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Influence of Intestinal Inflammation (IBD) and Small and Large Bowel Length on Fecal Short-Chain Fatty Acids and Lactate

HANNE HOVE, MD and PER BRØBECH MORTENSEN, MD, PhD

Treatment with short-chain fatty acids (SCFAs) seems promising in ulcerative colitis and changes in colonocyte oxidation of butyrate have been suggested to be of importance for the development of this disease. The influence of small and large bowel length after surgery on SCFAs is only partly known. SCFAs and lactate were measured in consecutive fecal samples from 300 patients with ulcerative colitis (103), Crohn's disease (127), and noninflammatory bowel disease (70); 205 had had surgery, 52 had short bowels (<200 cm). Lactate (mainly the L-isomer) was elevated in ulcerative colitis patients with pancolitis (mean ± SEM, 17 ± 5 mmol/liter) and proctitis (12 ± 3 mmol/liter) compared with quiescent ulcerative colitis (3 ± 1 mmol/liter, $P < 0.01$), and correlated with the index of Truelove ($R = 0.52$, $P < 0.0005$). Lactate was also increased in Crohn's colitis (21 ± 8 mmol/liter), but not in isolated ileitis (4 ± 2 mmol/liter), compared with quiescent Crohn's disease (7 ± 2 mmol/liter, $P < 0.02$), but did not correlate with the activity index (CDAI; $R = 0.18$, $P = 0.12$). In contrast to earlier reports, SCFAs (including butyrate) did not correlate with inflammatory activity or localization in either ulcerative colitis or Crohn's disease. The length of the small bowel had no influence on SCFAs and lactate in patients with either no colonic function (ileostomies), or with >50% and <50% preserved colorectal length, respectively. Fecal SCFAs from completely (100%) preserved large bowels (89 ± 5 mmol/liter), and from >50% (76 ± 7 mmol/liter) and <50% (72 ± 7 mmol/liter) preserved colons were not significantly different, in contrast to SCFAs from ileorectals (51 ± 10 mmol/liter), ileal reservoirs (57 ± 6 mmol/liter), and ileostomies (20 ± 2 mmol/liter). Fecal lactate is associated with proctocolitis, but not with ileitis. SCFAs were remarkably constant and not influenced by active inflammation in patients with inflammatory bowel disease or extreme differences in the length of the small or large intestine.

KEY WORDS: DL-lactate; short-chain fatty acids; volatile fatty acids; short bowel; Crohn's disease; ulcerative colitis; fermentation.

Short-chain fatty acids (SCFAs; mainly acetate, propionate, and butyrate) derive from bacterial degradation of carbohydrates and proteins in the large bowel. SCFAs are considered of importance for mucosal metabolism, and SCFAs are the major energy-yielding substrate to colonocytes (1) and also affect mucosal cell proliferation (2) and sodium absorption (3). It has been hypothesized that a lack of luminal SCFAs leads to mucosal atrophy and, in the long-term, to "nutritional colitis" (4). This suggestion has been substantiated by the curative effect of luminal-administered SCFAs in diversion colitis (5), which may arise after surgical diversion of the fecal stream

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From the Department of Medicine A, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.

Address for reprint requests: Dr. Hanne Hove, Department of Medicine A, 2151, Rigshospitalet, DK-2100 Copenhagen, Denmark.

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and abates after restoration of colorectal continuity (6, 7). The mucosal lesions seen in patients with diversion colitis have been compared with colonic lesions seen in ulcerative colitis, and decreased fecal concentrations of SCFAs have indeed been reported in patients wtih ulcerative colitis (8, 9) although some controversy exists (10).

Butyrate oxidation has been found to be severely compromised in isolated colonocytes from patients with both active and quiescent ulcerative colitis (11), and it has more recently been proposed that butyrate oxidation may be inhibited by luminal factors suggested to be present in the large bowel of these patients (12). Furthermore, clinical studies have demonstrated sigmoidoscopic and histologic inflammatory regression after treatment with SCFA enemas in patients with ulcerative proctosigmoiditis (13, 14). These observations have increased the expectations of a better understanding and hence treatment of ulcerative colitis and demand further investigations on how ulcerative colitis may change SCFA metabolism in comparison with the other inflammatory bowel disease (IBD), ie, Crohn's disease, and non-IBDs. A decreased luminal content of colonic SCFAs (8, 9) suggests treatment with enemas containing the acids of low fecal concentration. However, the opposite finding of high concentrations of butyrate in active ulcerative colitis (10) may indicate that further addition of this acid may be of minor benefit compared with other SCFAs (acetate and propionate). Lactate is an intermediary organic acid in the bacterial fermentation of carbohydrates and is further converted to SCFAs. However, lactate may also accumulate as a result of inflammation and has been suggested to cause inflammation (15).

The aim of the present study was to assess the influence of inflammatory activity and localization and the consequences of distinct differences in small and large bowel length after surgery by determination of SCFAs and lactate in 300 consecutive fecal samples from gastrointestinal patients.

MATERIALS AND METHODS

Patients. Both hospitalized patients from our gastrointestinal department and patients from the outpatient clinic were instructed to pass a stool into a plastic container. Sampling was conducted by nurses, and the stools were homogenized and frozen at −18°C within 30 min after defecation. Only one sample was collected from each patient and no selection according to diagnosis, disease activity, or age was introduced. No dietary restrictions or recommendations were given. The first 300 consecutive samples collected from a similar number of patients (121 males and 179 females; 11–90 years, mean age 43 years) were analyzed (Table 1). Twenty-six of the 42 nonoperated ulcerative colitis patients and 24 of the 78 Crohn patients with preserved colonic continuity had active inflammation. A further three of 41 patients with ileal reservoir had pouchitis, while only one of 30 Crohn patients with ileostomy had ileitis. Thirty-five non-IBD patients were operated [constipation: ileorectal anastomosis (1) or sigmoidostomy (1); intestinal bypass with jejunoileostomy due to obesity (8) and hyperlipidemia (1); ileus: jejuno- or ileotransversostomy (2), ileoascendostomy (2); mesenteric thrombosis: jejunotransversostomy (2), jejunoascendostomy (2), jejunostomy (1); polyposis coli: ileostomy (1), ileal reservoir (2); radiation enteritis: ileostomy (1), jejunostomy (3); ulcer or gastrinoma: gastroenteroanastomosis (2), Whippel's surgery (2); volvulus: jejunotransversostomy (1), ileoascendostomy (2), ileostomy (1)] (Table 1). Twenty-two patients had jejunostomy defined as functional small intestinal length ≤200 cm. The intestinal length was calculated, if not reported in the record, by subtracting the lengths of

TABLE 1. 300 GASTROINTESTINAL PATIENTS GROUPED ACCORDING TO DIAGNOSIS AND TYPE OF SURGERY

*Diagnosis**	*Patients (N)*
Ulcerative colitis, 103 (34%)	
Not operated	42
Ileorectal anastomosis	2
Ileotransversostomia	1
Pelvic J-pouch	25
Kock continent reservoir	11
Ileostomy	20
Jejunostomy, SB	2
Crohn's disease, 127 (42%)	
Not operated	18
Ileocecal resection	16
Hemicolectomy	15
Ileorectal anastomosis	15
Proctectomy with sigmoidostomy	2
Jejunotransversostomy, SB	12
Ileostomy	30
Jejunostomy, SB	16
Pelvic J-pouch	2
Kock continent reservoir	1
Non-IBD, operated, 35 (12%)	
Constipation	2
Hyperlipidemia, bypass	1
Ileus	4
Mesenteric thrombosis	5
Obesity, bypass	8
Polyposis coli	3
Radiation enteritis	4
Ulcer and gastrinoma	4
Volvulus	4
Non-IBD, not operated, 35 (12%)	
Chronic pancreatitis	2
Cirrhosis	1
Celiac disease	4
Protein-losing enteropathia	2
Gastroenteritis	3
IBS, abdominalia, dyspepsia	22
Lymphoma	1

*IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; SB: short bowel syndrome.

resections from an estimated total intestinal length of 500 cm. The severity of the inflammation in IBD patients was assessed after clinical examination by a physician according to the CDAI (16) and the criteria of Truelove and Witts (17) in immediate association with sample collection. Disease localization was evaluated according to clinical examination (sigmoidoscopy, colonoscopy, pouchoscopy, or x-ray examination). Control DL-lactate and SCFA concentrations in feces were obtained from 20 healthy subjects (8 males and 12 females, mean age 45 years, range 26–81 years) with no history of gastrointestinal disorders. Ethical permission for the study was granted by the Ethics Committee for Medical Research in Copenhagen, and informed consent was obtained from all patients and healthy individuals.

Preparation of Samples and Analysis. Fecal samples were thawed and homogenized with five times their weight of isotonic sodium potassium chloride (NaKCl, 100 mmol/liter NaCl; 50 mmol/liter KCl), and steam distillated as described by Zijlstra et al (18) prior to gas–liquid chromatographic analysis of SCFAs. Distilled sample (0.5 μl) was automatically injected splitless into a Hewlett-Packard 5890A gas chromatograph equipped with a wide-bore, 530-μm (internal diameter), 30-m-long HP-FFAP cross-linked fused silica capillary column with a film thickness of 1 μm (Hewlett-Packard, Palo Alto, California). Carrier and makeup gas was helium with a flow rate of 8 and 20 ml/min, respectively. Injection and flame ionization detector temperatures were 200°C. The oven temperature was 115°C for 2 min before the temperature was raised 5°C/min to 150°C. SCFA concentrations were calculated from areas of gas chromatographic peaks (internal standard was 2-ethylbutyrate) automatically calculated on a Hewlett-Packard 3396A integrator connected on-line to the gas chromatograph. DL-Lactate was measured as the increase in NADH absorbance at 340 nm on a LKB Biochrom 4050 spectrophotometer (Pharmacia, Alleroed, Denmark) using specific L- and D-lactate dehydrogenase (Boehringer Mannheim, Mannheim, Germany) (19). pH was determined by use of a pH-meter (Radiometer, Copenhagen, Denmark).

Statistics. Clinical groups were compared using Student's *t* test or one-way analysis of variance (ANOVA) with an evaluation of differences between individual groups by the test of least significant differences (20). Correlation coefficients were analyzed by simple linear regression. Calculations were performed on an IBM compatible PS/386 personal computer using the software of Statgrafics (Statistical Graphics Co, Inc), and results are reported as mean ± SEM.

RESULTS

A large proportion of the 300 patients had ulcerative colitis (103) or Crohn's disease (127); 205 had had previous surgery, of whom 52 had short bowels or intestinal bypass with 200 cm or less small intestine in function (Table 1), reflecting that our department is a referral center for gastrointestinal diseases.

Data analysis of fecal concentrations of SCFAs and lactate was compared with control subjects (Table 2) and divided into two sections. First, we analyzed the influence of the localization of active inflammation and the indices of inflammatory severity in ulcerative colitis (Tables 3 and 4) and Crohn's disease (Tables 5 and 6). Secondly, we analyzed the influence of the residual length of the small and large bowel in patients with quiescent IBD or non-IBD (Tables 7–9 and Figures 1 and 2).

TABLE 2. SHORT-CHAIN FATTY ACIDS, LACTATE, AND pH IN 20 CONTROLS

Mean ± SEM	*Controls*
mmol/liter	
Total SCFAs	93 ± 8
Acetate	60 ± 4
Propionate	15 ± 2
Butyrate	11 ± 1
Isobutyrate	2 ± 0
Valerate	2 ± 0
Isovalerate	2 ± 0
Hexanoate	1 ± 0
L-Lactate	2 ± 2
D-Lactate	2 ± 1
DL-Lactate	4 ± 3
pH	7.1 ± 0.2
Percent	
Acetate	64 ± 2
Propionate	16 ± 2
Butyrate	12 ± 1
iC4–6*	8 ± 1

*iC4–6: isobutyrate, valerate, isovalerate, and hexanoate.

Concentrations and ratios of SCFAs were normal in patients with quiescent ulcerative colitis, and active inflammatory involvement of an increasing part of the colon did not cause major changes in SCFAs, including butyrate (Table 3). The SCFA concentrations were also unchanged when inflammatory activity was measured by the index of Truelove (Table 4; total SCFAs, analysis of regression: $R = 0.25$, $P = 0.11$). Lactate was normal in patients with quiescent colitis, but increased as inflammation propagated (from 3 ± 1 to 17 ± 5 mmol/liter; $P < 0.01$; Table 3) or increased in indexed severity (from 3 ± 1 to 18 ± 4 mmol/liter; $R = 0.52$, $P < 0.0005$; Table 4), mainly due to an increase in L-lactate ($R = 0.48$, $P < 0.001$), although D-lactate was associated with inflammatory activity as well ($R = 0.42$, $P < 0.01$).

Patients with quiescent Crohn's disease were found to have slightly reduced levels of acetate and, as a consequence, a borderline decrease in total SCFAs in comparison with healthy controls (72 ± 5 and 93 ± 8 mmol/liter, respectively) with no major changes in the percentage of SCFAs (Table 5). Ileitis with or without simultaneous colonic inflammation did not change SCFAs, either when analyzed for site of inflammation (Table 5), or when correlated with the Crohn's disease activity index (CDAI, $R = 0.12$, $P = 0.31$; Table

TABLE 3. SHORT-CHAIN FATTY ACIDS, LACTATE, AND pH IN RELATION TO LOCALIZATION AND EXTENT OF LESION IN 42 NONOPERATED PATIENTS WITH ULCERATIVE COLITIS*

Mean ± SEM	*Quiescent (16)*	*Proctosigmoiditis (18)*	*Pancolitis (8)*	P *(ANOVA)*
mmol/liter				
Total SCFAs	90 ± 12	60 ± 9d	93 ± 25	0.14
Acetate	59 ± 10	38 ± 5d	67 ± 17	0.09
Propionate	13 ± 2	10 ± 2c	11 ± 5	0.60
Butyrate	12 ± 2	8 ± 2	13 ± 4	0.23
Isobutyrate	1 ± 0	1 ± 0	0 ± 0e	0.18
Valerate	2 ± 0	1 ± 0	0 ± 0e	0.12
Isovalerate	2 ± 0	2 ± 0	1 ± 0e	0.23
Hexanoate	1 ± 0	0 ± 0	0 ± 0c	0.02
L-Lactate	2 ± 1a	9 ± 3abd	12 ± 4be	0.01
D-Lactate	1 ± 0	3 ± 1	5 ± 2	0.06
DL-Lactate	3 ± 1a	12 ± 3abd	17 ± 5bd	0.01
pH	6.8 ± 0.1c	6.9 ± 0.1c	6.3 ± 0.2d	0.06
Percent				
Acetate	64 ± 2a	66 ± 2ab	75 ± 4bd	0.01
Propionate	16 ± 1	15 ± 1	11 ± 2c	0.17
Butyrate	14 ± 1	13 ± 1	12 ± 2	0.44
iC4–6	6 ± 1a	6 ± 1a	1 ± 0be	0.01

*iC4–6: isobutyrate, valerate, isovalerate, and hexanoate. One-way analysis of variance (ANOVA). Groups marked with identical letters (a or b) are not significantly different using the test of least significant differences, $P < 0.05$. Groups marked with c, d, or e are significantly different from healthy controls (Table 2); Student's t test: c, $P < 0.05$; d, $P < 0.01$; e, $P < 0.001$.

6). Isolated ileitis without colitis did not change lactate, whereas patients with Crohn's colitis had increased lactate in association with inflammation (from 7 ± 2 to 21 ± 8 mmol/liter, $P < 0.02$; Table 5) as was seen in the patients with ulcerative colitis. The elevation in lactate was primarily caused by the L-isomer, but in contradiction to the Truelove index, lactate did not correlate with the index of inflamma-

TABLE 4. SHORT-CHAIN FATTY ACIDS, LACTATE, AND pH IN RELATION TO SEVERITY OF INFLAMMATION ACCORDING TO TRUELOVE INDEX IN 42 NONOPERATED PATIENTS WITH ULCERATIVE COLITIS

Mean ± SEM	*Quiescent (16)*	*Mild (7)*	*Moderate (7)*	*Severe (12)*	P *(ANOVA)*
mmol/liter					
Total SCFAs	90 ± 12	87 ± 15	68 ± 12	61 ± 9	0.45
Acetate	59 ± 10	53 ± 9	48 ± 9	42 ± 13	0.66
Propionate	13 ± 2	16 ± 4	9 ± 2c	8 ± 4	0.30
Butyrate	12 ± 2	12 ± 2	8 ± 2	9 ± 3	0.55
Isobutyrate	1 ± 0	1 ± 0	1 ± 0	1 ± 0	0.30
Valerate	2 ± 0	2 ± 0	1 ± 0d	1 ± 0d	0.11
Isovalerate	2 ± 0	2 ± 0	1 ± 0c	1 ± 0d	0.32
Hexanoate	1 ± 0	1 ± 0	0 ± 0	0 ± 0c	0.06
L-Lactate	2 ± 1a	7 ± 6ab	9 ± 3abe	13 ± 3be	0.02
D-Lactate	1 ± 0	1 ± 0	4 ± 1	5 ± 2	0.04
DL-Lactate	3 ± 1a	8 ± 6ab	13 ± 4abd	18 ± 4be	0.01
pH	6.8 ± 0.1c	6.9 ± 0.1	6.6 ± 0.2d	6.7 ± 0.2c	0.75
Percent					
Acetate	64 ± 2	62 ± 2	71 ± 3	72 ± 3c	0.08
Propionate	16 ± 1	17 ± 2	14 ± 3	12 ± 2c	0.21
Butyrate	14 ± 1	14 ± 1	11 ± 2	13 ± 1	0.40
iC4–6	6 ± 1	7 ± 2	4 ± 2c	4 ± 1d	0.35

*iC4–6: isobutyrate, valerate, isovalerate, and hexanoate. One-way analysis of variance (ANOVA). Groups marked with identical letters (a or b) are not significantly different using the test of least significant differences, $P < 0.05$. Groups marked with c, d, or e are significantly different from healthy controls (Table 2); Student's t test: c, $P < 0.05$; d, $P < 0.01$; e, $P < 0.001$.

TABLE 5. SHORT-CHAIN FATTY ACIDS, LACTATE, AND pH IN RELATION TO LOCATION OF INFLAMMATION IN 78 PATIENTS WITH CROHN'S DISEASE AND PRESERVED COLONIC AND/OR RECTAL CONTINUITY*

Mean ± SEM	*Quiescent + resection (46)*	*Quiescent − resection (8)*	*Ileitis (13)*	*Ileocolitis (11)*	P *(ANOVA)*
mmol/liter					
Total SCFAs	70 ± 5	87 ± 16	80 ± 12	67 ± 12	0.51
Acetate	43 ± 3cd	51 ± 9	45 ± 6*	44 ± 7	0.78
Propionate	14 ± 2	17 ± 3	18 ± 4	10 ± 3	0.30
Butyrate	8 ± 1	12 ± 2	12 ± 3	9 ± 2	0.35
Isobutyrate	1 ± 0c	2 ± 1	1 ± 0	1 ± 0	0.17
Valerate	1 ± 0	2 ± 1	2 ± 1	1 ± 1	0.29
Isovalerate	2 ± 0	3 ± 1	2 ± 1	2 ± 1	0.19
Hexanoate	1 ± 0	1 ± 0	1 ± 0	1 ± 0	0.82
L-Lactate	4 ± 1a	2 ± 0a	3 ± 2a	14 ± 5bd	0.009
D-Lactate	4 ± 1	2 ± 1	1 ± 0	7 ± 5	0.29
DL-Lactate	8 ± 2a	3 ± 1a	4 ± 2a	21 ± 8bd	0.04
pH	6.4 ± 0.1e	7.0 ± 0.3	6.5 ± 0.2e	6.4 ± 0.2e	0.29
Percent					
Acetate	65 ± 2	60 ± 2	62 ± 4	70 ± 4	0.23
Propionate	19 ± 1	19 ± 1c	19 ± 3	13 ± 2	0.24
Butyrate	11 ± 1	13 ± 1	14 ± 3	12 ± 2	0.45
iC4–6	5 ± 1	9 ± 1	6 ± 1	5 ± 1c	0.20

*iC4–6: isobutyrate, valerate, isovalerate, and hexanoate. One-way analysis of variance (ANOVA). Groups marked with identical letters (a or b) are not significantly different using the test of least significant differences, $P < 0.05$. Groups marked with c, d, or e are significantly different from healthy controls (Table 2); Student's t test: c, $P < 0.05$; d, $P < 0.01$; e, $P < 0.001$.

tion used for Crohn's activity (CDAI; $R = 0.18$, $P = 0.12$).

Concentrations of SCFAs and lactate in relation to intestinal surgery in quiescent IBD and non-IBD patients are shown in Tables 7–9 and Figures 1 and 2.

TABLE 6. SHORT-CHAIN FATTY ACIDS, LACTATE, AND pH IN RELATION TO CDAI SCORE IN 78 PATIENTS WITH CROHN'S DISEASE AND PRESERVED COLONIC AND/OR RECTAL CONTINUITY*

	CDAI score			
Mean ± SEM	*<100 (52)*	*100–150 (12)*	*>150 (14)*	P *(ANOVA)*
mmol/liter				
Total SCFAs	76 ± 5	61 ± 13a	72 ± 10	0.45
Acetate	46 ± 3a	38 ± 7b	42 ± 5b	0.39
Propionate	15 ± 1	11 ± 4	15 ± 4	0.60
Butyrate	10 ± 1	7 ± 3	10 ± 2	0.56
Isobutyrate	1 ± 0	1 ± 1	1 ± 0b	0.70
Valerate	2 ± 0	1 ± 0b	2 ± 1	0.33
Isovalerate	2 ± 0a	2 ± 1	2 ± 0b	0.80
Hexanoate	1 ± 0	1 ± 0	1 ± 0	0.99
L-Lactate	4 ± 1	6 ± 2	8 ± 4	0.45
D-Lactate	3 ± 1	2 ± 1	5 ± 4	0.72
DL-Lactate	8 ± 2	8 ± 3	13 ± 7	0.59
pH	6.5 ± 0.1c	6.6 ± 0.2b	6.4 ± 0.2c	0.80
Percent				
Acetate	64 ± 2	71 ± 4	62 ± 4	0.18
Propionate	18 ± 1	15 ± 3	18 ± 3	0.51
Butyrate	12 ± 1	10 ± 2	14 ± 2	0.17
iC4–6	6 ± 1a	4 ± 1b	6 ± 1	0.56

*iC4–6: isobutyrate, valerate, isovalerate, and hexanoate. One-way analysis of variance (ANOVA). Groups marked with a, b, or c are significantly different from healthy controls (Table 2); Student's t test: a, $P < 0.05$; b, $P < 0.01$; c, $P < 0.001$.

Figure 1 illustrates that the length of the functioning small bowel does not influence the fecal concentrations of SCFAs in patients with 50–100% preserved large bowels (mainly fully intact colons, ileocecal resections, and hemicolectomies), in patients with less than 50% remaining colonic length (including colectomized patients with ileorectal anastomosis), and in patients with no colonic function (jejunostomies and ileostomies), or ileal pouch fermentation chamber. As a consequence, results were pooled without regard to the small bowel length and shown as a function of 100%, >50%, and <50% of remaining colonic length, with the ileorectals as a separate group. These groups were further compared with ileal reservoirs and jejuno-/ileostomies (Figure 2). Fecal concentrations of SCFAs tended to decrease with decreasing colonic length, but total colectomy with the formation of an ileorectal anastomosis or an ileal reservoir had to be performed before statistical significance was obtained. However, the total loss of a "chamber of fermentation" (colon, rectum, or ileal reservoir) did reduce SCFAs to very low levels in the jejuno-/ileostomy group. Detailed information on the influence of small and large bowel length on the individual SCFAs and lactate are given in Tables 7–9. The general impression was that preservation of the colorectal continuity ensured remarkably constant fecal levels and ratios of SCFAs and lactate, comparing groups of patients with considerable differences in

TABLE 7. SHORT-CHAIN FATTY ACIDS, LACTATE, AND pH IN RELATION TO BOWEL SURGERY IN 134 PATIENTS WITH QUIESCENT IBD OR NON-IBD AND PRESERVED COLONIC AND/OR RECTAL CONTINUITY*

	Preserved colon (%) and short bowel (−/+)					
	100%		*>50%*	*<50%*		
Mean ± SEM	− *(61)*	+ *(14)*	− *(15)*	− *(28)*	+ *(16)*	P *(ANOVA)*
mmol/liter						
Total SCFAs	87 ± 6a	101 ± 11a	76 ± 7ab	63 ± 7b	72 ± 10ab	0.03
Acetate	54 ± 4	51 ± 5	44 ± 4	41 ± 4	44 ± 5	0.23
Propionate	14 ± 1a	23 ± 2b	17 ± 3ab	11 ± 2a	14 ± 3ab	0.01
Butyrate	12 ± 1a	15 ± 2a	9 ± 1a	8 ± 1a	9 ± 2a	0.03
Isobutyrate	2 ± 0ab	2 ± 0a	2 ± 0ab	1 ± 0c	1 ± 0bc	$<10^{-3}$
Valerate	2 ± 0b	5 ± 1a	2 ± 1ab	1 ± 0c	1 ± 0c	$<10^{-4}$
Isovalerate	2 ± 0b	4 ± 1a	3 ± 0ab	1 ± 0c	2 ± 1bc	$<10^{-3}$
Hexanoate	1 ± 0b	2 ± 1a	0 ± 0bc	0 ± 0c	1 ± 0bc	$<10^{-3}$
L-Lactate	2 ± 1	2 ± 0	1 ± 0	5 ± 2	6 ± 2	0.14
D-Lactate	2 ± 1	2 ± 0	2 ± 1	3 ± 1	5 ± 2	0.45
DL-Lactate	4 ± 2	4 ± 1	4 ± 1	8 ± 3	13 ± 4	0.21
pH	6.9 ± 0.1a	6.4 ± 0.1ab	6.9 ± 0.2a	6.5 ± 0.1ab	6.1 ± 0.2b	$<10^{-3}$
Percent						
Acetate	63 ± 1a	51 ± 2b	60 ± 3ab	68 ± 2a	67 ± 4a	$<10^{-3}$
Propionate	16 ± 1a	23 ± 2b	20 ± 2ab	16 ± 2a	18 ± 2ab	0.01
Butyrate	14 ± 1	14 ± 1	12 ± 1	12 ± 1	11 ± 2	0.11
iC4–6	8 ± 1ab	11 ± 1a	8 ± 1ab	4 ± 0c	4 ± 1bc	$<10^{-4}$

*Preserved colonic length: 100%: full colonic length; >50% more than half the colon functional, <50% less than half the colon functional, including patients with ileorectal anastomosis. Short bowel is defined as functional small intestinal ≤200 cm. iC4–6: isobutyrate, valerate, isovalerate, and hexanoate. One-way analysis of variance (ANOVA), $P < 0.05$. Groups marked with identical letters (a, b, or c) are not significantly different using the test of least significant differences, $P < 0.05$.

TABLE 8. SHORT-CHAIN FATTY ACIDS, LACTATE, AND pH IN 38 PATIENTS WITH NONINFLAMED ILEAL RESERVOIRS (KOCK CONTINENT ILEOSTOMY OR PELVIC POUCH)*

	Ileal reservoir		
Mean ± SEM	*Kock (12)*	*J-pouch (26)*	P
mmol/liter			
Total SCFAs	56 ± 10	57 ± 8	0.89
Acetate	39 ± 6	41 ± 5	0.84
Propionate	10 ± 3	8 ± 2	0.58
Butyrate	6 ± 1	7 ± 1	0.57
Isobutyrate	0 ± 0	0 ± 0	0.97
Valerate	0 ± 0	0 ± 0	0.56
Isovalerate	0 ± 0	0 ± 0	0.86
Hexanoate	0 ± 0	0 ± 0	0.57
L-Lactate	2 ± 1	7 ± 3	0.29
D-Lactate	1 ± 1	2 ± 1	0.27
DL-Lactate	3 ± 1	8 ± 3	0.31
pH	6.8 ± 0.2	6.6 ± 0.2	0.41
Percent			
Acetate	74 ± 3	75 ± 2	0.73
Propionate	14 ± 2	12 ± 1	0.37
Butyrate	10 ± 1	11 ± 1	0.39
iC4–C6	2 ± 0	2 ± 0	0.84

*iC4–6: isobutyrate, valerate, isovalerate, and hexanoate. Student's t test, $P < 0.05$.

small and large bowel length, despite the fact that sporadic changes were encountered (Table 7).

DISCUSSION

Roediger reported butyrate oxidation to be reduced in the colonic mucosal cells of patients with ulcerative colitis (11) and subsequently measured elevated concentrations of fecal SCFAs in patients with ulcerative colitis, discovering that rised levels of butyrate correlated with the activity of inflammation (10). He concluded that a failure to utilize butyrate could be a primary factor in the etiology of ulcerative colitis, and in a recent work Roediger et al proposed that luminal factors in patients with ulcerative colitis may inhibit butyrate metabolism (12). However, investigations on butyrate oxidation in biopsy specimens done by Finnie et al (21) did not support the hypothesis that ulcerative colitis is caused by a deficiency of butyrate metabolism. The data demonstrating increased fecal concentrations of SCFAs have also been contradicted by two reports from Vernia et al (8, 9), who found decreased concentrations of SCFAs in patients with ulcerative colitis and, in contrast to the earlier investigation, that low concentrations of butyrate correlated with increasing severity of inflammation. Treem et al (22) investigated 12 pediatric patients with quiescent/mild UC and five patients with moderate/severe UC, finding that total SCFAs

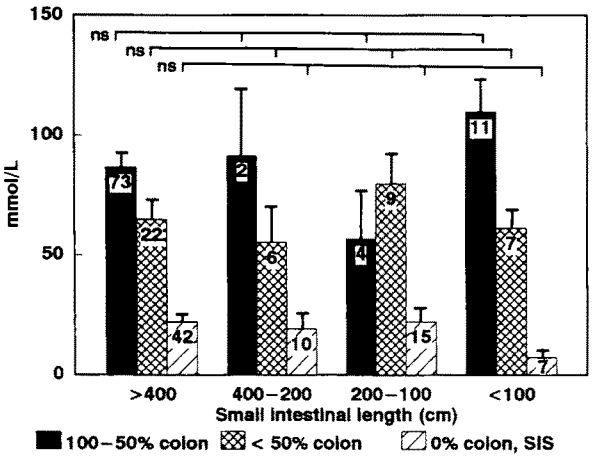

Fig 1. Fecal concentrations (mean ± SEM) of total short-chain fatty acids (SCFAs) in relation to decreasing small intestinal length and residual preserved colon of 100–50%, below 50% (including ileorectal anastomosis) or 0% (ileo- and jejunostomies). Patients with ileal reservoirs and active IBD are not included. The number of patients in each group is indicated in the columns.
Abbreviations: SIS: small intestinal stomy, ie, either ileo- or jejunostomy, ns: not significantly different using one-way analysis of variance (ANOVA).

were decreased in moderate/severe UC, while butyrate was increased in quiescent/mild but not in moderate/severe disease compared with healthy controls.

The knowledge concerning SCFAs and especially butyrate levels in patients with ulcerative colitis is therefore confusing, and our results are thus in between previous results, showing neither elevated nor lowered concentrations of SCFAs (including butyrate), in patients with both quiescent and active ulcerative colitis. However, in accordance with Vernia et al (8), we found lactate to be significantly increased in patients with active colitis. The L-isomer of lactate predominated, which probably indicates that it originates from mammalian tissue, ie, inflamed mucosa or leukocytes, and not from bacterial metabolism, which usually produces equal amounts of D- and L-lactate (23). Accumulation of lactate is also known to occur in extraintestinal inflammation (24) and is clearly not restricted to ulcerative colitis as Crohn's colitis demonstrated similar changes (25) (Table 5). L-Lactate does not persist long among the colonic bacteria, which convert some to D-lactate and metabolize both D- and L-lactate to SCFAs (23). Therefore, lactate from localized Crohn's ileitis has few chances to appear unchanged in feces, which may explain the normal values found in feces from this group of patients. Hence, lactate is probably a sensitive marker of distal proctocolitis of any etiology, but useless in monitoring proximal intestinal inflammation.

The mucosal absorption of SCFAs is associated with an increased absorption of sodium (26–29), which is of particular importance in patients with short bowels, who have considerable fecal losses of sodium and water. Bowling et al (3) revealed that infusion of SCFAs directly into the cecum reversed the fluid secretion seen during enteral feeding. Ramakrishna and Mathan (30) reported that luminal-supplied SCFAs restored net water absorption in patients with acute watery diarrhea and returned sodium absorption to normal. Nightingale et al (31) demonstrated that patients with short bowels and preserved colons had a lower need for intravenous supply of both electrolyte solutions and calories than short bowel patients with no colonic function, and the colonic conversion of malabsorbed carbohydrates to quickly absorbed SCFAs may supply the body with approximately 500 kcal/day in short bowel patients (32). The colon and its production of SCFAs may therefore be of special importance in patients who have had extensive bowel resections, and the general impression of the present results is that fecal and probably also colonic concentrations are quite stable as long as even a small part of the colon remains functional.

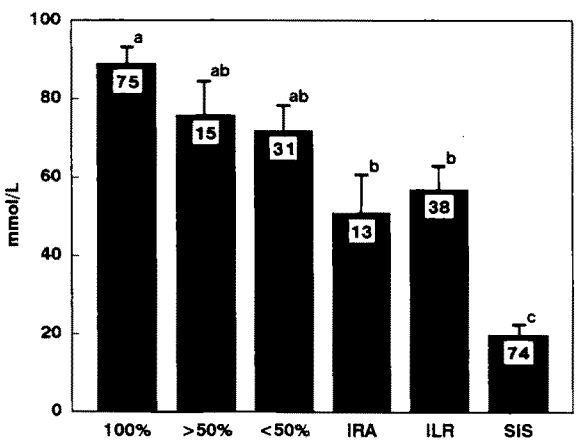

Fig 2. Fecal concentrations (mean ± SEM) of total short-chain fatty acids (SCFAs) in patients with decreasing colonic length, ileal reservoirs, and ileo- or jejunostomies. Patients with active IBD are not included. The number of patients in each group is indicated in the columns.
Abbreviations: IRA: ileorectalanastomosis; ILR: ileal reservoir ie, either pelvic J-pouch (n = 26) or Kock continent reservoir (n = 12); SIS: small intestinal stomy, ie, either ileostomy (n = 52) or jejunostomy (n = 22). Columns marked with identical letters (a, b, or c) are not significantly different using the test of least significant differences, $p < 10^{-4}$.

TABLE 9. SHORT-CHAIN FATTY ACIDS, LACTATE, AND pH IN RELATION TO SMALL INTESTINAL LENGTH IN 74 PATIENTS WITH QUIESCENT IBD OR NON-IBD AND ILEO- OR JEJUNOSTOMY*

	Length (cm)				
Mean ± SEM	*>400 (42)*	*400–200 (10)*	*200–100 (15)*	*<100 (7)*	P *(ANOVA)*
mmol/liter					
Total SCFAs	22 ± 3	19 ± 6	22 ± 7	7 ± 1	0.32
Acetate	18 ± 3	15 ± 5	14 ± 5	5 ± 1	0.29
Propionate	1 ± 0	1 ± 0	2 ± 1	1 ± 0	0.31
Butyrate	2 ± 0	3 ± 1	4 ± 1	1 ± 0	0.15
Isobutyrate	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.28
Valerate	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.06
Isovalerate	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.29
Hexanoate	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.42
L-Lactate	3 ± 0a	8 ± 4b	2 ± 1a	3 ± 2ab	0.02
D-Lactate	1 ± 0	2 ± 1	1 ± 0	1 ± 0	0.05
DL-Lactate	4 ± 1ab	10 ± 4bc	3 ± 1a	4 ± 3ab	0.02
pH	7.0 ± 0.2a	6.6 ± 0.2ab	6.4 ± 0.2ab	5.6 ± 0.6b	0.01
Percent					
Acetate	76 ± 2a	74 ± 2ab	58 ± 5b	69 ± 6ab	$<10^{-2}$
Propionate	8 ± 1	9 ± 1	10 ± 1	9 ± 2	0.43
Butyrate	12 ± 2a	13 ± 3ab	23 ± 3b	16 ± 4ab	0.01
iC4–6	4 ± 1a	4 ± 1a	9 ± 2a	6 ± 2a	0.02

*iC4–6: isobutyrate, valerate, isovalerate, and hexanoate; IBD: inflammatory bowel disease. One-way analysis of variance (ANOVA). Groups marked with identical letters (a, b, or c) are not significantly different using the test of least significant differences, $P < 0.05$.

Despite extensive small intestinal resection, some resulting in short bowels, patients with similar lengths of residual colon had fecal concentrations of SCFAs on the same order of magnitude independent of the small bowel length, indicating that colonic concentrations of SCFAs are able to adapt to very large incoming volumes of fluid and fermentable carbohydrates from the small intestine (Figure 1). This does not indicate that the colonic production of SCFAs is constant, since fermentation of carbohydrates and hence SCFA production would be expected to increase considerably as the length of the small intestine decreases. Rather, the constant levels of fecal SCFAs indicate that the colonic absorption of SCFAs parallels formation. The length of the large bowel was also of minor importance for the concentrations of SCFAs, and total colectomy with the formation of an ileorectal anastomosis or ileal pouch had to be performed before SCFAs decreased to levels still much higher than in the ileostomies.

Similar studies of the impact of colonic surgery on fecal SCFAs levels have found comparable results, ie, no changes after hemicolectomy and significant decreases after total proctocolectomy with the formation of an ileostomy, although both lowered (33) and unaltered (34) concentrations have been reported after subtotal colectomy in small series of three and six patients. The effect of small bowel length on large bowel concentrations of SCFAs has, to our knowledge, not been examined before.

In conclusion, fecal SCFA concentrations are remarkably resistant to extensive small bowel resections and more than 80–90% of the colon apparently has to be removed before concentrations of SCFAs trend to downward. Selected patients with well-functioning ileorectal and ileal reservoirs may even have normal concentrations of SCFAs (35). Several studies have now demonstrated the beneficial effects of SCFAs in both the healthy and diseased gut. If the remaining bowel anatomy after surgery results in an intestinal chamber for bacterial growth and SCFA formation, then it seems that SCFA production and absorption are synchronized to ensure rather constant fecal concentrations of SCFAs. Bacterial SCFA production is probably mainly associated with the type and amount of carbohydrates (and proteins) offered to the bacteria. The mechanisms by which absorption then adapts to different production rates and keeps the luminal concentrations surprisingly constant are still obscure.

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