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Review article: short chain fatty acids in health and disease

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SUMMARY

Short chain fatty acids (SCFAs) have been the subject of much research over the past few decades. They play a vital role in maintenance of colonic integrity and metabolism. They are produced when dietary fibre is fermented by colonic bacteria. SCFAs are avidly absorbed in the colon, at the same time as sodium and water absorption and bicarbonate secretion. Once absorbed, SCFAs are used preferentially as fuel for colonic epithelial cells and have trophic effects on the epithelium. Clinically, SCFAs have been studied as possible therapeutic agents in diversion colitis, ulcerative colitis, radiation proctitis, pouchitis and antibiotic-associated diarrhoea. Although some promising effects have been observed in uncontrolled studies, a specific therapeutic role for SCFAs remains to be defined. SCFAs may be the effector of the beneficial role of fibre in prevention of colon cancer.

INTRODUCTION

Understanding of the role of short chain fatty acids (SCFAs) in gastrointestinal physiology has evolved considerably over the last three decades. Previously they were considered a major factor in the aetiology of carbohydrate-induced diarrhoea, but several basic studies by 'rumen' physiologists, prompted by the fact that cows derive most of their energy from cellulose, demonstrated that SCFAs are easily and rapidly absorbed by the large intestine, which has led to a more general assessment that SCFAs may be beneficial. Present investigations have expanded the role of SCFAs beyond ion transport to include their role as nutrients for the colonic epithelium; as modulators of intracellular pH, cell volume, and other functions associated with ion transport; and as regulators of proliferation, differentiation and gene expression. This, in turn, has led to clinical trials, some of which are promising while others are less clear. In this paper, we review the biological effects underlying the rationale for clinical trials, then discuss results and future roles for SCFAs in clinical medicine.

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SHORT CHAIN FATTY ACIDS

SCFAs are organic fatty acids with 1–6 carbons which arise from bacterial metabolism from 'malabsorbed' carbohydrates entering the colon along with hydrogen gas. A large proportion of this gas volume is consumed by three bacterial reactions: (i) approximately 50% of the population carries methanogenic bacteria that reduce CO_2 to CH_4 consuming H_2 in the process; (ii) non-methane producers habour large numbers of sulphate-reducing bacteria that reduce SO_4 to sulphides, including H_2S; (iii) variable amounts of H_2 are consumed by acetogenic bacteria which reduce CO_2 to acetic acid. Lactic acid is an intermediary product of carbohydrate fermentation, it accumulates only when SCFA production is inhibited in an acidic milieu of pH less than 5.5.[1] There is pathophysiological carbohydrate malabsorption which exists in certain disease states such as sprue and lactose malabsorption. There is also physiological carbohydrate malabsorption, i.e. fermentable substrates entering the colon. These include plant cell wall polysaccharides, referred to as dietary fibre or non-starch polysaccharides, as well as resistant starches that escape digestion in the small intestine.

Table 1. The degree of fermentation of non-starch polysaccharides. Water-soluble polysaccharides such as pectin and psyllium are almost completely fermented by bacterial flora while the insoluble polysaccharides such as cellulose and lignin are minimally fermented.

Non-starch polysaccharides (NSP)	Fermentation (%)
Mono/oligosaccharides	100
Pectin/psyllium	90–95
Bran	70
Cellulose	20
Lignin	0–5

Protein, mucus, sloughed cells and gastrointestinal secretions may also contribute to SCFA production (Table 1).

The type of dietary fibre will determine the rate and degree of fermentation: insoluble fibre is resistant to colonic microflora fermentation and contributes greatly to faecal bulk. Examples of this include cellulose and lignin, of which only 5–20% undergoes anaerobic fermentation in the colon. Water-soluble fibre such as pectin is almost completely fermented by colonic microflora (Figure 1).

Resistant starches make up 10–20% of all starch in the Western diet. The proportion of resistant starch ranges from 75% in green bananas, to 2–10% in bread, to less than 1% in cooked rice.[1] Sugars such as lactose, raffinose and stachyose may not be absorbed in the small intestine and enter the colon. Therefore diets high in fibre, resistant starches and complex carbohydrates will lead to an increased rate of SCFA formation. The major SCFAs involved in mammalian physiology are the straight chain fatty acids acetate c2, propionate c3 and butyrate c4. Valerate c5, hexanoate c6, isobutyrate c4 and isovalerate c5 also occur in the colon but in smaller amounts (5–10% of total SCFAs). The branched chain SCFAs originate from the breakdown of protein and are not produced from carbohydrates.[2] The scope of this paper will be limited to acetate, propionate and butyrate. The normal concentration range of these is 70–100 mM, with a relative ratio of 1 ac : 0.31 prop : 0.15 but.[1, 3]

The principal site of colonic fermentation is the caecum and right colon. Also, pH is lowest in the caecum and increases distally. However, molar ratios of acetate, propionate and butyrate vary little (right colon 1 ac : 0.38 prop : 0.36, but left colon 1 ac : 0.36 prop : 0.37but).[4] SCFA production may shift distally depending on transit time and carbohydrate substrate.

ABSORPTION

Daily production of SCFAs in man is ≈ 100–200 mM. The majority of this is absorbed by the colon. *In vivo*, SCFAs are rapidly absorbed in the colon, associated with enhanced sodium absorption and bicarbonate secretion (Figure 1). The relative proportion of ionized (A-) and protonated (HA) SCFAs is determined by pH. HA is lipid soluble and readily diffuses across cell membranes. A- is not lipid soluble, cannot diffuse into the cell, and therefore requires different pathways across the epithelium. Like all weak electrolytes, the HA/A- equilibrium of SCFAs is dependent on pH and modest differences in pH across membranes can result in significant movement of SCFAs. At normal pH, ≈ 1% of SCFAs is in the protonated form. Two possible mechanisms of absorption have been proposed. (i) *Diffusion of protonated SCFAs*. Luminal protons (from Na/H exchange, $K+H^+$-ATPase, or bacterial metabolic activity) may acidify the colonic lumen leading to increased HA and subsequent diffusion into the cell. The colonic luminal pH is normally somewhat acidic compared to the systemic circulation;

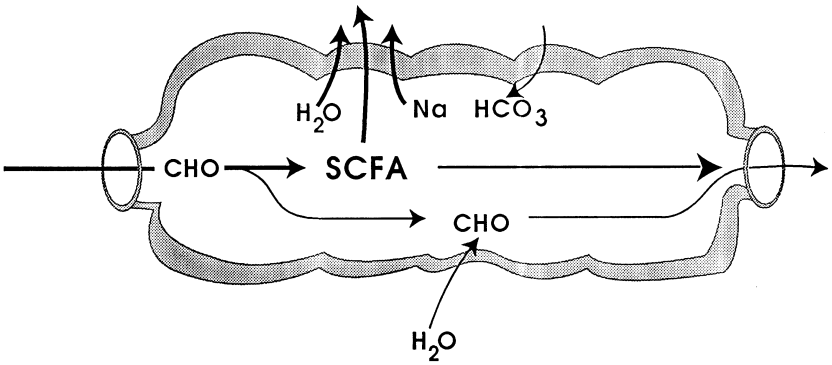

Figure 1. Unabsorbed carbohydrates entering the colon. They are then fermented by bacterial flora to SCFAs. SCFAs are then absorbed with resultant stimulation of sodium and water absorption. If the capacity of colonic flora to metabolize the polysaccharides is exceeded, an osmotic diarrhoea may occur.

this pH gradient may, by itself, promote a diffusive movement of SCFAs. (ii) *Anion exchange*. Studies in membrane vesicles have found evidence for a family of anion exchangers that mediate SCFA : HCO_3 exchange and entry across the apical membrane.[3, 11] Basolateral transport may also use this method; these two anion exchangers differ in kinetic characteristics but share a high degree of specificity for C2–C5 fatty acids.[1]

SCFAs alter the transport of other solutes and electrolytes in the colon and stimulate Na absorption. After protonated SCFAs diffuse into colonocytes, they dissociate, releasing a proton and presumably stimulating an apical Na–H exchanger and electroneutral Na absorption. Charney *et al.* showed that SCFAs inhibit cAMP-mediated Cl^- secretion in rat distal colon.[5] Thus, SCFAs may have both pro-absorptive and antisecretory properties. Finally, SCFA absorption may lead to the formation of discrete pH compartments in the crypts which may alter other acid–base transport and the movement of weak electrolytes. Montrose has shown that SCFA absorption is associated with alkalinization of crypt lumens.[6]

In summary, unabsorbed carbohydrates are fermented to SCFAs which are then absorbed, either by diffusion or anion exchange, and Na and water absorption is stimulated. If the capacity of colonic flora to metabolize carbohydrates is overwhelmed, carbohydrates remain in the colonic lumen, which lacks any appropriate nutrient absorptive pathways, and an osmotic diarrhoea may occur.

Metabolism

Once the SCFAs are absorbed by the colonocyte, they are used locally as fuel for the colonic mucosal epithelial cells. Butyrate is the most important SCFA in colonocyte metabolism, and 70–90% of butyrate is metabolized by the colonocyte. Butyrate is used preferentially over propionate and acetate in a ratio of 90 : 30 : 50. The dependence of the colon on SCFA oxidation increases from caecum to rectum and may be important in the pathogenesis of colitis.[1] Roediger showed that enterocyes oxidize glutamine, ketone bodies and glucose, respectively. On the other hand, 70% of oxygen consumption by colonocytes is due to SCFA oxidation. Acetate and propionate are less avidly metabolized than butyrate and are transported to the liver.

Propionate is a substrate for hepatic gluconeogenesis.[4] It has also been reported to inhibit cholesterol synthesis in hepatic tissue. Thus, the cholesterol-lowering effects of fibre may be secondary to propionate production in the colon.[7] Acetate is utilized in the synthesis of long chain fatty acids, glutamine, glutamate and beta-hydroxybutyrate.[4]

Cell proliferation and blood flow

Diets lacking fibre will lead to mucosal atrophy in the colon. The addition of fibre increases DNA synthesis and DNA content as well as mucosal weight. This trophic effect is mediated by SCFAs. Cecectomized rats fed with a fibre-free diet but infused intracolonically with a 40 mM butyrate solution or a combination of SCFAs showed significant colonic growth as measured by increased mucosal mass, protein, RNA and DNA.[8] *In vitro* studies with normal colonic specimens showed that SCFAs stimulated cell proliferation in the basal 60% of the crypts.[9] The mechanism for locally mediated colonotrophism is multifactorial and may include increases in visceral blood flow, aerobic oxidation of SCFAs for energy, increased production of enterotrophic hormones, and stimulation of the enteric nervous system.[10]

SCFAs also exert a distant trophic effect on small intestinal mucosa.[2] SCFA infusion into innervated rat caecum increased jejunal DNA, villous height, surface area, crypt depth and gastrin levels. In denervated intestine, SCFAs did not significantly affect these variables. Thus, the jejunotrophic effects of SCFAs are, in part, mediated systematically through the extrinsic autonomic nervous system. Gastrin and peptide YY may play a role in SCFA-induced jejunotrophism.[10]

SCFAs, both separately and in combination, have relaxant effects on the colonic resistance arteries *in vitro*. These effects are not mediated by endothelium-derived relaxing factors or prostaglandins; the exact aetiology is unclear.[9] SCFAs also increase blood flow in the dog colon and the human rectum,[10, 11]. Furthermore, intravenous infusion of butyrate into rats increases the mechanical strength of colonic anastomoses as evidenced by an increased bursting pressure and bowel wall tension.[12]

Diversion colitis

Appreciation of the profound biological effects of SCFAs on the colon led to clinical trials in various disease states. The first trials were with diversion colitis. Diversion colitis is an inflammatory process that occurs

in segments of the colorectum after surgical diversion of the faecal stream. Endoscopic appearance of the mucosa includes erythaema, oedema, nodularity, friability, aphthous ulceration, exudates and sometimes even frank bleeding. Histological changes include crypt abscesses, mucin granulomas and lymphoid follicular hyperplasia.[13] Onset occurs between 3 and 36 months after operation. Patients are generally asymptomatic, although abdominal pain, bleeding and stricture formation may occur.[4] Diversion colitis can be difficult to distinguish from active inflammatory bowel disease, but in diversion colitis the inflammation uniformly disappears after surgical reanastomosis.[13] Treatment with topical corticosteroids is not effective.

Harig *et al.*[13] hypothesized that diversion colitis was secondary to a nutritional deficiency of the colonic epithelium, specifically due to the absence of SCFAs normally present in colonic contents. They studied four patients with diversion colitis in whom other sources for a colitis were ruled out. The excluded segment of the rectosigmoid contained negligible concentrations of SCFAs. Rectally instilled D-glucose did not undergo anaerobic fermentation. On the other hand, instillation of an SCFA solution twice daily resulted in an improvement in the endoscopic score over a period of 4–6 weeks compared to saline enemas. Interruption of treatment for 2 weeks resulted in definite worsening of the endoscopic scores. The authors thus concluded that diversion colitis may represent a nutritional deficiency of the diverted colonic epithelium. Replacement of SCFAs (the missing nutrients) resolves the inflammation.[13]

In contrast, Guillemot *et al.*,[14] in a prospective, randomized, double-blind study of 13 patients with diversion colitis, examined the effects of butyrate enemas vs. placebo. There was no improvement in endoscopic or histological parameters in either group after 14 days of therapy. They concluded that SCFAs were not effective in treating diversion colitis. The reason for the differences in these two trials is unclear and thus more work is necessary.

Ulcerative colitis

Studies demonstrating defects in colonic SCFA metabolism in ulcerative colitis have led to clinical trials of SCFA enemas as treatment for distal colitis. Roediger observed impairment in the oxidation of butyrate in isolated colonocytes in patients with active and quiescent ulcerative colitis; this impairment was more marked in the distal colon.[15] This study suggested that ulcerative colitis may be a nutritional deficiency disease. Metabolic inhibition of colonic epithelial SCFA oxidation in rats may induce colitis.[16] Roediger *et al.*[17] showed an increased production of sulphides in ulcerative colitis (up to four times normal). Hydrogen sulphide interacts with co-enzyme A, which may block SCFA dehydrogenase, therefore inhibiting ketogenesis from butyrate. The observation that sulphated polysaccharides such as carrageenan, and dextran sulphate sodium can produce an experimental colitis in rodents provides circumstantial evidence that reducing sulphur compounds may play a role in ulcerative colitis through interference with SCFA metabolism.[18]

If there is a metabolic defect, simple replacement of SCFAs may not correct the underlying deficiency in the oxidation of SCFAs; however, pharmacological replacement may overcome a partial defect. Vernia *et al.*[19] found faecal lactate to be increased in patients with active ulcerative colitis, reaching very high concentrations in severe colitis. This suggests that lactate may be a damaging factor in the human colonic mucosa. In contrast, concentrations of each SCFA, especially butyrate, were reduced. Thus, the colonic mucosa in moderate and severe colitis is deprived of its preferred energy source. This suggests that there may be other changes in SCFA production in the ulcerative colitis colon in addition to a metabolic defect. SCFAs may also modify immune and inflammatory responses.[20] This prompted investigators to see if replacement of SCFAs, particularly butyrate, in luminal contents would have an effect on the inflammation in ulcerative colitis.

Breuer *et al.*[21] conducted a 6-week non-randomized trial in 12 patients with distal colitis. Ten patients were able to complete the study. Each patient used twice daily rectal irrigation with 100 mL of a solution containing acetate (80 mM), propionate (30 mM) and butyrate (40 mM). Nine of the 10 improved clinically and histologically. Scheppach *et al.*[22] treated 10 patients with distal ulcerative colitis unresponsive to standard therapy with Na butyrate enemas for 2 weeks and placebo for 2 weeks. After butyrate instillation, stool frequency decreased and bleeding ceased in 9 of 10 patients. Endoscopic scores improved as well but no changes were seen in the placebo group. Vernia *et al.*[23] studied nine patients with distal ulcerative colitis refractory to standard therapy which included oral 5-ASA and corticosteroids for 6 weeks. They were treated with intrarectal administration of Na butyrate

solution and 5-ASA. Seven of the nine patients showed a marked clinical and endoscopic improvement as evidenced by decreased diarrhoea and bleeding. There was also a small histological improvement seen. Patz *et al.*[15] conducted an open trial involving 10 patients with distal ulcerative colitis who failed to respond to rectal and oral treatment with 5-ASA and corticosteroids. They were treated with twice daily SCFA enemas for 6 weeks. Five of 10 patients improved with four achieving a clinical remission as reflected by a decrease in degree of bleeding, tenesmus, and by global self-assessment. Endoscopic improvement occurred in five patients, but no histological improvement was noted.

Steinhart *et al.*[16] carried out a randomized placebo-controlled trial involving 38 patients with distal ulcerative colitis who received either a nightly butyrate enema or saline/placebo enemas. Clinical improvement was seen in 7 of 19 (37%) butyrate-treated patients and 9 of 19 (47%) placebo-treated patients. Thus, the authors concluded that restoration of SCFAs in luminal contents was not effective in the treatment of ulcerative colitis.

Breuer *et al.*[24] studied 91 patients with distal ulcerative colitis in a 6-week double-blind, placebo-controlled, multicentre trial. More patients using SCFA enemas than those using placebo showed improvement in their clinical and histological activity scores, but these were not significant. Patients with a shorter episode of colitis showed improvement over placebo. Thus, open studies suggest SCFAs may be of benefit, but randomized studies do not clearly show efficacy.

Radiation proctitis

Patients with radiation proctitis may benefit from SCFAs. Injury to the colon can occur after radiation therapy for pelvic malignancies, with radiation-induced proctosigmoiditis the most common clinical presentation.[25] Symptoms of chronic radiation injury include tenesmus, diarrhoea and rectal bleeding. Endoscopically the mucosa appears granular and friable with multiple telangectasias.[26] Histologically the rectum shows marked overall thinning of the mucosa, depletion of mucus cells, crypt abscesses and petechiae. Management of these symptoms has included 5-ASA enemas, steroids and formalin and to-date has been disappointing. Al-Sabbagh *et al.*[27] examined the role of SCFA enemas in radiation proctitis. In this open-labelled study, seven patients with prior pelvic irradiation were treated with SCFA enemas. Treatment was associated with a decrease in the severity score for bleeding but no significant improvement in pain or tenesmus. There were modest improvements in endoscopic and inflammatory scores which were not statistically significant. The authors hypothesized that the beneficial effect of SCFAs may be related to improving regional blood flow, accelerating wound healing, providing a general trophic effect, or ensuring more adequate epithelial energy sources. There is currently a large placebo-controlled multicentre trial under way examining the role of SCFA enemas in radiation proctitis.

Pouchitis

Pouchitis is a non-specific inflammation of the mucosa of the ileal reservoir, following total proctocolectomy for ulcerative colitis and familial polyposis. It occurs in between 8 and 44% of patients.[28] Symptoms include diarrhoea, fever, bloody discharge and malaise. The aetiology of the pouchitis is unclear; bacterial overgrowth has been implicated but has not been clearly proven. Much focus has been placed on the role of SCFAs in this process. Clausen *et al.*[29] found that faecal concentrations of SCFAs in patients with pouchitis were markedly reduced in comparison to asymptomatic patients after colectomy. The 24-h production of total SCFAs in faecal homogenates in patients with pouchitis was decreased, but could be overcome by the addition of saccharides to the homogenates. Thus it was felt that the large volume outputs in pouchitis may affect bacterial fermentation through dilution of available carbohydrates, decreasing the production and concentration of SCFAs. This could then lead to electrolyte and water malabsorption. DeSilva *et al.*[30] treated two patients with pouchitis resistant to 5-ASA, mesalamine and corticosteroids with SCFA enemas. There was no improvement noted in symptoms. Wischmeyer *et al.*[31] also found faecal SCFA levels to be significantly lower than those in asymptomatic control patients. Replacing SCFAs in the form of butyrate suppositories did not improve symptoms. Thus, although SCFA levels may be decreased in pouchitis, there is no evidence to-date that replacement provides a therapeutic benefit.

Antibiotic-associated diarrhoea (AAD)

Diarrhoea in patients on antibiotic therapy is a frequently encountered problem in clinical medicine. One

culprit felt to be responsible for this is *Clostridium difficile*, but the toxin is not present in the majority of cases.[1] Thus, other factors may be important in the aetiology of AAD.

Clausen *et al.*[32] investigated colonic carbohydrate fermentation in three groups of patients—a control group, a group of patients with AAD, and a group of patients receiving antibiotics, but without diarrhoea. Colonic fermentation was markedly impaired in patients with AAD, as reflected by low concentration and production rates of SCFAs. In the antibiotic-treated group without diarrhoea, several of the patients had reduced concentrations and production rates of SCFAs, similar to those in patients with diarrhoea. Impaired colonic fermentation may be a pre-condition for AAD, but does not universally result in diarrhoea. Other factors must be involved. The patients who do develop diarrhoea with antibiotic usage may have a habitually low colonic capacity for fermentation.[32] Decreased SCFA production may impair colonic absorption of sodium and water (see above).[33]

Colon cancer and polyps

Dietary fibre may reduce the risk of colon cancer, but the exact mechanism by which fibre prevents colon cancer is unclear. Several theories have been proposed: fibre increases intestinal transit rate and bulk, therefore decreasing exposure to carcinogens in the diet. It also adsorbs carcinogens, modifies intestinal microflora (and therefore may alter bile salt and carcinogen metabolism). Fibre alters faecal bile salt excretion and lowers the colonic pH.[34] Finally, fibre may exert its protective effects through SCFAs (Table 2).

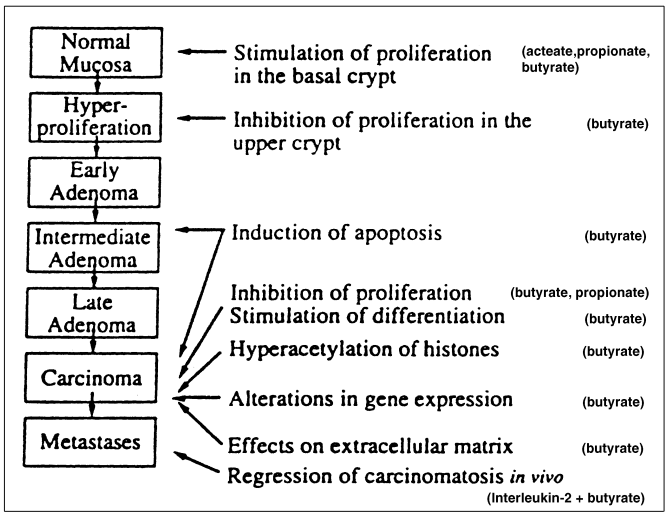

Figure 2. Scheppach article (Figure 1. *Effects of short-chain fatty acids (SCFAs) on colonic epithelial cells at different stages of the adenoma–carcinoma sequence.*).

McIntyre *et al.*[35] looked at different types of dietary fibre in relation to tumorigenesis. It has previously been shown that guar gum and oat bran, while highly fermentable, are associated with decreased butyrate levels in the distal colon, while wheat bran causes much higher butyrate concentrations. Rats were fed these fibres 3 weeks before, 10 weeks during, and for 20 weeks after the administration of the carcinogen dimethylhydrazine; rats were then sacrificed and examined for tumours. Significantly fewer tumours were seen in the rats fed wheat bran compared to the ones fed guar or oat bran. Rats on a no-fibre-added diet had an intermediate tumour mass. Stool analysis showed that the concentration of butyratem but not of acetate, correlated inversely with tumour mass. The authors concluded that dietary fibre associated with increased butyrate concentration in the distal colon is protective against large bowel cancer, while soluble fibres that do not raise distal butyrate concentrations are not protective.

Weaver *et al.*[36] looked at the distribution of SCFAs in enema samples taken from subjects before sigmoidoscopy to see if there was a difference between normals compared to those with polyps/colon cancer or inflammatory bowel disease and diverticulosis. There was a significantly higher ratio of acetate and a decreased ratio of butyrate to total SCFAs in the polyp/colon cancer group compared to normals. There were no significant differences in SCFA ratios between the diverticulosis group, inflammatory bowel disease groups, and the normal controls. These results suggest an alteration in SCFAs may be correlated with the risk for polyps or cancer.

SCFAs have multiple effects on colonic epithelial cells at different stages in growth, development, transformation

Table 2. Protective effects of fibre

1.	Increase in intestinal transit rate.
2.	Increase in intestinal bulk.
3.	Adsorbs carcinogens.
4.	Modifies intestinal microflora.
5.	Alters faecal bile salt excretion.
6.	Lowers the colonic pH.
7.	Productions of SCFAs.

and cell death that may explain a decrease in cancer risk (Figure 2). For tissue homeostasis, the balance between cell gain via mitosis and cell loss by differentiation and programmed cell death (apoptosis) is critical.[37] The disruption of this balance may be important in the pathogenesis of carcinogenesis. SCFAs have an effect on apoptosis in colonocytes, but there appears to be a dichotomy between the effects on normal cells and cancer cell lines. SCFAs induce apoptosis in multiple adenoma and carcinoma cell lines (RG/C2 and AA/C1).[38]

All three SCFAs induce apoptosis, but butyrate does so more efficiently. Certain cancer cells may become relatively resistant to the induction of apoptosis by butyrate. In contrast, butyrate withdrawal caused both a time-dependent hypoplasia and a rapid triggering of massive apoptosis in guinea pig colon *in vitro*, primarily in the G0/G1 phase of the cell cycle.[39]

The difference between SCFA effects on normal and cancer cells can also be seen with proliferation. Although SCFAs have a trophic effect on the normal colon, they may exert an opposite effect on cancer cells. Butyrate has also been shown to inhibit proliferation and stimulate differentiation of human colon cancer cell lines. Kim *et al.*[45] incubated human colonic adenocarcinoma cell lines with Na butyrate (5 mmol/L) for 8 days. Doubling times increased between 1.8- and 7.6-fold while cell viability was not affected. Once butyrate was removed from the medium, rapid cell growth resumed. Barnard & Warwick[40] demonstrated that HT-29 colon adenocarcinoma cell lines were reversibly growth inhibited and induced to differentiate by butyrate at concentrations as low as 0.1–1.0 mM.

The effects of butyrate modulation of proliferation and differentiation in neoplastic cells occurs at the molecular level. Hass *et al.*[46] showed that removal of butyrate from colonic tissue induces increased expression of Bax proteins, which are death-promoting proteins present mainly in the upper region of the crypt, paralleled by rapid apoptosis of colonocytes *in vitro*. Whitlock *et al.*[47] showed that at a concentration of 1–5 mmol/L, butyrate increased histone acetylation dose-dependently by inhibiting histone deacetylase activity. Scheppach *et al.*[41] theorized that the consequence of hyperacetylation may be a release of bonds between DNA and histones, resulting in an increased accessibility of DNA to nucleases and to various factors involved in the control of gene expression. A relatively specific inhibitor of histone hyperacetylation, trichostatin A, can reproduce many of butyrate's effects on cell lines *in vitro*.

The anti-neoplastic effects of SCFAs may be related to altered cell adhesion. Urokinase is secreted by normal[48] and neoplastic[49] colonocytes and may facilitate the penetration of malignant cells into the substratum. Gibson *et al.*[50] showed that butyrate (0.001–4 mmol/L) caused a concentration-dependent inhibition of both secreted and cell-associated urokinase.

Cell-to-cell adhesion, an important event in the differentiation and maintenance of appropriate tissue architecture, is impaired during cancer metastasis. E cadherin is a glycoprotein that mediates cell-to-cell adhesion. Thus, the potential role of SCFAs in colon cancer prevention is diverse, involving apoptosis, proliferation and adhesion.

SCFAs and haemoglobinopathies

Sickle cell anaemia and the beta-thalassaemia syndromes are disorders caused by mutations affecting the adult globin chain of haemoglobin A. In the normal foetus, a switch from production of haemoglobin F to haemoglobin A occurs at 28–34 weeks of gestation. Infants of diabetic mothers were found to have both a delay in this switch and a high plasma level of alpha-amino-*n*-butyric acid.[42] Perrine *et al.*[43] set out to determine whether butyrate can stimulate foetal globin production. They treated three patients with sickle cell anaemia and three patients with beta-thalassaemia syndromes with an intravenous infusion of arginine butyrate. Treatment increased foetal globin synthesis, the proportion of F reticulocytes and the level of foetal globin mRNA. Collins *et al.*[44] treated 11 patients with beta-thalassaemia and one sickle-beta-thalasaemia patient with an oral solution of sodium phenylbutyrate. All patients showed an increase in the percentage of F reticulocytes, but only four patients responded by increasing their haemoglobin levels by greater than 1 g/dL. Butyrate increases haemoglobin in some patients with thalassaemia, but the precise mechanism of action is unknown. The use of SCFAs in the treatment of beta-globin disorders is promising, but further studies on larger populations are warranted.

Mode of delivery

As the role of SCFAs becomes more defined in the treatment of colonic disease, modes of delivery of the

drug to its site of action will also need to be enhanced. Oral SCFAs are absorbed in the small intestine, minimizing the effect on the colon. One method of delivery would be in the form of fibre—but the type of fibre may be an important factor in SCFA production. Soluble fibres are almost 100% fermented in the colon, whereas lignin and cellulose are only partially fermented in the colon. Subtle variations in the type of fibre may result in differences in the ratio of SCFAs produced. Another mode of delivery would involve compounds such as lactulose which are not absorbed in the small intestine but are subject to fermentation in the colon. Finally, pharmacologically designed congeners of SCFAs such as tributyrin or pectin-based systems may provide an oral route of delivery, with bacterial degradation providing targeted release in the colon similar to sulfasalazine.

SCFAs have protean effects on the colon, modulating multiple functions from fluid absorption to cell kinetics. Although there have been many promising reports on the therapeutic benefits of SCFAs in a variety of colitides, most of these studies have been open-labelled or non-randomized. When subject to more rigorous clinical scrutiny, the beneficial effects of SCFAs have been less clear-cut. Although the rationales for treatment may be sound, a convincing demonstration of the efficacy of SCFAs in ulcerative colitis and/or radiation proctitis has not been demonstrated. The role of SCFAs in colon cancer is complex with an unknown clinical significance. The last decade has seen an increased understanding of the basic physiology of SCFAs; perhaps the next decade will more clearly define the clinical role of SCFAs.

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