Bacterial Short Chain Fatty Acids: Their Role in Gastrointestinal Disease

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The human colon harbors vast numbers of bacteria which exceed the number of cells comprising the human body. Short chain fatty acids (SCFAs), namely acetic, propionic and butyric acids, are the principal end products of fermentative metabolism by these bacteria. Polysaccharides of plant cells, conventionally called fiber, have been considered to be the major carbon source for these fatty acids in man [1, 2]. However, recent studies indicate that many types of starch incompletely digested in the small intestine contribute significantly to the production of SCFAs in the colon [3–5]. Of lesser importance as substrates for fermentation are food gums, mucin glycoproteins and sloughed goblet cells, in addition to unabsorbed glucose and oligosaccharides [6, 7]. Protein fermentation occurs to a minor degree in the colon and results in the formation of those SCFAs which are present in only small amounts in the human colon such as isobutyrate, valerate and isovalerate [8].

As SCFAs are rapidly absorbed from the colon, total daily production cannot be readily measured, but indirect estimates range from 200 to 700 mmol/day [9, 10]. SCFA concentrations in feces and fecal water have been summarized elsewhere [1]. Recent studies of victims of sudden death [11] show that concentrations of SCFAs are highest in the cecum (131 mmol/kg of colonic contents) and lowest in the descending colon (80 mmol/kg). SCFA concentrations in the small bowel lumen were low (jejunum < 1 mmol/kg; ileum 13 mmol/kg).

Although some studies suggest that total excretion of fecal SCFAs is independent of dietary composition [12–14], others have demonstrated raised fecal SCFA concentrations when fiber is added to the diet [15, 16]. The molar ratio of individual fatty acids (acetate:propionate:butyrate) can be varied by dietary manipulation. Thus, increased generation of n-butyrate has been observed with starch both in vitro and in vivo [17, 18], a fact that may be of clinical significance.
Role in Gastrointestinal Disease

SCFAs are an important component of the colonic milieu. They play a major physiological role in the normal function of the colon where they affect sodium absorption, epithelial cell nutrition, epithelial proliferation and epithelial cell differentiation, factors which may all be clinically important. Furthermore, they lower colonic luminal pH, leading to effects on bacterial metabolism. The importance of SCFAs in gastrointestinal disease derives largely from these physiological actions. A possible role for SCFAs in various gastrointestinal disorders is considered in the following paragraphs.

Acute Diarrheal Disease

SCFAs are the major anions in the colon and their transport is associated with stimulation of sodium transport from the colon in several species including man [19–21]. This effect may be particularly important in acute diarrheal disease where fasting and purging may deplete the colon of SCFAs [22]. Luminal SCFA levels in the colon may then be a factor determining the duration and severity of acute diarrheal disease. SCFAs have been shown to be clinically important in at least one diarrheal disease of animals – transmissible gastroenteritis of swine [23]. Animals infected with this virus develop an acute enteritis with marked fluid loss from the small intestine. Young animals develop severe diarrhea as their colonic mucosa is incapable of absorbing fluid, whereas older infected animals increase their colonic absorption sevenfold over control. This compensatory response prevents severe diarrhea and is related to the development of colonic fermentation with production of SCFAs [23].

Oral rehydration therapy has dramatically changed the management of acute diarrheal disease. However, oral rehydration therapy is still in the process of being refined and a 'second generation' of solutions attempts to increase the efficiency of rehydration and to shorten the duration of diarrhea by including substrates that may be fermented to SCFAs [28]. Some of the effects of rehydration therapy may lie in understanding the response of the colonic mucosa to bacterial enterotoxins in the presence of SCFAs. Direct application of cholera toxin to the colonic mucosa in experimental animals results in fluid secretion [24]. Similarly, colonoscopic perfusion studies indicate that the large bowel mucosa may be in a secretory state in clinical cholera [25]. Yet, indirect estimates of colonic absorption from ileocecal flow and fecal output in clinical cholera in humans and animals indicate near maximal colonic absorption [26, 27]. Higher levels of luminal SCFAs in the latter situation may explain this apparent contradiction [22].

Experiments were undertaken to test this hypothesis in rats. Fluid secretion was induced in ileal and colonic loops by the application of cholera toxin and Escherichia coli heat-stable enterotoxin. The addition of 40 mmol/l sodium butyrate in the luminal solution significantly reversed fluid secretion in the colon, but not in the ileum (unpublished observations). These results suggest that clinical benefit may derive from measures to increase colonic SCFA levels in acute diarrheal disease. This conclusion is supported by the recent demonstration that addition of food to the standard WHO oral rehydration solution in children with cholera decreased fluid losses and the need for oral rehydration by 50% [28]. The inference is that colonic
SCFA generated from unabsorbed carbohydrate was responsible for at least some of the observed improvement.

**Bile Acid-Induced Diarrhea**

Diarrhea induced by bile acids can be a troublesome side effect after resection of the terminal ileum and ascending colon [29]. SCFAs may play an important role in modifying the response of the mucosa to the entry of bile acids into the colon [30]. Particularly in the proximal colon, SCFAs protect against the secretory effects of bile acids on the mucosa [30], suggesting that preservation of the ascending colon would be desirable in resections of the terminal ileum.

**Postoperative, Starvation and Antibiotic-Associated Diarrhea**

SCFAs are used by colonic epithelial cells as respiratory fuels to provide energy for their various metabolic activities [31, 32]. Human colonocytes use butyrate in preference to glucose or glutamine or ketone bodies as an energy source [31]. Thus, in contrast to small intestinal cells, colonic epithelial cells derive the major part of their energy supplies from the lumen rather than from the blood. This proportion (70% for the entire colon) is greater for the distal than the proximal colon. Removing luminal nutrition of the mucosa by defunctioning the colon induces fluid secretion [33]. This observation may have implications in several diarrheal states characterized by a lack of luminal SCFA in the colon.

Diarrhea is not uncommon after abdominal operations, particularly after closure of a temporary colostomy [34]. This postoperative diarrhea has been attributed to a lack of luminal SCFAs in the colon and may perhaps be reversed by the intake of fermentable substrate [34, 35]. Lengthy preoperative bowel preparations and diminished luminal nutrition probably determine the development of postoperative diarrhea [35].

Lack of luminal SCFAs can similarly explain the diarrhea often seen in the terminal stages of malnutrition. In this situation, specific infections can often not be implicated and it seems likely that diarrhea is a manifestation of organ-specific malnutrition of the colon [36].

Diarrhea is also often associated with the use of broad spectrum antibiotics. Colonization by toxin-producing *Clostridium difficile* accounts for only a third of these cases [37]. The use of oral antibiotics suppresses the formation of SCFAs from fermentable carbohydrate [38], a feature which may also be responsible for diarrhea.

**Ulcerative Colitis**

A failure of SCFA oxidation by colonic epithelial cells has been demonstrated both in vitro [39] and in vivo [40] in ulcerative colitis. Further analysis of diseased colonocytes revealed that utilization of alternative fuels such as glucose and glutamine is comparatively increased. The impairment of fatty acid oxidation persists in the quiescent phase of the disease. Inhibition of fatty acid oxidation experimentally results in the production of colitis [41]. These observations led to the metabolic hypothesis of causation of ulcerative colitis wherein impaired oxidation of fatty acids in colonocytes is postulated to be a primary event in the disease process [42]. This hypothesis may explain the characteristic distribution of the disease, commencing in the distal rectum with proximal spread, as the greatest dependence on SCFAs as metabolic fuels is in the distal colon.
SCFAs may also play a role in some of the clinical manifestations of the disease. The ability of the colonic mucosa to absorb SCFAs in these individuals is impaired [43, 44]. Carbohydrate fermentation in the colon probably continues normally [45]. The diarrhea that follows ingestion of milk in colitics who are hypolactasic has been attributed to the inability of the colonic bacteria to ferment lactose to SCFA [45].

**Diversion Colitis**

Diversion colitis, first described in 1981, is an inflammatory process affecting usually the distal colon and rectum following surgical diversion of the fecal stream [46]. The inflammation disappears after surgical reanastomosis and topical steroids are usually ineffective [46, 47]. Rectal instillation of SCFA has resulted in the disappearance of symptoms and of endoscopic changes over a period of 4–6 weeks, and remission has been maintained for over a year by regular rectal SCFA treatment [48]. This condition therefore probably represents an extreme form of malnutrition of the colonic mucosa. In this situation, management may be guided by a trial of rectal SCFA, which will help to distinguish between diversion colitis and recurrence of inflammatory bowel disease [48].

**Intestinal Adaptation**

Bypass of the hindgut in rats reduces parameters of mucosal growth and replication not only in the colon, but also in the small bowel, suggesting that SCFAs are trophic to the small bowel mucosa as well [49]. After extensive small bowel resection, the introduction of total parenteral nutrition induces intestinal mucosal atrophy [50]. The inclusion of SCFAs in the total parenteral nutrition solution produces significant increases in ileal mucosal protein [50]. Hence, SCFA may be clinically useful in facilitating adaptation to small bowel resection, particularly when total parenteral nutrition is required.

**Healing of Colonic Anastomoses**

After colonic anastomosis, the use of low-residue diets or diverting colostomy is associated with colonic atrophy [51]. In rats, the addition of fermentable substrate or SCFAs significantly improves the healing and strength of anastomoses in the ascending colon [52, 53]. It is presumed that SCFAs stimulate mucosal coverage of the wound by their trophic effects, thus inhibiting excessive inflammation and forming a barrier to bacteria. The effects of SCFAs on the underlying collagenous layer are not known, although this layer is presumably responsible for the strength of the anastomosis. Stimulation of colonic blood flow by SCFAs [54] may also be relevant to anastomotic healing. The clinical inference is drawn from these experiments that SCFAs in the colonic lumen may strengthen anastomoses or accelerate anastomotic healing, particularly in cases where the distal colon has been defunctioned [35].

**Colonic Neoplasia**

Burkitt’s [55] observations were instrumental in linking intake of dietary fiber to the incidence of colon cancer. Some years and numerous studies later, no clear link is yet proven, and dietary factors other than fiber may play a role [56, 57]. However, SCFAs, particularly butyrate, are still believed to be important in colonic carcinogenesis.

SCFAs stimulate cell growth and turnover in the colonic mucosa [58]. Mixtures of SCFAs at physiologic concentrations [59,
perfused through the colonic lumen of anesthetized rats rapidly stimulate labelling and mitotic indices. The proliferative effects of SCFAs were thought to be mediated by the lowering of intraluminal pH, although recent evidence suggests that this is not so [61], and that SCFAs may act directly through specific receptors [60].

The interest in butyrate stems from its pronounced effects on nucleic acid metabolism [62]. It induces cell differentiation in various mammalian cells, including several different human colorectal cancer cell lines [63–65]. Butyrate also suppresses the growth of these cell lines and increases their doubling time. Thus, butyrate is seen as promoting growth and proliferation of the normal colonic mucosa, while suppressing cancer cells. The effects of butyrate on colonic nutrition and proliferation are greatest and its luminal concentrations lowest in the distal colon [11, 66], which is also the site where colonic polyps and cancers occur most frequently. The protective effect of fiber during colorectal carcinogenesis is associated with high rates of proliferation in the normal mucosa [67], suggesting an effect due to SCFAs. However, not all the evidence supports a protective role for butyrate, and under certain experimental circumstances, butyrate may actually increase the development of colonic tumors [68].

Collateral evidence suggesting a role for SCFAs in colon cancer comes from the finding that a low fecal pH – but not dietary fiber intake – correlates closely with the risk of colon cancer [69]. Unabsorbed starch, which is not usually measured as fiber, may be quantitatively more important than fiber as a source of colonic SCFAs [70] and is the usual source of butyrate in the colon [17, 18]. Small bowel absorption of starch is very efficient in patients with colonic polyps compared to normal subjects [71]. It has been suggested that this would lead to a reduction in colonic butyrate levels, and that this may be a key metabolic defect in persons prone to colon cancer. A recent study of fecal SCFAs in patients with cancer or polyps of the colon does confirm a low ratio of butyrate to total SCFAs in these patients [72]. It seems likely that the role of SCFAs in colonic neoplasia will continue to be a worthwhile field of enquiry.

**Cholelithiasis**

An association of gallstones with decreased fiber intake appears to be substantiated by studies in which the addition of wheat bran led to a fall in the cholesterol saturation index of initially supersaturated bile [73, 74]. It has been suggested that this effect is mediated by SCFAs as the same observations have been made with lactulose [75]. Lowering of colonic pH induced by SCFAs is proposed to alter bacterial metabolism of bile salts in the colon, leading to a relative deficiency of the secondary bile acid, deoxycholic acid [75]. This in turn increases biliary levels of chenodeoxycholic acid and decreases the cholesterol saturation of bile. However, this mechanism may not explain similar effects of other fibers on bile composition [76].

**Portal Systemic Encephalopathy**

The clinical benefit from the use of lactulose in chronic portal systemic encephalopathy is attributed to colonic fermentation, either due to increased nitrogen incorporation into bacteria [77] or its effect on ammonia metabolism, as well as the low luminal pH induced by SCFAs which traps ammonia [78, 79]. Diets of vegetable protein have also
been shown to be effective in chronic portal systemic encephalopathy [80]. This may at least partly be attributed to the effects of colonic fermentation and SCFA generation.

**SCFAs and Small Bowel Motility**

As early as 1912 SCFAs, especially acetic acid, were shown to increase peristalsis of small bowel producing either diarrhea or vomiting [81]. SCFAs infused in the human ileum stimulate motility with symptoms of abdominal pain, cramps and an urge to defecate [82]. Clinically, this may be of relevance in bacterial overgrowth syndromes of the small bowel where considerable SCFAs are produced [83].

In summary, SCFAs produced by the anaerobic bacterial flora of the colon play an important role in many diseases of the gastrointestinal tract. Although their use in therapy is presently limited, further research may reveal clinical use for them in the future.

**References**

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