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BIOLOGICAL EFFECTS OF SHORT-CHAIN FATTY ACIDS IN NONRUMINANT MAMMALS

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CONTENTS

INTRODUCTION

Dietary fibers from natural or semisynthetic sources have gained increasing attention because of their value as a supplement to the normal Western diet, which is poor in bulking substances, and as a therapeutic treatment of disorders such as atherosclerosis and colon cancer (31, 54, 62, 115, 116, 120, 128, 135). Over the last 50 years, numerous studies have shown that plant fibers are fermented in the gastrointestinal tract of mammals to short-chain fatty acids (SCFAs), also known as volatile fatty acids (VFAs), that are readily absorbed by the mucosa and metabolized by body tissues. Thus, production, absorption, and metabolism of SCFAs (acetate, propionate, and butyrate), as

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well as their physiological effects, have been subjects of intense research and, consequently, of numerous published comments and reviews (22, 38, 65, 71, 185, 191, 193, 210, 225, 232). We therefore focus our attention here on some research areas that have benefited from recent developments and that are of interest in human nutrition and health. Bovine milk fat digestion as a source of butyrate, the effects of propionate on cholesterol homeostasis, and those of butyrate on cell proliferation are the major subjects emphasized in this review.

OCCURRENCE IN THE DIGESTIVE TRACT

Microbial Fermentation

Adult monogastric mammals of all species, including *Homo sapiens*, have a microbial flora indigenous to their alimentary canal and primarily localized in the hindgut (cecum and large intestine) (202). The microbial populations are composed of several hundred different microorganism species (prokaryotes and eukaryotes) and in aggregate can exceed 1×10^{11} cells per gram dry weight of intestinal content. They resemble rumen populations in their size and complexity. For example, the genera *Bacteroides, Bifidobacterium,* and *Enterococcus*, and the species *Escherichia coli,* are predominant in the feces of formula-fed babies (15). Substrates for microbial fermentation in the large intestine are macromolecules that come from endogenous (sloughed epithelial cells, lysed microbial cells. mucus, and other intestinal excretions) and exogenous (mostly fibrous components of food) sources and that cannot be digested by host enzymes (149). Dietary fibers are complex polysaccharide polymers that derive from the plant cell wall, which is made up of water-insoluble cellulose microfibrils coated with soluble hemicelluloses and embedded in a gel of pectins (62). Variable amounts of starch that escape digestion in the small intestine (this fraction is called resistant starch) also pass into the colon and become available as substrate for microbial fermentation, as does dietary fiber (166, 204, 229). Reflecting the anaerobic environment of the colon, most biochemical reactions catalyzed by microbial enzymes do not involve oxygen. The SCFAs acetate, propionate, and *n*-butyrate, and the gases H_2, CH_4, and CO_2, which can be detected in respiratory expiration (231), are major end products of microbial fermentation. Formate, valerate, caproate, and the branched-chain acids isobutyrate and isovalerate (144) also occur in the large intestine, though in smaller proportions (10–20 mol% of total SCFAs). SCFAs are present at total concentrations ranging from about 30 to 190 mM in the feces of individuals consuming an ordinary diet (202), irrespective of the hindgut size and the herbivorous status of mammalian species (22, 38, 185). SCFAs make up the predominant anions

Table 1 SCFA molar percents from 24-hr fermentation of dietary fibers in in vitro incubation systems inoculated with fresh human fecal flora[a]

Substrate	Acetate	Propionate	Butyrate
Pectin	81	11	8
Gum arabic	68	23	9
Oat bran[b]	65	19	16
Wheat bran[b]	63	16	21
Cellulose[c]	53	21	26

[a]Means recalculated from (2, 152, 222, 236, 240).
[b]α-cellulose and hemicelluloses are 7% and 19% dry total dietary fiber, respectively, in oat bran, and 19% and 38%, respectively, in wheat bran (36).
[c]48-hr fermentation.

in the large intestine of mammals and create a slightly acidic pH level (6.0–7.0) (38, 55, 73). The acids vary widely in their relative proportions, depending upon the fiber source in the diet (Table 1). SCFAs in human feces, following consumption of different defined polysaccharides, have been measured, on average, in the molar ratio of acetate:propionate:butyrate of 53:27:20 (202).

Bovine Milk Fat Digestion

Milk fat from domestic (cow, sheep, and goat) and wild ruminants is made up of triacylglycerols in excess of 95%. The chain length of the three acyl moieties esterified to glycerol ranges from 2 to 26 carbon atoms (146). Ruminant milk fat contains appreciable proportions of SCFAs, including butyric acid (10 mol%), caproic acid (5 mol%), and acetic acid as a minor component (168), but SCFAs are absent in the milk of other mammalian species, including humans. Bovine milk fat consists of thousands of individual stereospecific triacylglycerols (213), of which 223 molecular species were recently determined (93). We found that the three major triacylglycerols, 4-16-18:1 (4.2 mol%), 4-16-16 (3.2 mol%), and 4-14-16 (3.1 mol%), contained one butyric acid per molecule, as a result of the specific esterification of SCFA at the *sn*-3 position.

Bovine milk and dairy products contain small amounts of free fatty acids generated by endogenous lipoprotein lipase activity. Lipoprotein lipase, which is the major enzyme responsible for hydrolysis of serum triacylglycerols, is synthesized in extrahepatic organs, including the mammary gland (20, 238). The molecular cloning of bovine lipoprotein lipase cDNA was achieved by Senda et al (209). Lipoprotein lipase belongs to the lipase superfamily that also includes hepatic and pancreatic lipases (103). In the lactating mammary gland, the active enzyme is released partly in association with milk lipid globules from differentiated mammary epithelial cells (21, 44, 125), and thus

bovine milk is an abundant source of the enzyme (6 mg liter^{-1} of skim milk). Although lipoprotein lipase preferentially attacks the ester bond in the *sn*-1 position, it catalyzes the rapid release of fatty acids, including butyric and caproic acids, in the primary position. Indeed, the rate of hydrolysis in vitro (176) or in vivo (173) is similar for triacylglycerols containing short chains (tributyrin), medium chains, long chains (Intralipid®: purified soybean oil emulsified with egg phosphatidylcholine), or mixed chains (milk fat globules) as substrates. The feature distinguishing lipoprotein lipase from other lipases is that it requires apolipoprotein C-II for maximal activity. The enzyme has maximal activity between pH 8.6 and 9.0 (176, 237). Thus, it is uncertain whether, in the stomach of humans swallowing bovine milk, lipoprotein lipase is still active in the absence of the serum factor and because of stomach acidity, and, therefore, whether it is important in milk fat digestion. The digestive enzyme bile salt-stimulated lipase has been found in the milk of humans, higher primates, and carnivores, but not in that of ruminants (217).

The first important step of dietary triacylglycerol lipolysis is catalyzed by a preduodenal acid lipase that is active in the stomach (95). The enzyme is known by various names, including lingual lipase (rat), gastric lipase (man and rabbit), and pregastric esterase (calf) (80). In each mammal, the preduodenal lipase activity is associated mainly with a single tissue, which is located in the lingual (mouse and rat), pharyngeal (calf and sheep), or gastric (horse, dog, cat, rabbit, guinea pig, hog, baboon, and macaque) area (59, 160). In humans, it was first believed that the lipase activity of the gastric juice originated from Ebner's lingual glands (95). More recently, it was clearly shown that human gastric lipase is mainly localized in the chief cells of the fundic mucosa (1, 58–60, 159, 161). The output of the enzyme is stimulated by intravenous infusion of pentagastrin (162, 163) or by gastric nutrient infusion (216) in healthy adults. Gastric lipolysis is of primary importance for milk fat digestion in infants because of the low pancreatic lipase level (137a). A 7-fold decrease in human gastric lipase activity of the fundic mucosa has been observed in persons over 60 years of age (161).

Human gastric lipase is a glycoprotein with an apparent molecular mass (MM) of ~50 kd as determined by SDS polyacrylamide gel electrophoresis (33, 158, 221). The amino acid sequence obtained from a cloned cDNA (33) consists of 379 amino acids (MM = 43 kd), including four potentially glycosylated asparagine residues and three cysteine residues, one of which is essential for the expression of enzyme activity (78, 79). Human gastric lipase is closely related to rat lingual lipase (377 amino acids) (61), with an overall homology of 78% (33), but is unrelated to porcine pancreatic lipase (56). The pH optimum of human gastric lipase is in the range of 3.5–5.5, which makes the enzyme ideally suited to act in the stomach, where the pH after the ingestion of a meal is in such a range (95). Human gastric lipase is remarkably

stable at a low pH and remains active after incubation at pH values close to 1.0 (69, 160). It has often been reported that human gastric lipase displays a high specificity towards short-chain triacylglycerols in vitro, whereas the enzyme appears to be able to catalyze the hydrolysis of alimentary long-chain triacylglycerols in vivo. In fact, establishing the optimal assay conditions with short-chain (tributyrin) and long-chain (Intralipid) triacylglycerols, Gargouri et al (84) demonstrated that human gastric lipase had no intrinsic specificity for short-chain triacylglycerols and that the apparent specificity, when observed, depended on pH and the presence of amphiphile molecules (bile salts, bovine serum albumin, or dietary proteins such as β-lactoglobulin and ovalbumin) in the incubation medium (see also 58, 81, 82, 140, 221). Interestingly, Bernbäck et al (23) found that the rate of hydrolysis of human milk fat globule triacylglycerol, which is made up of about 6% medium-chain fatty acids (114), was comparable to that obtained with an artificial emulsion of long-chain triacylglycerol (25). It must be emphasized that the free fatty acids released by human gastric lipase hydrolysis of triacylglycerol strongly inhibit the enzyme activity when their chain length exceeds six carbons (23). This inhibition may be connected with the fact that, under in vivo conditions, only 10–20% of the hydrolysis of dietary lipids occurs within the stomach (14, 96). The enzyme appears to be partially specific for the *sn*-3 position when hydrolyzing synthetic long-chain triacylglycerols (119, 221).

To date, no data is available concerning human gastric lipase hydrolysis of bovine milk fat globule triacylglycerol. However, in view of the features of the enzyme, short-chain residues in bovine milk triacylglycerols, which are at the *sn*-3 position, probably are the first to be released to yield medium- and long-chain *sn*-1,2 diacylglycerols. The released SCFAs are rapidly absorbed by the gastric mucosa (27a, 201). Lipid digestion is completed in the proximal part of the small intestine by pancreatic colipase-dependent lipase, giving rise to *sn*-2 monoacylglycerols and free fatty acids, and more modestly by pancreatic bile salt-dependent lipase (88). It is now recognized that the generation of limited quantities of free long-chain fatty acids by the action of human gastric lipase on native milk fat globule triacylglycerols is of major importance in promoting the subsequent lipolysis by pancreatic lipase in the presence of colipase and bile salts (23, 24, 83). A concerted action of the different lipolytic enzymes in the gastrointestinal tract is probably one important mechanism responsible for the efficient digestion of dietary lipids (24, 141).

ABSORPTION AND METABOLISM

Daily production of SCFAs in the human colon is estimated to be greater than 300 mmol day^{-1}, but fecal excretion is only about 10 mmol day^{-1} (104). The

colonic absorption rate of SCFAs is remarkably similar among nonruminant species, including humans, and ranges from 6 to 12 μmol $(cm^2)^{-1}$ h^{-1} (191). Thus, SCFAs in vivo appear to be absorbed rapidly and nearly completely. Clearance rates of SCFAs have generally been observed to increase with chain length, even though there are differences between rates in the distal and proximal colon (72, 186, 192). Several models have been proposed to explain SCFA transport and to account for the large number of observations describing the dependence of SCFA absorption rates on luminal pH and P_{CO_2}, as well as on fluxes of water, protons, and inorganic ions (Cl^-, HCO_3^-, Na^+ and K^+) through the colonic mucosa (38, 185, 223). It is widely believed that the transmural movement of SCFAs is a concentration-dependent, passive diffusion process, whereby SCFAs, at least in part, are transported in the protonated form. Hydrogen ions, which are needed for SCFA protonation because 99% of SCFAs (pKa = 4.8) are in the ionized form at the colonic pH, may be available from Na^+-H^+ exchange and from hydration of luminal CO_2 to HCO_3^- and H^+. SCFAs may also be transported in the ionized form via an SCFA-HCO_3^- exchange mechanism. Most results from recent investigations in vivo (72, 148, 167, 186, 235) and in vitro (29, 30, 97, 98, 188, 192, 194, 208) in the colon of mammals agree with this outline. However, the precise mechanism for the absorptive process of SCFAs remains undefined.

Studies using in situ loops of rabbit hindgut (147), isolated colonocytes of rat (13, 52, 70, 74, 189), and biopsy specimens of human colon (242), all incubated in the presence of [^{14}C]substrates, have shown that SCFAs, once taken up, were metabolized at a high rate inside the cecal and colonic mucosal cells. Furthermore, butyrate was used as an important respiratory fuel in preference to acetate, propionate, and even to glutamine, glucose, and ketone bodies. Such findings have stimulated considerable research regarding the role of SCFAs in maintaining the health of colonic mucosa and in preventing colonic diseases (130, 215).

The SCFAs that escape colonic metabolization enter the hepatic portal blood, where their concentration varies in a wide range, depending on intestinal production rates and, therefore, on the diet. For example, values ranging from 0.3 to 3 mM have been reported in the rat (50, 110, 112, 157). In contrast, the relative proportions of the three major acids in the portal blood reflect quite well the relative proportions of those found in the intestinal contents. Table 2 shows that butyrate and propionate are extensively taken up by the liver, sometimes so much so that they are no longer detected (<2 μM) in the peripheral blood (57, 179, 181). There is also substantial clearance of acetate in the liver, with further uptake occurring in peripheral tissues. Indeed, utilization of SCFA in hepatocytes from rats fed a high fiber diet was 0.1, 0.6, and 0.9 μmol min^{-1} g^{-1} cells when incubated in the presence of 1.0 mM acetate, propionate, and butyrate, respectively (57). Propionate is used by the

Table 2 SCFA concentrations (μmol ml^{-1}) in rats fed a standard diet[a] and sudden-death human victims[b]

	Acetate	Propionate	Butyrate
Cecal content			
Rat	93.0	23.2	43.1
Man	69.1	25.3	26.1
Hepatic portal blood			
Rat	0.98	0.22	0.39
Man	0.258	0.088	0.029
Hepatic venous blood			
Rat		—	—
Man	0.115	0.021	0.012
Peripheral blood			
Rat (arterial blood)	0.40	0.02	0.03
Man (venous blood)	0.070	0.005	0.004

[a]Data from (111).
[b]Data from (55).

liver as a substrate for gluconeogenesis, and butyrate leads to ketone body production.

BIOLOGICAL EFFECTS

Propionate and Cholesterol Levels

Coronary heart disease is a leading cause of death in the Western countries. Epidemiological data show that elevated blood cholesterol, especially low-density-lipoprotein cholesterol, is a major risk factor. Dietary therapy is the mainstay in treatment of moderate hypercholesterolemia. Water-soluble dietary fibers, such as pectins, gums, and oat cereals, are widely believed to reduce total and low-density-lipoprotein cholesterol levels in serum of both hypercholesterolemic (6–9, 18, 19, 37, 45, 124, 126, 137, 153) and nonhypercholesterolemic (47, 187) humans, but insoluble fibers, such as wheat bran or cellulose, do not seem to lead to such reduction. Soluble fibers also decrease liver cholesterol levels, as observed in several species of laboratory animals (12, 68, 105, 122, 150, 212), and increase the hepatic LDL-receptor number (68, 226). Although fiber has an important sequestering effect (63, 113), the precise mechanism of cholesterol-lowering remains unclear. The decrease in serum cholesterol concentrations has been partially attributed to the ability of fibers to inhibit lipid absorption (35, 108, 249) and to increase biliary (67, 106, 109, 196) and fecal (10, 46, 109, 196) bile acid excretion. This would then cause the liver to convert

more cholesterol to bile acids, thereby reducing body cholesterol. However, as some fibers are associated with a significant decrease in serum cholesterol without increasing fecal bile acid excretion (5, 46, 137, 155), we can conclude, as did Kritchevsky (135), that the "effects of fiber on bile acid metabolism represent, at best, a small part of the overall mechanism(s) related to hypolipidemia."

Researchers agree that the highly polymeric structure of fibers is a prerequisite for the potent cholesterol-lowering effect of nonabsorbable carbohydrates. However, Topping et al (227) reported that methylcellulose, a modified polysaccharide resistant to microbial metabolism, which therefore is not fermented in the colon to SCFAs, had no effect on plasma cholesterol, hepatic cholesterol synthesis, and fecal excretion of bile acids. Moreover, Ide et al (106) recently showed that guar gum hydrolysate had the same decreasing effects on cholesterol levels as did intact guar gum. In this experiment, tenfold increases in cecal SCFA contents were observed with both kinds of substrates. Such results suggest that the action of absorbed SCFAs on hepatic and peripheral metabolism of cholesterol may be an alternative mechanism for the effect of fermentable carbohydrates on body cholesterol concentrations (183). The idea that SCFAs (particularly propionate) derived from colonic fermentation may suppress liver cholesterol synthesis was based on the initial observation that 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase in bovine liver was inhibited by 0.5 mM propionyl-CoA or 15 mM propionate (39). Moreover, it was known that the liver is the principal site of propionate metabolism and cholesterol synthesis (Figure 1). Ide et al (107) showed that feeding medium-chain triacylglycerols lowered the activity of rat liver HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, whereas feeding long-chain triacylglycerols did not. Thus, inhibition of cholesterol synthesis might be achieved in animals by the inclusion of propionate in the diet. The pig has often been chosen as a model because it is similar to the human in diet, lipoprotein profile, and responsiveness to hypercholesterolemic diets. In 1981, Boila et al (34) using young male, castrated pigs made hypercholesterolemic by addition of 15% tallow in the diet, were the first to observe an inhibitory effect of dietary propionate (5%) on the rate of cholesterol synthesis. Inhibition of cholesterol synthesis by propionate was confirmed in vitro by Anderson & Bridges (4) incubating isolated rat hepatocytes in the presence of 15–30 mM propionate. The same research group (49) reported that both serum and liver cholesterol levels were significantly lowered in rats when only 0.5% propionate was included in a 0.3% cholesterol-supplemented diet, but no effect was observed in rats fed a nonsupplemented diet. Propionate was thought to decrease cholesterol synthesis by inhibiting HMG-CoA reductase, but some studies in rat liver have

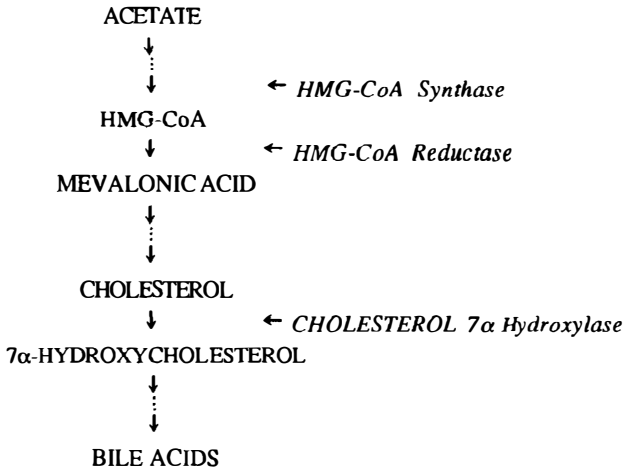

Figure 1 Key reactions in the cholesterol and bile acid biosynthetic pathways. HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA. Modified from Shefer et al (211).

led to conflicting results (151, 182), like those obtained in studies of rats fed dietary fiber (68, 106, 171, 172, 184).

In contrast to the above data, Thacker and colleagues (218–220), who also used pigs fed diets containing high levels (3–9%) of propionate, noted reductions in serum cholesterol concentrations but slight increases in cholesterol concentrations of liver and backfat. The authors suggested that propionate may reduce the transport of cholesterol from peripheral tissues to the liver rather than reducing liver cholesterol synthesis. In keeping with these results, similar studies in vivo in the rat indicated that inhibition of hepatic and intestinal cholesterol synthesis was not responsible for the hypocholesterolemic effects of dietary propionate (111) or soluble dietary fibers (11, 66, 109, 226). Hepatic portal venous plasma propionate concentrations do not exceed 1 mM in animals fed high levels of propionate (111) or dietary fibers (10, 50, 109, 110, 157), or in patients after caecal lactulose instillation (179). Studies with perfused livers (111) or isolated hepatocytes (170, 245) from nonfasted rats indicated that propionate at a concentration of 1 mM or lower did not alter cholesterol synthesis, as measured by tritium incorporation into sterols from $^{3}H_2O$. Sterologenesis was inhibited solely when nonphysiological concentrations (1 mM) of propionate were present in the medium (245), as originally observed (4). Although conflicting results have been obtained when using [^{14}C]acetate or $^{3}H_2O$ as the tracer (170), the cholesterol synthesis rate

generally appears to be fairly independent of the substrate used, i.e. $^{3}H_2O$, [^{14}C]acetate, or [^{14}C]mevalonate (143, 171, 245).

Recently, propionate supplements (7.5 g day^{-1}) were given to healthy human volunteers for one week (224) or seven weeks (223), and in both studies, total serum cholesterol was unchanged. Similar results were obtained in pigs (34) and rats (49) given standard diets supplemented with propionate but without lipids. Venter et al (234) designed a study in the baboon, which is regarded as a more suitable animal model for examining the association of fiber-depleted diets and atherosclerosis. Baboons were fed a Western diet, with or without supplements of 2% propionate or of 5% soluble dietary fiber concentrate, for periods of nine weeks. Total serum cholesterol values were increased in the baboons fed the unsupplemented Western diet, and soluble fiber prevented this increase while propionate did not. However, propionate and fiber increased the high-density-lipoprotein cholesterol concentration (234). Similar results were obtained in humans (233), and such an increase is considered to be a beneficial effect. Furthermore, the liver cholesterol concentration was lowered by propionate or fiber supplementation (234).

If we summarize data showing how propionate given orally to humans and animals (rat, pig, and baboon) affects cholesterol metabolism, conflicting results have been obtained regarding not only the rate of biosynthesis of cholesterol but also its serum and liver levels. The in vivo studies designed with propionate-supplemented diets have been criticized because whereas dietary propionate is rapidly absorbed in the upper gastrointestinal tract (stomach), as shown by Illman et al (111) in the rat and the pig, propionate arising by bacterial digestion of fiber is absorbed gradually in the lower part of the digestive tract (cecum + colon), and the metabolic effects of propionate may not be the same. Furthermore, the effects of propionate (or fiber) in oral supplementation cannot be studied independently from upper intestinal effects on digestibility of nutrients and enterohepatic bile acid metabolism. To overcome these difficulties, rectal or cecal infusions of propionate have been carried out in humans (243, 244) and in pigs with a cecal cannula (17). It was found that propionate either had no effect on, or raised, total serum cholesterol concentration. These results were in keeping with the findings of Ahrens et al (3), who had examined the effects on blood lipids of oral and intracecal pectin administration for four weeks in hypercholesterolemic minipigs. Total serum cholesterol concentration was lowered by 50% after feeding, while the intracecal infusion of the same amount of pectin had no effect. These studies demonstrated that the passage of fiber through the small intestine is necessary for its hypercholesterolemic action. To date, even if propionate concentrations in the hepatic portal vein of fiber-fed rats were found to be related to the cholesterol-lowering effect (109, 110), the hypothesis that propionate may mediate the hypercholesterolemic effects of

high-fiber diets is becoming less and less satisfactory (66). Colonic fermentation of fiber also produces acetate and butyrate, but we cannot yet draw clear-cut conclusions from a few works concerning the effects of the two SCFAs on sterol synthesis (26, 27, 48, 85, 170) and serum cholesterol concentrations (27, 244).

Trophic Effects on the Colon Mucosa

Several laboratories have shown that ingestion of fiber or resistant starch exerts a trophic effect, when estimated by parameters such as mucosal weight or protein content, on the hindgut mucosa of rats (42, 64, 117). Conversely, fiber-free diets or total parenteral nutrition induce atrophy in the intestinal mucosa. Complex carbohydrates may also cause an increase in crypt cell proliferation when measured by various techniques including labeling with bromodeoxyuridine (64) or [^{3}H]thymidine (40, 73, 117, 145), counting of S phase cells by flow cytometry (64) or arrested metaphases (92), and assessing of thymidine kinase activity (42, 43, 139, 178). In fact, these studies have revealed that dietary fibers stimulated colonic cell proliferation more or less, depending on several factors, including the source and quantity of the dietary fiber and the intestinal site (cecum, proximal, or distal colon). Furthermore, some conflicting results have been reported. For example, high starch diets either increase (40, 42) or decrease (28, 40, 41) colonic crypt cell proliferation. Of the various possible explanations regarding the effects of dietary fibers on colonic cell proliferation, a hypothesis has emerged suggesting that these effects are mediated by SCFAs via luminal fermentation. Indeed, intraluminal infusions of SCFAs have a stimulatory effect on colonic mucosa proliferation under various experimental conditions in rats (134, 190, 197–200) and patients (165). Effects of SCFAs were dose-dependent and varied among the acids (butyrate propionate acetate) (198). Similar results were obtained in vitro by Scheppach et al (205) when cell proliferation was measured in biopsies of normal human cecal mucosa after labeling with [^{3}H]thymidine. However, a few differing results have been obtained. In patients with distal ulcerative colitis, the same authors (206) observed that 100-mM butyrate enemas resulted in amelioration of inflammation while upper crypt proliferation was diminished. Furthermore, when cecal tissue pieces of normal rats were incubated in the presence of SCFAs in a physiological range (0.01–100 mM) and then examined for frequencies of colchicine-arrested metaphases, epithelial proliferation was inhibited, and butyrate alone had an equivalent effect to that of a mixture of SCFAs (198). Lastly, no correlation has been established between cell proliferation and the consumed quantity of water-soluble dietary fibers (which are fermented to a greater extent than water-insoluble dietary fibers) or the SCFA concentrations in luminal contents (73, 145).

Trophic effects of SCFAs on the intestinal mucosa cannot be explained solely by direct luminal effects of the SCFAs absorbed and used as a major energy source in the mucosa. The in vivo effects of SCFAs are probably indirect, because intakes of short-chain triacylglycerols, which are rapidly hydrolyzed and absorbed in the upper digestive tract, have been shown to stimulate colonic mucosal growth in rats (133). Conversely, SCFAs infused into the rat hindgut lumen stimulate mucosal cell proliferation in the intact or disconnected jejunum (134, 198, 199). Moreover, parenteral or intravenous infusion of SCFAs reduces the mucosal atrophy associated with total parenteral nutrition in the rat (123, 131, 132). A humoral mechanism in which enteroglucagon may play a role has been suggested (92). The beneficial effect of SCFAs on mucosal cell trophicity may also be due, at least in part, to an increase in the mucosal blood flow (164). Stimulation of the microcirculation could result from a direct action on the resistance arteries, as demonstrated in vitro in the rat (174) and human (165), and vasorelaxation might be related to increases in artery tissue cAMP levels (174). In summary, a true cause-and-effect relationship between fermentable fiber or SCFAs and cell proliferation is still disputable, and the mechanism(s) of action of SCFAs on the intestinal mucosa remains uncertain.

Butyrate and Colon Cancer

Various human epidemiological and case-control studies have shown that colonic cancer is negatively correlated with fiber intake (31). In animal models of colorectal cancer with lesions induced by carcinogens such as 1,2-dimethylhydrazine (DMH), wheat bran and cellulose appear to have a consistently protective effect against chemical carcinogenesis, but no consensus exists for the water-soluble fibers, gums, and pectins (115, 116, 118). The suggestion that dietary fibers are protective in colorectal cancer is based on the fact that fibers increase large intestinal contents, speed up transit time, and bind carcinogens, which could reduce exposure of the mucosa to carcinogens. However, because dietary fibers differ in their physicochemical properties and because other dietary components, particularly fat, can induce reverse effects on the colonic mucosa, it remains difficult to identify a single mechanism by which fibers modify colon carcinogenesis. For example, some effects of fibers may be mediated via epidermal growth factor (EGF), since it has been reported that the addition of 10% wheat bran to a diet decreases the EGF level in the rat colon mucosa (203) and that the EGF receptor is overexpressed in human colonic carcinomas (246).

In cultured cell lines, butyrate is a well-recognized antitumor agent, whereas the other SCFAs are much less active in this respect (136). Some dietary fibers may therefore produce an antineoplastic effect through their fermentation products, especially butyrate. Microbial fermentation of insoluble fibers such

as wheat bran is often associated with a higher production of butyrate than is fermentation of soluble fibers (Table 1; see also 154). Thus, in DMH-treated rats given diets supplemented with guar gum (85% soluble), oat bran (51% soluble), or wheat bran (25% soluble), Young et al (248) observed that the more insoluble the fibers, the more effective they are in elevating concentrations of butyrate in the distal large bowel and protecting against colorectal cancer. Conversely, when the SCFA distribution was investigated in enema samples taken from human subjects, a significantly lower ratio of butyrate to total SCFAs was found for polyp-colon cancer subjects than for normal subjects (239). Similarly, when studying SCFA production velocities from fiber in in vitro fecal incubation systems, Clausen et al (51) observed that the relative production rate of butyrate was reduced in patients with colonic cancer and adenomas, as compared to healthy controls. On the other hand, butyrate, when given orally, does not slow down the development of colonic neoplasia in DMH-treated rats (76). We can therefore conclude that high levels of luminal butyrate may have protective effects against colon cancer in vivo.

In vitro, the exposure of a number of cultured human colon cancer cell lines to butyrate induces alteration of several growth properties and morphological and biochemical changes consistent with a more differentiated phenotype. The changes generally include increased doubling times, reduced colony-forming ability in soft agar, morphological alterations, and increases in alkaline phosphatase and other enzymes (75, 94, 102, 121, 127, 169, 177, 230, 241). Induction of carcinoembryonic antigen (86, 169, 228, 230, 241), modifications in proto-oncogene expression (16, 53, 75, 207, 214), alterations in glycoprotein synthesis (16a, 86, 121, 127, 230), and an increase in the expression of the cytochrome c oxidase subunits encoded by mitrochondrial genes (99, 100) and of the basolateral Na^+/H^+ exchanger (32) have also been reported. These butyrate-induced alterations concern regulatory mechanisms of gene expression. Histone hyperacetylation, resulting from inhibition of histone deacetylase (101) and leading to weakening of histone/DNA interactions (175) and, then, to enhanced expression of some genes, is almost constantly observed (136, 180). Scaffold-attached regions may mediate the action of butyrate at the level of the chromatin structure (129). This description at the DNA level of the mechanisms that underlie the apparently pleiotropic effects of butyrate can suggest a nonspecific action of butyrate on gene expression. However, a more localized effect of butyrate, involving specific 5′-flanking DNA sequences that control butyrate-sensitivity of proximal genes, has been described in different genomic contexts (57a, 77, 89–91, 138, 247), and a 17-nucleotide consensus sequence has been identified (77). An explanation for the role of a specific 5′-upstream DNA sequence in butyrate-responsiveness may be that butyrate modifies the activity of transcriptional factors. That may, in turn, affect the interactions of these factors with proteins

bound to the promoter. Because the molecular process of colon carcinogenesis likely involves both activated and repressed genes (195), it is of great interest to understand the molecular mechanisms involving the action of butyrate.

The intestinal epithelium can respond to a wide variety of stimuli by altering its rates of proliferation. We reported above that in many studies, but not all, dietary fibers increase colonic cell proliferation in healthy animals. Furthermore, despite some conflicting results, evidence exists that the products of hindgut fermentation, particularly butyrate, have a trophic effect on the normal intestinal epithelium in vivo. In contrast, epidemiological studies have revealed the protective role of some dietary fibers against the development of colon cancer in human subjects, and a few experimental studies have suggested that these effects may be mediated by butyrate, which is a potent antitumor agent in vitro. Moreover, according to some researchers, increased cellular proliferation may be a marker of gastrointestinal cancer risk (142). If butyrate does play a role in mediating the effects of fibers on the colonic mucosa, there is an apparent contradiction between the proliferating effects of fiber or butyrate in the normal mucosa, on the one hand, and their protective effects against colon cancer on the other hand. Recently, Gibson et al (86) compared the in vitro effects of butyrate on the differentiation of normal colonic epithelial cells (isolated cells and organ culture) with those on a colon cancer cell line. All the markers used to assess differentiation (glycoprotein synthesis, alkaline phosphatase activity, and carcinoembrionic antigen expression) were increased in neoplastic cells and unchanged or decreased in normal cells. These data indicate that butyrate has differing actions on normal and neoplastic cells.

CONCLUSION

Contribution to Energy Requirements

SCFAs can be an important source of carbon and energy for the nonruminant mammals. Bugaut (38) and Bergman (22) summarized estimates obtained in various species regarding the contribution of SCFAs to the basal energy requirements. Values from 5 to 30% were obtained; as expected, the highest figures were for herbivores such as rabbits and ponies, but they showed considerable variation, probably because of methodology used and assumptions made by the authors. In fact, substantially more energy would be available to nonruminants if fiber could be digested in the small intestine. In the case of farm animals, one of the applications of recombinant DNA technology would be to obtain the expression and secretion of heterologous cellulases and xylanases in the digestive tract of transgenic animals (87). As for humans, SCFA could contribute 6 to 10% of the energy requirements in developed countries (156). Dietary fiber intakes are often much higher in the

Third World, and it is likely, therefore, that greater amounts of energy via SCFAs are made available by large intestinal fermentation. Accurate studies need to be designed to assess the contribution of SCFAs to energy supplies in man.

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