated Cl^- secretagogue which stimulates net Cl^- secretion in other intestinal epithelia by inhibiting apical Na^+ coupled Cl^- uptake, has a different effect in the human transverse and distal colon, where it stimulates electrogenic Cl^- secretion, a process which involves the activation of apical Cl^- channels.[9] Other in vitro studies have shown that, to a degree, active Cl^- absorption in human distal colon reflects an electroneutral, Na^+ independent process consistent with Cl^-–HCO_3^- exchange.[8 36] Indeed, in vivo perfusion studies indicate that roughly 25% of the Cl^- absorbed by human colon reflects Cl^-–HCO_3^- exchange, the remainder reflecting passive Cl^- transport along the favourable electrical gradient (lumen negative potential difference) generated by electrogenic Na^+ absorption.[37] Taken together, these observations suggest that electroneutral NaCl absorption throughout the human colon (apart from the caecum) reflects dual apical Na^+–H^+:Cl^-–HCO_3^- exchanges (fig 2), although the presence of a simpler Na^+ coupled Cl^- uptake process cannot be excluded.

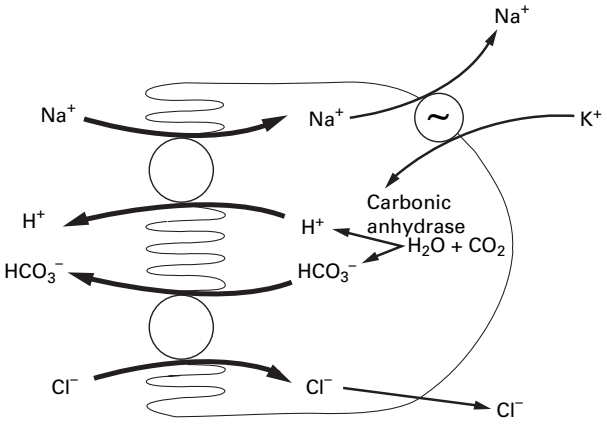

Figure 2 Proposed cellular model of electroneutral NaCl absorption in human colon. This process is localised to surface colonocytes. Apical Na^+ uptake is mediated by Na^+–H^+ exchange, most likely linked by intracellular pH to apical Cl^-–HCO_3^- exchange.[8 9 36] It is not known whether human colonic crypts cells exhibit an electroneutral Na^+ absorptive process similar to that identified in rat distal colonic crypts.[4 38]

SHORT CHAIN FATTY ACID COUPLED Na^+ ABSORPTION

Recent studies have highlighted the role of short chain fatty acid (SCFA) coupled Na^+ absorption in the colonic salvage of carbohydrate, Na^+ and water. Human caecum and proximal colon have high luminal concentrations of organic nutrients (non-starch polysaccharides from plant cell walls, and proteins not absorbed by the small intestine) which maintain high bacterial growth rates.[39] Against this fermentative background, antiperistalsis ensures retention and thorough mixing of faeces in the proximal colon, which is the site of maximal SCFA production.[40] SCFA absorption is concentration dependent and occurs most readily in the proximal colon, which is the prime site for both energy conservation and SCFA dependent Na^+ and water absorption.[41 42] Nutrient concentrations, bacterial growth rates and fermentation rates decrease steadily moving in a caudad direction, and there is a 30% fall in total SCFA concentration and a progressive rise in luminal pH in the distal colon compared with the proximal colon.[43] Of the three SCFAs (acetate, propionate and butyrate) present within the colonic lumen, butyrate is the most important physiologically despite accounting for only about 20% of the total in molar terms. Butyrate serves as a major source of energy for human colonocytes[44] and plays a crucial role in colonocyte growth and differentiation.[45–47]

Although it has been clear for some time that SCFAs enhance Na^+, Cl^- and water absorption in human colon,[41] details of the underlying mechanisms have had to await studies in rat distal colon isolated under voltage clamp conditions. Thus, under HCO_3^--free conditions, 25 mM mucosal butyrate produces a twofold increase in both Na^+ absorption and Cl^- absorption without changing short-circuit current, in keeping with stimulation of electroneutral NaCl absorption.[48] Mucosal addition of 1 mM amiloride inhibits both butyrate stimulated Na^+ and Cl^- absorption, and Cl^- removal from the bathing solution inhibits butyrate stimulated Na^+ absorption. These observations suggest that Na^+–H^+ and Cl^-–butyrate exchanges operate in parallel at the apical membrane.[48] Furthermore, the Cl^-–butyrate exchange and the Cl^-–HCO_3^- exchange seem to be two entirely distinct apical anion transport mechanisms.[49] From these experimental findings arose the initial model linking butyrate absorption to electroneutral NaCl absorption, which entailed protonated butyrate moving across the apical membrane by non-ionic diffusion (fig 3).[48] One problem associated with this model is that the pK_a of SCFA (4.2–4.8) is considerably lower than the luminal pH (7.0–7.4), so that <1% of luminal SCFA is protonated.[50] This obviously runs counter to the idea that non-ionic diffusion is the dominant SCFA absorptive mechanism.

Recent studies using apical membrane vesicles (AMV) prepared from rat distal colon and human proximal and distal colon have provided additional insights into the apical butyrate uptake mechanism and its relation to butyrate stimulated electroneutral NaCl absorption. Firstly, non-ionic diffusion is an insignificant component of total butyrate uptake, and is probably restricted to paracellular pathways.[49] Secondly, an outwardly directed HCO_3^- gradient is an absolute requirement for butyrate uptake, which is consistent with the notion that butyrate–HCO_3^- exchange is the dominant apical butyrate uptake mechanism.[49 51] Thirdly, butyrate stimulated Cl^- absorption reflects recycling of intracellular butyrate via an apical Cl^-–butyrate exchange.[48] In addition, butyrate stimulated electroneutral NaCl absorption is negligible in the distal colon of aldosterone treated rats, in which the mineralocorticoid abolishes apical Na^+–H^+ exchange while simultaneously inducing apical Na^+ channels, providing strong evidence that functional Na^+–H^+ exchange is critical for

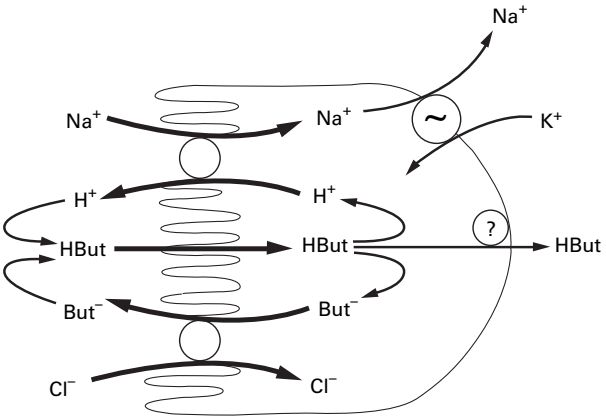

Figure 3 Initial proposed cellular model linking butyrate (But) absorption to electroneutral NaCl absorption (see text for details). Adapted from Rajendran and Binder.[50]

SCFA stimulated electroneutral NaCl absorption.[52] Taken together, these observations support the currently proposed model of butyrate enhanced electroneutral NaCl absorption (fig 4). The main features of this model are: predominantly transcellular butyrate absorption, involving apical butyrate uptake mediated via butyrate–HCO_3^- exchange, leading to intracellular acidification and activation of apical Na^+–H^+ exchange; partial recycling of intracellular butyrate to the lumen via an apical Cl^-–butyrate exchange; and a relatively small component of butyrate absorption by paracellular non-ionic diffusion.

Na^+ AND WATER ABSORPTION BY COLONIC CRYPTS

The idea that (Na^+) absorptive processes are restricted to surface colonocytes and small intestinal villous cells, whereas (Cl^-) secretory processes are restricted to colonic and small intestinal crypt cells, is convenient and has been generally accepted for more than 20 years. This spatial distribution model of intestinal electrolyte transport evolved from studies in mammalian small intestinal and colonic epithelia using a variety of experimental approaches.[53–55] However, the results of studies using microelectrode[56] and voltage scanning[57] techniques challenged the idea of a clear demarcation between the sites of electrolyte absorption and secretion in intestinal epithelia. Thus, both crypt *and* surface/villous cells were found to secrete Cl^- and water when stimulated by cAMP or cAMP mediated secretagogues.

The next milestone in the evolution of our view about the distribution of absorptive processes, at least in the colon, was the suggestion by Naftalin *et al* that crypt cells

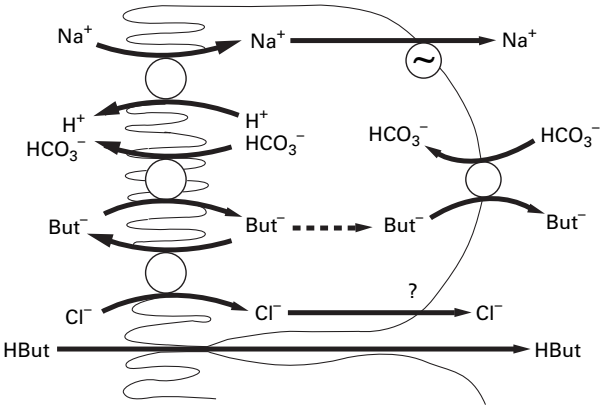

Figure 4 Current proposed cellular model of butyrate (But) stimulated electroneutral NaCl absorption (see text for details). Adapted from Rajendran and Binder.[50]

were capable of Na^+ and water absorption. In a series of studies they showed that rat, rabbit and ovine colonic crypts absorb a Na^+-rich hypertonic fluid.[58–60] This led to the proposal that a large osmotic pressure difference is present across the crypt wall, resulting in a considerable negative hydrostatic pressure within crypt lumina which acts to remove water (by "suction") from faecal material.[58–61] Although those studies forced us to reappraise the functional role of colonic crypts, they provided no direct evidence regarding the mechanisms responsible for crypts functioning in either the absorptive or the secretory mode. However, recent studies from Geibel *et al*, involving microperfusion of hand-dissected single crypts isolated from rat distal colon, have shown that crypts exhibit Na^+ dependent net water absorption in the basal state, whereas the addition of cAMP or calcium mediated Cl^- secretory agonists reverses net water absorption to net water secretion.[4] Thus, water absorption seems to be an inherent function of colonic crypts, and water secretion may occur in response to the release of neurohumoural agents from adjacent cells in the lamina propria.[4] Although the precise nature of the Na^+ transport mechanism(s) responsible for basal Na^+ dependent water absorption is unknown, the same group has located a novel Cl^- dependent Na^+–H^+ exchange in the apical membrane of rat distal colonic crypt cells, which differs from the Cl^- independent apical Na^+–H^+ exchange (NHE-3 isoform) present in surface epithelial cells from the same colonic segment.[38] Although these studies have been performed exclusively in rat distal colon, the use of microperfusion, patch clamp, and cell/molecular biological techniques opens up the exciting possibility of exploring the mechanisms and regulation of electrolyte and water absorption along the surface cell–crypt cell axis in different segments of the human colon.

Salt and water absorption in the diseased colon

INFLAMMATORY BOWEL DISEASE

Decreases in net Na^+ and Cl^- absorption, resulting in impaired water absorption or water secretion, are the main electrolyte transport abnormalities in ulcerative colitis and Crohn's disease of the colon.[62] Despite recent studies showing that soluble inflammatory mediators released from inflamed human colonic mucosa elicit electrogenic Cl^- secretory responses in normal rat distal colonic mucosa,[63] there is no convincing evidence that Cl^- secretion contributes to the pathogenesis of diarrhoea in these two colitides. In active ulcerative colitis, the inflamed colonic mucosa has the features of a "sick" epithelium, with an increased electrical conductance and an enhanced permeability to monovalent ions.[64] In the descending/sigmoid colon and rectum, inflammation results in a notable decrease or loss of the lumen negative transmucosal potential difference, a consequence of both the increase in epithelial permeability and the virtual absence of electrogenic Na^+ transport.[18 64] This reflects a notable (>70%) decrease in basolateral Na^+,K^+-ATPase activity, and possibly also a defect in amiloride sensitive apical Na^+ channels.[64] Loss of the lumen negative potential difference from the inflamed colon results in a decrease in passive Cl^- absorption. It can therefore be seen that impaired water absorption secondary to impaired Na^+ and Cl^- absorption (rather than Cl^- secretion) is a major pathogenic factor in the diarrhoea of acute colitis. It is presently unclear whether inflammation impairs electroneutral NaCl absorption in the human colon, but this seems highly likely as basolateral Na^+,K^+-ATPase is also an essential component of this Na^+ transport process.

Abnormalities in colonic salt and water transport have also been described in microscopic colitis and collagenous colitis. Whether these two conditions should be regarded as related or distinct entities, and whether they occupy a spectrum of colonic inflammatory disorders that includes ulcerative colitis and Crohn's colitis, remains controversial.[65 66] The few studies that have been reported in these relatively uncommon diarrhoeal diseases have been done in vivo. In microscopic colitis, mucosal inflammation is diffuse and variable, and associated with decreases in net water, Na^+ and Cl^- absorption, and Cl^-–HCO_3^- exchange.[67] In contrast to ulcerative colitis, where mucosal damage is usually more severe, the mucosa in microscopic colitis has a normal potential difference and the epithelial permeability to Na^+ and Cl^- seems to be decreased.[67] Thus, impaired colonic water absorption in microscopic colitis may be secondary to a reduction in electroneutral NaCl absorption rather than electrogenic Na^+ absorption. In a single patient with collagenous colitis, saline perfusion of the colon revealed net secretion of Na^+, Cl^- and water, a rise in transmucosal potential difference, and increased intraluminal levels of prostaglandin E_2, which suggests that prostaglandin E_2 stimulated electrogenic Cl^- secretion may contribute to the watery diarrhoea which is typical of this disease.[68] In the light of these rather limited studies, it is tempting to speculate that the range of electrolyte transport defects seen in microscopic, collagenous, and ulcerative/Crohn's colitis reflects different stages of an evolving pattern of epithelial transport dysfunction which is manifested maximally in acute ulcerative colitis. Although in vivo approaches to the study of human colonic fluid and electrolyte transport are generally unfashionable, new and more detailed studies of this type are required in patients with microscopic and collagenous colitis if we are to unravel the pathogenesis of diarrhoea and develop more effective therapeutic strategies for these diseases.

The ability of glucocorticoid hormones to decrease diarrhoea in patients with ulcerative colitis and Crohn's colitis is well known, and generally regarded as part of the general improvement in mucosal function that occurs during suppression of the underlying inflammatory process. However, despite the notable decreases in distal colonic and rectal Na^+, Cl^- and water absorption present in patients with acute ulcerative colitis, single doses of hydrocortisone (100 mg) and methylprednisolone (40 mg) administered parenterally increase net salt and water absorption and stimulate transmucosal potential difference after five hours to the same extent as in normal subjects.[18] It would therefore appear that the high doses of glucocorticoids used in the treatment of ulcerative colitis decrease diarrhoea by exerting a direct stimulatory effect on electrogenic Na^+ absorption (and hence Cl^- and water absorption), in addition to their more general anti-inflammatory action. The "mineralocorticoid-like" effects of high dose hydrocortisone and methylprednisolone reflect considerable cross-over binding to mineralocorticoid receptors, as well as the activation of glucocorticoid receptors.[69 70] Glucocorticoid receptor activation results in the stimulation of electroneutral NaCl absorption,[70] and the glucocorticoids used to treat inflammatory bowel disease probably stimulate both electrogenic Na^+ absorption and electroneutral NaCl absorption in the distal colon and rectum. In colitic patients with strictly distal disease, it is likely that the reduction in stool frequency and volume also reflects stimulation of predominantly electroneutral NaCl absorption (and consequently, water absorption) in the non-inflamed proximal and transverse colonic segments.

COLONIC RESECTION

There is surprisingly little information available about the effects of segmental resection of the human colon on the ability of the remaining colon to absorb salt and water.

Human proximal colon is the site of maximal intraluminal concentrations of SCFAs,[40] as well as having the greatest capacity for Na^+, Cl^-, and water absorption per unit area (a considerable portion of which is likely to be SCFA dependent), compared with other colonic segments.[11–15] However, despite these inherent characteristics of the proximal colon, significant diarrhoea is uncommon in patients after right hemicolectomy if the remainder of the colon is healthy. This raises the possibility that the processes mediating Na^+, Cl^-, and water absorption in the transverse and distal colon and rectum undergo adaptation, as shown in rat distal colon following resection of the proximal segment.[71] As undigested complex carbohydrates and proteins continue to enter the transverse colon after right hemicolectomy, it is also possible that this segment functions as a neo-proximal colon, generating greater than normal intraluminal SCFA concentrations which enhance salt and water absorption throughout the remaining colonic epithelium. Patients undergoing left hemicolectomy are even less likely to develop diarrhoea, given that the descending colon and sigmoid colon normally make a relatively small contribution to the intact colon's overall capacity for salt and water absorption.[11–15] However, these distal regions of the colon are the site of aldosterone regulated electrogenic Na^+ absorption,[10] so that patients with left hemicolectomies may, in theory, be disadvantaged in terms of colonic Na^+ salvage when there is restriction of oral Na^+ intake, excessive sweating, or large fluid losses via high enterocutaneous fistulae.

Future research

This article highlights our current views about the mechanisms of salt and water absorption in healthy and inflamed human colon. Colonic electrolyte transport processes and their regulation remain an active research area. Studies are usually performed in laboratory animals, but species dependent as well as segment dependent differences in basal transport processes mean that much of the data cannot be extrapolated readily to the human colon. In addition to the above-mentioned in vivo and in vitro techniques, the application of molecular biological techniques to colonoscopic biopsy material means that we are poised to make considerable progress in understanding human colonic Na^+ (as well as other electrolyte) transport processes at the intact epithelial, cellular, and molecular levels. Some areas ripe for study have already been mentioned. At present we know little about the role of dysfunctional Na^+ transport in the pathogenesis of diarrhoea in ulcerative colitis. We therefore need to map the distribution of apical Na^+ channel subunits, Na^+–H^+ exchange isoforms and basolateral Na^+,K^+-ATPase (at the levels of both transport proteins and their corresponding mRNAs) along the surface cell–crypt cell axis in different regions of the human colon, and determine the effects of mucosal inflammation. Although right hemicolectomy removes the main site of SCFA production and the most efficient region for Na^+ absorption, the implications for colonic Na^+ salvage remain unclear. Determining the effects of mineralocorticoid and glucocorticoid hormones on the distribution of colonic Na^+ transport proteins will improve our understanding about the changes in Na^+ transport that occur during Na^+ deprivation, following segmental resection, and during corticosteroid treatment of patients with inflammatory bowel disease.

G I SANDLE
Molecular Medicine Unit,
St James's University Hospital,
Beckett Street, Leeds LS9 7TF, UK.

The author's work on colonic Na^+ transport has been supported by the Medical Research Council, Wellcome Trust, Royal Society, North West Regional Health Authority, and British Heart Foundation.

1 Phillips SF, Giller J. The contribution of the colon to electrolyte and water conservation in man. *J Lab Clin Med* 1973;**81**:733–46.
2 Debongnie JC, Phillips SF. Capacity of the human colon to absorb fluid. *Gastroenterology* 1978;**74**:698–703.
3 Edmonds CJ. Absorption of sodium and water by human rectum measured by a dialysis method. *Gut* 1971;**12**:356–62.
4 Singh SK, Binder HJ, Boron WF, *et al*. Fluid absorption in isolated perfused colonic crypts. *J Clin Invest* 1995;**96**:2373–9.
5 Devroede GJ, Phillips SF. Conservation of sodium, chloride, and water by the human colon. *Gastroenterology* 1969;**56**:101–9.
6 Sandle GI, Wills NK, Alles W, *et al*. Electrophysiology of the human colon: evidence for segmental heterogeneity. *Gut* 1986;**27**:999–1005.
7 Sandle GI, McGlone F. Segmental variability of membrane conductances in rat and human colonic epithelia. Implications for Na, K and Cl transport. *Pflügers Arch* 1987;**410**:173–80.
8 Hubel KA, Renquist K, Shirazi S. Ion transport in human cecum, transverse colon, and sigmoid colon in vitro. *Gastroenterology* 1987;**92**:501–7.
9 Sellin JH, De Soignie R. Ion transport in human colon in vitro. *Gastroenterology* 1987;**93**:441–8.
10 Sandle GI. Segmental heterogeneity of basal and aldosterone-induced electrogenic Na transport in human colon. *Pflügers Arch* 1989;**414**:706–12.
11 Levitan R, Fordtran JS, Burrows BA, *et al*. Water and salt absorption in the human colon. *J Clin Invest* 1962;**41**:1754–9.
12 Devroede GJ, Phillips SF. Failure of the human rectum to absorb electrolytes and water. *Gut* 1970;**11**:438–42.
13 Devroede GJ, Phillips SF, Code CF, *et al*. Regional differences in rates of insorption of sodium and water from the human large intestine. *Can J Physiol Pharmacol* 1971;**49**:1023–9.
14 McNeil NI. Differences in electrolyte handling through the human large intestine. In: Skadhauge E, Heintze K, eds. *Intestinal absorption and secretion*. Falk Symposium 36. Lancaster: MTP Press, 1984:111–16.
15 Schiller LR, Santa Ana CA, Morawski SG, *et al*. Effect of amiloride on sodium transport in the proximal, distal and entire human colon in vivo. *Dig Dis Sci* 1988;**33**:969–76.
16 Wills NK, Alles WP, Sandle GI, *et al*. Apical membrane properties and amiloride binding kinetics of the human descending colon. *Am J Physiol* 1984;**247**:G749–57.
17 Sandle GI, Gaiger E, Tapster S, *et al*. Enhanced rectal potassium secretion in chronic renal insufficiency: evidence for large intestinal potassium adaptation in man. *Clin Sci* 1986;**71**:393–401.
18 Sandle GI, Hayslett JP, Binder HJ. Effect of glucocorticoids on rectal transport in normal subjects and patients with ulcerative colitis. *Gut* 1986;**27**:309–16.
19 Benos DJ, Awayda MS, Ismailov II, *et al*. Structure and function of amiloride-sensitive Na^+ channels. *J Memb Biol* 1995;**43**:1–18.
20 Rask-Madsen J, Hjelt K. Effect of amiloride on electrical activity and electrolyte transport in human colon. *Scand J Gastroenterol* 1977;**12**:1–6.
21 Rafestin-Oblin HE, Lombes M, Michel JB, *et al*. Mineralocorticoid receptors in the epithelial cells of human colon and ileum. *J Steroid Biochem* 1984;**20**:311–15.
22 Canessa CM, Horisberger J-D, Rossier BC. Epithelial sodium channel related to proteins involved in neurodegeneration. *Nature* 1993;**361**:467–70.
23 Lingueglia E, Voilley N, Waldmann R, *et al*. Expression cloning of an epithelial amiloride-sensitive Na^+ channel. *FEBS Lett* 1993;**318**:95–9.
24 Canessa CM, Schild L, Buell G, *et al*.Amiloride-sensitive epithelial Na^+ channel is made of three homologous subunits. *Nature* 1994;**367**:463–67.
25 McDonald FJ, Snyder PM, McCray PB, *et al*. Cloning, expression and tissue distribution of a human amiloride-sensitive Na^+ channel. *Am J Physiol* 1994;**266**:L728–34.
26 McDonald FJ, Price MP, Snyder PM, *et al*. Cloning and expression of the β- and γ-subunits of the human epithelial sodium channel. *Am J Physiol* 1995;**268**:C1157–63.
27 Voilley N, Lingueglia E, Champigny G, *et al*. The lung amiloride-sensitive Na^+ channel: biophysical properties, pharmacology, ontogenesis, and molecular cloning. *Proc Natl Acad Sci USA* 1994;**91**:247–51.
28 Baker EH, Boot-Handford RP, Sandle GI. Expression of the human colonic Na^+ channel α-subunit in Xenopus oocytes. *Clin Sci* 1996;**90**(suppl 34):6P.
29 Lingueglia E, Renard S, Waldmann R, *et al*. Different homologous subunits of the amiloride-sensitive Na^+ channel are differently regulated by aldosterone. *J Biol Chem* 1994;**269**:13736–9.
30 Li X-J, Xu R-H, Guggino WB, *et al*. Alternatively spliced forms of the α subunit of the epithelial sodium channel: distinct sites for amiloride binding and channel pore. *Mol Pharmacol* 1995;**47**:1133–40.
31 Hatch M, Freel RW. Electrolyte transport across rabbit caecum in vitro. *Pflügers Arch* 1988;**411**:333–8.
32 Sellin JH, Dubinsky WP. Apical nonspecific cation conductances in rabbit cecum. *Am J Physiol* 1994;**266**:G475–84.
33 Foster ES, Zimmerman TW, Hayslett JP, *et al*. Corticosteroid alteration of active electrolyte transport in rat distal colon. *Am J Physiol* 1983;**245**:G668–75.
34 Binder HJ, Foster ES, Budinger ME, *et al*. Mechanism of electroneutral sodium-chloride absorption in distal colon of the rat. *Gastroenterology* 1987;**93**:449–55.
35 Rajendran VM, Binder HJ. Ion transport in rat colon. *Adv Comp Environ Physiol* 1993;**16**:113–37.
36 Hawker PC, Mashiter KE, Turnberg LA. Mechanisms of transport of Na, Cl, and K in the human colon. *Gastroenterology* 1978;**74**:1241–7.
37 Davis GR, Morawski SG, Santa Ana CA, *et al*. Evaluation of chloride/bicarbonate exchange in the human colon in vivo. *J Clin Invest* 1983;**71**:201–7.
38 Rajendran VM, Geibel JP, Binder HJ. Chloride dependent Na-H exchange: a novel mechanism of Na^+ transport in colonic crypts. *J Biol Chem* 1995;**270**:11051–4.
39 Macfarlane GT, Cummings JH. The colonic flora, fermentation, and large bowel digestive function. In: Phillips SF, Pemberton JH, Shorter RG, eds. *The large intestine: physiology, pathophysiology, and disease*. New York: Raven Press, 1991:51–92.

40 Cummings JH, Pomare EW, Branch WJ, *et al*. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* 1987;**28**: 1221–7.
41 Ruppin H, Bar-Meir S, Soergel KH, *et al*. Absorption of short chain fatty acids by the colon. *Gastroenterology* 1980;**78**:1500–7.
42 Roediger WEW, Moore A. Effect of short chain fatty acid on sodium absorption in isolated human colon perfused through the vascular bed. *Dig Dis Sci* 1981;**26**:100–6.
43 Sandle GI. Segmental differences in colonic function. In: Binder HJ, Cummings J, Soergel K, eds. *Short chain fatty acids*. Falk Symposium 73. Lancaster: Kluwer Academic Publishers, 1994:29–43.
44 Roediger WEW. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa of man. *Gut* 1980;**21**:793–8.
45 Whitehead RH, Young GP, Bhathal PS. Effects of short chain fatty acids on a new human colon carcinoma cell line (LIM 1215). *Gut* 1986;**27**:1457–63.
46 Kim YS, Tsao D, Siddiqui B, *et al*. Effects of sodium butyrate and dimethylsulphoxide on biochemical properties of human colon cancer cells. *Cancer* 1980;**45**:1185–92.
47 Willson JKV. Biology of large bowel cancer. *Hematol Oncol Clin North Am* 1989;**3**:19–34.
48 Binder HJ, Mehta P. Short chain fatty acids stimulate active Na and Cl absorption in vitro in the rat distal colon. *Gastroenterology* 1989;**96**:989–96.
49 Mascolo N, Rajendran VM, Binder HJ. Mechanism of short chain fatty acid uptake by apical membrane vesicles of rat distal colon. *Gastroenterology* 1991;**101**:331–8.
50 Rajendran VM, Binder HJ. Short chain fatty acid stimulation of electroneutral Na-Cl absorption: role of apical SCFA-HCO_3 and SCFA-Cl exchanges. In: Binder HJ, Cummings J, Soergel K, eds. *Short chain fatty acids*. Falk Symposium 73. Lancaster: Kluwer Academic Publishers, 1994: 104–16.
51 Ramaswamy K, Harig J, Soergel KH. Short chain fatty acid transport by human intestinal apical membranes. In: Binder HJ, Cummings J, Soergel K, eds. *Short chain fatty acids*. Falk Symposium 73. Lancaster: Kluwer Academic Publishers, 1994:93–103.
52 Binder HJ, Mehta P. Characterization of butyrate-dependent electroneutral Na-Cl absorption in the rat distal colon. *Pflügers Arch* 1990;**417**:365–9.
53 Nasset ES, Ju JS. Micropipet collection of sucus entericus at crypt ostia of guinea pig jejunum. *Digestion* 1973;**9**:205–11.
54 Welsh MJ, Smith PL, Fromm M, *et al*. Crypts are the site of intestinal fluid and electrolyte secretion. *Science* 1982;**218**:1219–21.
55 Halm DR, Frizzell RA. Ion transport across the large intestine. In: Schultz SG, ed. *Handbook of physiology, section 6: The gastrointestinal system*. Bethesda, MD: American Physiological Society, 1991:257–73.
56 Stewart CP, Turnberg LA. A microelectrode study of responses to secretagogues by epithelial cells on villus and crypt of rat small intestine. *Am J Physiol* 1989;**257**:G334–43.
57 Kockerling A, Fromm M. Origin of cAMP-dependent Cl^- secretion from both crypts and surface epithelia of rat intestine. *Am J Physiol* 1993;**264**:C1294–301.
58 Naftalin RJ, Pedley KC. Video enhanced imaging of the fluorescent Na^+ probe SBFI indicates that colonic crypts absorb fluid by generating a hypertonic interstitial fluid. *FEBS Letters* 1990;**260**:187–94.
59 Bleakman D, Naftalin RJ. Hypertonic fluid absorption from rabbit descending colon in vitro. *Am J Physiol* 1990;**258**:G377–90.
60 Pedley KC, Naftalin RJ. Evidence from fluorescence microscopy and comparative studies that rat, ovine and bovine colonic crypts are absorptive. *J Physiol (Lond)* 1993;**460**:525–47.
61 McKie AT, Goecke AI, Naftalin RJ. Mechanical aspects of fecal dehydration. *Am J Physiol* 1990;**258**:G391–4.
62 Binder HJ, Sandle GI, Rajendran VM. Colonic fluid and electrolyte transport in health and disease. In: Philips SF, Pemberton JH, Shorter RD, eds. *The large intestine: physiology, pathophysiology, and disease*. New York: Raven Press, 1991:141–68.
63 Wardle TD, Turnberg LA. Potential role for interleukin-1 in the pathophysiology of ulcerative colitis. *Clin Sci* 1994;**86**:619–26.
64 Sandle GI, Higgs N, Crowe P, *et al*. Cellular basis for defective electrolyte transport in inflamed colon. *Gastroenterology* 1990;**99**:97–105.
65 Lee E, Schiller LR, Vendrell D, *et al*. Subepithelial collagen table thickness in colon specimens from patients with microscopic colitis and collagenous colitis. *Gastroenterology* 1992;**103**:1790–6.
66 Jawhari A, Talbot IC. Microscopic, lymphocytic and collagenous colitis. *Histopathology* 1996;**29**:101–10.
67 Bo-Linn GW, Vendrell DD, Lee L, *et al*. An evaluation of the significance of microscopic colitis in patients with chronic diarrhea. *J Clin Invest* 1985;**75**: 1559–69.
68 Rask-Madsen J, Grove O, Hansen M, *et al*. Colonic transport of water and electrolytes in a patient with secretory diarrhea due to collagenous colitis. *Dig Dis Sci* 1983;**28**:1141–6.
69 Marusic ET, Hayslett JP, Binder HJ. Corticosteroid-binding studies in cytosol of colonic mucosa of the rat. *Am J Physiol* 1981;**240**:G417–23.
70 Turnamian SG, Binder HJ. Regulation of active sodium and potassium transport in the distal colon of the rat. *J Clin Invest* 1989;**84**:1924–9.
71 Luboshits J, Goldberg G, Chubadi R, *et al*. Functional adaptation of rat remnant colon after proximal hemicolectomy. *Dig Dis Sci* 1992;**37**:175–8.