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Energy Contributions of Volatile Fatty Acids From the Gastrointestinal Tract in Various Species

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I. INTRODUCTION

The volatile fatty acids (VFA) are also known as short-chain fatty acids (SCFA), and their dissociated anions are sometimes abbreviated as SCFAA. Even though only the acid forms are volatile, the term VFA has persisted and, for the purposes of this review, VFA is used interchangeably for both the acid and the anion forms.

The VFA as a group contain one to seven carbon atoms and exist as straight- or branched-chain compounds, which include formic, acetic, propionic, butyric, isobutyric, valeric, isovaleric, 2-methylbutyric, hexanoic, and heptanoic acid. All are produced, along with small amounts of other organic compounds, such as methane, carbon dioxide, lactate, and alcohol, in several parts of the gastrointestinal tract of humans and animals through the processes of microbial fermentation.

Acetic, propionic, and butyric acids are the predominant forms of VFA and are produced mainly from the fermentation of plant materials, such as celluloses, fiber, starches, and sugars. Because mammals do not produce enzymes that are able to split long-chain structural carbohydrates, microbial fermentation can be of great advantage to the body. The VFA thus are produced in greatest amounts in herbivorous animals and to a lesser extent in omnivores, such as swine and humans. The gastrointestinal tracts of carnivores produce even smaller amounts of VFA, since their food typically contains a much larger proportion of readily digestible nutrients and a smaller proportion of plant cells.

Because the VFA are weak acids with a pK of $\leq$4.8 and because the pH of the gastrointestinal fermentation chambers is more nearly neutral, 90–99% of the VFA are present in the gastrointestinal tract as anions rather than as free acids. In all mammals examined, the anion form of acetic acid, or acetate, is the main VFA present; in fact, acetate usually is present in higher concentrations than all other organic anions combined. Propionate and butyrate also are present in large concentrations, although their amounts can vary considerably with diet. Commonly, molar ratios of acetate to propionate to butyrate are found to vary from ~75:15:10 to 40:40:20.

Historically, it was Tappeiner (289), from 1882 to 1884, who showed that microorganisms of the rumen

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and the equine large intestine fermented cellulose, with methane, carbon dioxide, and acetic, propionic, and butyric acids as end products. Later, in 1891, Mallevre (197) proved that acetate could be utilized by rabbits and postulated that VFA were utilized by ruminants. It was, however, more than 50 years later that the nutritional importance of VFA started to be realized. In the 1940s, workers, mainly at Cambridge University, showed that most of the ruminant's feed is fermented in the rumen (36, 233, 235). Furthermore, they proved that end products of fermentation are at least partially determined by the nature of the feed.

Extensive investigations over the last 40 years have shown that the VFA are utilized by many tissues, and a number of reviews have been published on specific aspects of VFA production or metabolism (e.g., see Refs. 9, 10, 113, 279, 308, 328). At least for ruminants, VFA constitute the major source of energy for the animal. Recent evidence also indicates that there is considerable fermentation in the cecum and colon of both humans and animals, and, in addition, there are several other potentially beneficial effects of VFA. Some of these may be exerted intraluminally, some may be exerted within the mucosal cells, and others may be exerted after absorption of the VFA into the bloodstream.

II. PRODUCTION OF VOLATILE FATTY ACIDS IN DIFFERENT SPECIES

A. Sites of Volatile Fatty Acid Production in Gastrointestinal Tract

In addition to classifying animals as herbivores, omnivores, or carnivores, mammals have been categorized as forestomach fermenters or hindgut fermenters (238, 280). Briefly, the forestomach fermenters have a fermentation chamber cranial to the acid-secreting part of the stomach and consist of animals such as ruminants, camels, hippopotamuses, and some monkeys and marsupials. In hindgut fermenters, the cecum and large colon serve as chambers for microbial action, and these animals consist of species such as rodents, lagomorphs, horses, elephants, and all omnivores and carnivores. There are more species of herbivores with hindgut fermentation than there are with forestomach fermentation (148, 184).

The concentrations of VFA at different sites in the gastrointestinal tract are a direct function of the bacterial population and thus are proportional to the time or extent to which digesta are retained. This was first demonstrated over 40 years ago in the classic studies of Elsden et al. (104; Fig. 1). They compared total VFA concentrations at different sites in the gastrointestinal tract of many mammalian species and found that ruminants (sheep, cows, and deer) had the highest VFA concentrations in the rumen, a fall to less than one-fifth of these values in the small intestine, and a second peak in the cecum and colon; some VFA were present in the rectum. These studies thus showed that even in forestomach fermenters considerable further digestion of fiber occurs in the large intestine. Later studies using intestinal and cecal cannulation techniques (e.g., see Refs. 109, 125, 269, 280) and measurements of VFA in blood draining the cecum (36) proved this to be true.

In nonruminant herbivores and pigs (Fig. 1), the highest VFA concentrations were in the cecum and, secondly, in the large colon. Concentrations of VFA in the stomach and small intestine were low in rats and rabbits but were slightly higher in pigs and horses, suggesting slight gastric fermentation in these latter two species. These findings of slight gastric fermentation have been more recently confirmed in pigs and horses (19, 21, 76, 281) and have been extended to other nonruminant herbivores or omnivores, such as rabbits, raccoons, rock hyraxes, and dugongs (74, 75, 216, 302). In dogs, VFA concentrations are highest in the colon (35; Fig. 1); if fed an all meat diet, however, carbohydrate is unlikely to be a significant source of VFA. Instead, dietary protein residues, mucus, and sloughed cells probably are the major substrates for fermentation in these species.

Over the last 50 years, animal studies thus have shown that many plant cell walls and various other plant constituents are fermented to VFA in the gastrointestinal tracts of all herbivores, most omnivores, and, depending on the diet, even some carnivores. Also produced are methane in most species, and carbon dioxide, hydrogen, heat, and microbial cells. Independent of the location of the fermentation chamber, VFA are readily absorbed by the animal. In forestomach fermenters, vitamins are synthesized and protein from microbial cells is digested and absorbed from the small intestine. Hindgut fermenters, however, have the problem that the colon wall does not have proteolytic enzymes and is believed to be devoid of transport systems for amino acids and vitamins. To use microbial cells, hindgut fermenters must reingest their feces, and this is practiced by many rodents. Rabbits and other lagomorphs and even rodents such as beavers and ground squirrels, however, show a more sophisticated or efficient fecal reingestion called cecotrophy (147, 302). In this practice, poorly digestible or less nutritious ingesta particles are separated and disposed of in hard feces. Bacteria, liquid, and small particles are largely retained in the cecum by retrograde transport through the proximal colon (57). From these materials, soft feces enclosed in mucus are produced largely at night and consumed directly from the anus.

In humans, it had been considered for many years that VFA production in the large intestine was minimal, and VFA had been discounted as an energy source. Recent evidence, however, indicates that the quantity of VFA production in humans can be of significance (17, 113, 149, 209). However, because of limitations on sampling digesta from the colon of healthy humans (149, 209), animal models must be used to more precisely study VFA production, absorption, and metabolism as related to humans. Diet and transit time surely must be factors that influence VFA availability (298), and since mammals differ widely in these aspects of digestion,

these differences undoubtedly affect the reliability of data that can be applied to humans.

For example, ruminants are unsuitable for direct extrapolation to humans, because they are predominantly forestomach fermenters, and there is a selective retention in the rumen of fibrous materials relative to the liquid components. Rabbits also are unsuitable, because they have a diurnal excretion of two types of feces (hard and soft) that contain different amounts of VFA, and they normally are coprophagous (134, 147, 302). Furthermore, dogs are a poor animal model, since they are carnivores and have a short, nonsacculated, nonvoluminous gastrointestinal tract. As a result, transit time is rapid in dogs, there is little selective retention of digesta, and VFA production is marginal (22, 35). Rats and other rodents possess a voluminous cecum but smaller colon, and thus the cecum must be the major site for digesta retention and fermentation (22). On the other hand, pigs not only have a voluminous cecum, they have a sacculated colon with anatomic and physiological similarities to the human colon. High concentrations of VFA are found throughout the large intestine of pigs (19, 76), and the large intestine thus must be the major site of VFA production in both pigs and humans. Thus, even though the molar ratios of acetate, propionate, and butyrate are reasonably consistent among various species, including pigs, rats, rabbits, ruminants, and horses (84, 233), it appears that pigs are the most reliable animal models for studying VFA production and metabolism in humans (17, 113).

B. Microbial Fermentation

The gastrointestinal tracts of mammals characteristically are dark, warm, moist, anaerobic, and filled with food. These, of course, are all conditions that favor the growth of microorganisms. The microbial ecosystem of the gastrointestinal tract thus contains hundreds of species of anaerobic bacteria, protozoa, and fungi, and each species occupies a particular niche. Rumen microorganisms, for example, have evolved together over millions of years, and there are numerous interrelationships among them. Commensalism, mutualism, competition, and predation all occur, and individual species can be involved in more than one type of interaction (153, 256). All species ferment some component of the digesta and together produce the microbial bodies and VFA used as food by the host. Diet can change the metabolic activities of the microorganisms by providing new or different substrates, and thus diet influences the quantities and nature of the fermentation end products (153, 256, 262, 265, 307).

Major genera of bacteria that occupy both the

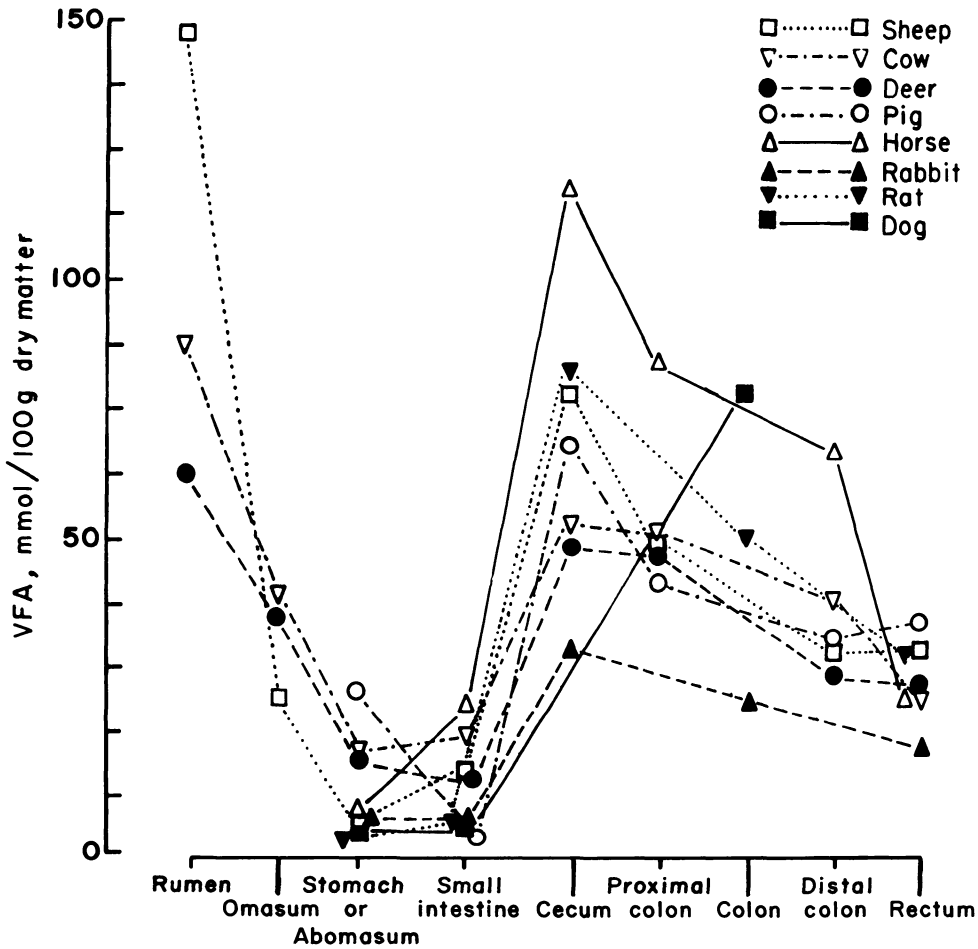

FIG. 1. Concentrations of VFA along gastrointestinal tract of different mammalian species. [Redrawn from Elsden et al. (104) and Phillipson (232).]

rumen and large colon of animals and humans are *Bacteroides*, *Eubacterium*, and *Peptostreptococcus* (5, 88, 138, 153, 262, 322). *Bifidobacterium* and *Fusobacterium*, among others, also are usually found in the colons of humans, and, in the rumen, genera of bacteria such as *Ruminococci*, *Butyrivibrio*, *Streptococci*, and *Methanobacteria* are usually present (3, 280). Further examples of rumen and intestinal bacteria and the substrates they utilize have been given by Hungate (153) and Wolin (322). Thus there are widely diverse bacterial fermentation types, and together they utilize various carbohydrates as well as proteins and miscellaneous substrates.

For the protozoa, their association with the rumen must be ancient. There are no free-living, close relatives of the rumen protozoa. The only descendants that survived adapted as their rumen habitat evolved (153). Most of the rumen protozoa are ciliates of which there are two main types (77, 153), the holotrichs and the entodiniomorphs. The holotrichs reportedly consume bacteria but also rapidly absorb sugars when feed first enters the rumen. The sugars are fermented in part, but if a high concentration is present, then a large fraction is stored as starch within the protozoa. When sugars are no longer available, the starch within the protozoa is digested and fermented. Thus the period of energy availability is extended. The food of the entodiniomorphs consists of cellulose, starch, and bacteria. Some species are carnivorous on other protozoa.

C. *Substrates and Pathways for Volatile Fatty Acid Production*

The major substrates for fermentation, regardless of the location of the fermentation chamber, are complex carbohydrates originating from plant cells, and these, for the most part, consist of cellulose, hemicellulose, pectins, starches, dextrans, and soluble carbohydrates (mono- and disaccharides) (e.g., see Refs. 102, 187). The principal end products of this fermentation are now well documented and are the VFA, especially acetate, propionate, and butyrate, and the gases, carbon dioxide and methane. In most species, any hydrogen produced is usually used by methanogenic bacteria to reduce carbon dioxide to methane. Only negligible amounts of methane, however, are found in the stomachs of kangaroos, various marsupials, and the large intestine of most humans (280). It has been suggested that a lower rate of methane production may be because of a more rapid transit time of digesta, which would tend to inhibit establishment of the slow-growing methanogenic bacteria (151).

The molar ratio of acetate to propionate to butyrate found in the bovine rumen (65:20:15) is similar to the ratio of 74:18:8 found by the same investigators in human feces (212, 323, 324). Fermentation equations (322, 323) thus have been estimated as follows: rumen, 58 $C_6H_{12}O_6 \rightarrow$ 65 acetate + 20 propionate + 15 butyrate + 60 CO_2 + 35 CH_4 + 25 H_2O, and human feces, 56 $C_6H_{12}O_2 \rightarrow$ 74 acetate + 18 propionate + 8 butyrate + 55 CO_2 + 38 CH_4 + 17 H_2O. Overall, VFA production represents nearly 75% of the energy content of the carbohydrate; the remaining 25% is used by the microbes for growth or lost as hydrogen and methane. Although there are many differences in details, this must mean there are general similarities in fermentation pathways in the large intestine compared with those in the rumen. The actual biochemical pathways of VFA production from the fermentation of carbohydrates were the subject of earlier reviews (31, 113, 187, 324).

Cellulolytic bacteria produce extracellular cellulase and other enzymes that degrade the cellulose and hemicellulose fractions to oligosaccharides and finally to glucose, glucose 6-phosphate, fructose 6-phosphate, and triosephosphates. Both noncellulolytic and cellulolytic organisms utilize the products of cellulase action and directly produce VFA. Pectins and hemicellulose at first are largely degraded to xylose and other pentoses. The major pathway of pentose utilization then seems to involve hexose synthesis with the final products being fructose 6-phosphate and triosephosphates, as in the case of cellulose fermentation. Starches and dextrans are degraded by amylases to maltose and then by maltases with the formation of glucose 1-phosphate. All of the above hexose and triosephosphates, however, are rarely detectable in rumen or intestinal fluid and, instead, undergo rapid transformation to pyruvate through the Embden-Meyerhof pathway of glycolysis. Pyruvate, in turn, is then rapidly converted mostly to acetate, propionate, and butyrate, and, as a result, even pyruvate rarely occurs in measurable quantities in rumen or intestinal fluids.

Lactate can be produced from pyruvate, but it usually is not an important intermediate (4, 123, 174, 223, 302); lactic acid production is aided principally by a low pH, which favors the growth of lactobacilli. In humans, high lactate concentrations are present only in very acid stools associated with defective carbohydrate digestion or malabsorption (174, 305, 312). In the rumen, ingestion of abnormally large quantities of rapidly fermentable carbohydrate also will result in a marked fall of pH and thus produce high lactate concentrations and even systemic acidosis (82, 83, 93, 98, 101, 133, 194). In fact, sodium bicarbonate or other buffers are frequently fed to dairy cattle to help prevent acidosis and reduce lactate concentrations (63, 284).

The reactions involved in the formation of acetate and butyrate from pyruvate are interrelated (31, 187, 324), and all proceed through acetyl-CoA. Furthermore, acetate and butyrate are interconvertible (127, 128, 187, 191), and an early study in sheep showed that by infusion of [^{14}C]VFA, 60% of the rumen butyrate carbon was in equilibrium with 20% of the acetate carbon (51). The conversion of butyrate to acetate seems to be advantageous for microbial metabolism, since there is a net gain of ATP. The formation of propionate from pyruvate is separate from that of acetate and butyrate and involves two major pathways. The first pathway involves the formation of oxaloacetate and succinate, and the second pathway involves the formation of acrylate (31, 51, 187, 324). Isotope labeling patterns have shown

that both pathways are operative. The five-carbon VFA, valerate, is formed by condensation of acetate and propionate (127).

In addition to fermentation of carbohydrates, proteolysis can be a major fermentation process that produces peptides and amino acids that then can be used for energy or for biosynthetic processes. Proteolysis is largely accomplished by bacteria, and most amino acids are deaminated to form ammonia, carbon dioxide, and VFA (12, 60, 81, 153, 307). In the rumen, <10% of labeled nitrogen or carbon in a free amino acid is assimilated into microbial cells (153, 326). A similar intracolonic degradation of protein with VFA and ammonia production also seems to occur in both humans and animals (121, 167, 205, 332). Some microbial proteins, at least in rabbits and ponies (325), are further digested in the large colon, possibly by bacterial enzymes, and some free amino acids do seem to be absorbed across the colonic mucosa (248, 249). Proteolysis, whether occurring in the colon or in the rumen, produces not only acetate, propionate, and butyrate but also the branched-chain VFA. The latter are principally isobutyric, isovaleric, and 2-methylbutyric acids that arise from the branched-chain amino acids valine, leucine, and isoleucine (12, 89, 105, 211, 332).

III. RUMEN VOLATILE FATTY ACIDS

A. Concentrations of Volatile Fatty Acids

The concentrations of VFA in the rumen are highly variable, although the total amount present usually is between 60 and 150 mM. Even though considerable information on this subject has accumulated in the last 40 years, the results obtained by different investigators are rarely strictly comparable. This is because the pattern of VFA production in the rumen is dependent on both the composition of diet and the time after feeding. Exceptionally high values rising to 200 mM may occur when animals graze on fresh grass or when fed starch-rich diets. Maximal concentrations usually occur 2-4 h after feeding (36), but diets of hay produce smaller fluctuations throughout the day. The rate of fermentation usually is slower on a hay diet, and concentrations <100 mM are common. On most diets, it takes over 48 h for rumen fermentation and VFA absorption to decrease to ≤5% of its maximal value (53, 250).

Results typical of total and individual rumen VFA concentrations as affected by diet are shown in Table 1. Acetate predominates under most conditions, but substantial amounts of propionate and butyrate are always present (12, 102, 131, 296). Valeric and higher acids usually constitute <5% of the total. Diets rich in starch, such as cereal grains, favor propionate production, and in general, those diets that are rapidly fermented give rise to less acetate. The pH of rumen fluid usually is in the range of 5.8–6.8, but a rapid fermentation can lower the pH to <5.0. This seems to encourage growth of organisms that especially produce both propionate and lactate (30, 98).

TABLE 1. *Examples of VFA concentrations in rumen*

Diet	Species	Total VFA, mM	Molar Proportions of VFA, %			Reference
			Acetic	Propionic	Butyric	
Hay	Sheep	106	69	20	11	51, 127
Grain	Sheep	76	53	34	13	12, 234
Grass	Cow	148	70	19	11	30
Grain	Cow	122	46	42	12	30, 316

Valeric and higher acids usually constitute 5% or less of total VFA.

The above molar proportions of individual VFA in the rumen are of considerable interest and importance. This is a result of the fact that, because of fermentation of carbohydrates, only small amounts of glucose are absorbed from the digestive tract of ruminants (48, 155). Gluconeogenesis thus is a continuous and a major metabolic activity. Propionate is the only VFA that makes a significant net contribution to glucose synthesis, and it is quantitatively the most important single precursor of glucose (45, 46, 52). The higher chain VFA with odd numbers of carbon atoms, such as valerate and heptanoate, will produce glucose, but the amounts produced are too small to be of much quantitative importance. Enough propionate obviously has to be produced to satisfy the animal's needs for glucose. On the other hand, and to complicate matters further, very large amounts of propionate sometimes are associated with a disorder called low-milk fat syndrome (194).

It would seem, therefore, that optimal amounts of propionate need to be produced for the animal's overall economy, and, in this regard, considerable research has been performed on the effects of diet and other factors that can alter the microbial community and thus influence the molar proportions of individual VFA in the rumen. Experiments on the effect of the ionophore antibiotics monensin and lasalocid on pure cultures of rumen bacteria have shown that the ruminococci and butyrivibrios are inhibited by very low concentrations of the antibiotics (71, 324). These species are important producers of acetate, butyrate, and the substrates for methane production, hydrogen and carbon dioxide. Other organisms, which are important in the production of propionate, are either relatively insensitive or rapidly become resistant to the antibiotics. Thus the above antibiotics must alter rumen fermentation not by changing total VFA production but by selecting for organisms that produce more propionate and against organisms that produce more acetate, butyrate, and the precursors of methane (71, 246, 324). These results also have been confirmed in vivo, as shown by the fact that when monensin is added to the feed of cattle, rumen propionate concentrations usually increase (23, 253, 272, 297). In one study, for example, the molar percentage of propionate in the rumen increased from 16 to 18%, and this was at the expense of acetate so that total VFA production was unchanged (23).

Thus concentrations of total and individual VFA in the rumen are highly variable and depend on the time

after feeding and also on the composition of the diet. The relative amounts of roughage, fiber, cereal grains, or readily fermentable feeds therefore are of importance. Changing the rumen fluid dilution rate (23) or feeding bicarbonate or ionophores, such as monensin, will alter individual rumen VFA concentrations. Considerable research has been performed on these aspects of VFA production in attempts to increase the efficiency and economics of animal growth and performance.

B. Rates of Volatile Fatty Acid Production and Absorption

Production and absorption rates of VFA from the rumen have been measured or predicted by a variety of techniques and have been the subject of several extensive, although early, reviews (8, 108, 153, 187, 308). In brief, the main techniques for estimating VFA production in the rumen have involved *1*) incubation and fermentation of rumen contents in vitro, *2*) disappearance of added VFA from the intact and washed out or nonfermenting rumen, *3*) perfusion of the isolated rumen with heparinized blood, *4*) infusion of labeled VFA into the blood and calculating turnover (or entry) rates in the blood, *5*) infusion of labeled VFA into the rumen and calculating production rates from isotope dilution in the rumen contents, and *6*) measurements of net VFA absorption by analysis of arterial and portal blood together with measurements of rates of portal blood flow. As expected, many of these methods, or variations thereof, gave qualitative rather than quantitative information. In other instances the data were not directly applicable to the intact animal (308). In recent years, considerable use has been made of the last two techniques listed above, i.e., dilution of labeled VFA after infusion into the rumen and analyses of arterial and portal blood together with measurements of portal blood flow. Only the results obtained by these two more modern techniques are discussed in this review.

The isotope dilution procedure for calculating production rates of VFA in the rumen depend on estimating the rate of dilution of a continuously infused [^{14}C]- or [^{3}H]VFA (44, 51, 128, 190, 191, 314). Labeled acetate, propionate, and butyrate have been used, and the label usually has been 1-^{14}C. Samples of rumen fluid are obtained from sites in the rumen widely separated from the site of infusion, and the specific activities of each acid are then determined. After ≥1 h of infusion or when the specific activities become constant (plateau period), the rate of production (mmol/h) can be calculated by dividing the rate of infusion (μCi/h) of the individual VFA by its mean specific activity (μCi/mmol). Although the ^{14}C label of propionate does not significantly label acetate or butyrate, interconversions of label between acetate and butyrate definitely do occur, and thus production rates of acetate and butyrate have to be corrected for interconversions (51, 187). Two separate studies in sheep have shown that ~60% of the butyrate carbon in the rumen is in equilibrium with 15–20% of the acetate carbon (51, 187). This was true even when the animals were fed different diets.

The above type of rumen isotope dilution experiments concluded that when sheep were fed dried grass, alfalfa, or wheat hay, the energy in kilocalories of the acetate, propionate, and butyrate produced in the rumen on a daily basis was equivalent to 54–62% of the digestible energy of the feed (51, 128). After subtracting such energy losses as methane in the eructated gases and nitrogenous compounds in the urine, the three VFA then would account for 65–75% of the total metabolizable energy. When it is realized that the higher or five- to seven-carbon VFA can add up to about an additional 5% of the energy and that some VFA are produced and absorbed from the cecum and large intestine, it is obvious that the total VFA produced make up a very large part of the useful energy made available to the animal. The total available VFA easily could account for 80% of the animal's daily energy requirements. The rate of production of VFA in the rumen thus obviously depends on the amount and kind of feed eaten and can be highly variable. As an example, for a 55 kg sheep on a maintenance dried-grass diet, rumen production rates obtained for acetate, propionate, and butyrate were 3.7, 1.0, and 0.7 mol/day, respectively, and these had the energy equivalents of 773, 386, and 357 kcal/day, respectively (51). Acetate thus provided about one-half and propionate and butyrate each provided about one-fourth of the caloric energy contained in the three VFA. More recently, the rate of total VFA production in the rumen has been calculated to be ~5 mol/kg dry matter intake (32, 247).

Several investigators have attempted to predict the precise production of VFA from their concentrations present in the rumen (128, 187, 190, 315). In fact, the concentration of a particular VFA in the rumen represents a balance between the rate of production and the rate of removal of the acid from the rumen. If the VFA rumen concentration remains nearly constant because of frequent feeding, then statistical analyses do indeed show that the production rates of the individual VFA are roughly related to their rumen concentrations. Leng (187) and Leng and Brett (190) have calculated from experiments on sheep that when the rumen concentration (in mM) is multiplied by 0.038, the product will roughly predict the rumen production rate in terms of millimoles per minute. At a rumen total VFA concentration of 100 mM, this would then amount to a VFA production rate of 3.8 mmol/min or 5.5 mol/day. This type of calculation does have usefulness, but, as stated by the authors, the calculated rate has a high coefficient of variability (28%). Attempts to use this equation solely for precisely predicting VFA availability on a variety of diets therefore result in large quantitative errors.

In recent years, rates of VFA production in the gastrointestinal tract of ruminants also have been estimated by measuring the amounts of VFA directly absorbed or appearing in the bloodstream. This type of experiment is done by multiplying the rate of portal blood flow by the concentration differences of individ-

ual VFA between arterial and portal blood (42, 112, 117, 170, 172, 250, 264). It should be pointed out, however, that the amounts appearing in portal blood are not equal to the amounts produced in the ruminant stomach. This is because each of the individual VFA is metabolized to different extents by the rumen mucosa during the process of absorption (206, 225, 282). Furthermore, rates of absorption into the portal blood include any VFA produced and absorbed from the cecum and colon. Numerous studies have been performed, however, and a considerable body of knowledge has been obtained. Several methods have been used for measuring portal blood flow, but the most commonly used method at the present time is based on the infusion of *p*-aminohippuric acid into a small mesenteric vein and sampling downstream in the portal vein just as the blood enters the liver (170, 172). Although these studies are technically difficult, numerous experiments have been performed on both sheep and cattle; chronically catheterized animals have been used, with the animal fed different diets (26, 28, 44, 52, 53, 154–156, 181, 195, 245, 250).

Table 2 compares typical results on VFA absorption into the portal blood of sheep with those values obtained on similar animals for VFA production in the rumen itself. In these studies, all three of the major VFA were produced in the sheep rumen at higher rates than appeared in the portal blood. Roughly 30, 50, and 90% of the acetate, propionate, and butyrate, respectively, did not reach the portal blood, at least as VFA, and thus must have been metabolized mainly by the rumen epithelium. These results also are compared with data on VFA absorption from the lumen side of isolated sheets of rumen epithelium (Table 2). In these in vitro experiments, rumen epithelial metabolism accounted for 45, 65, and 85% of the acetate, propionate, and butyrate, respectively, disappearing from the lumen side. This close agreement between in vivo and in vitro results thus emphasizes not only the fact that VFA are metabolized by the rumen epithelium but also shows that only little agreement should be expected between measurements of VFA production in the rumen itself and VFA appearance in the portal blood. Thus there must be a very active metabolism in the portal-drained viscera, which includes the energetic costs of the digestive and absorptive processes. In fact, oxygen consumption of the portal-drained viscera of cows has accounted for 18% of the total heat production of the whole body (157).

TABLE 2. *Comparison of rumen production of VFA with portal absorption and rumen epithelial metabolism*

	Volatile Fatty Acids			
	Acetic	Propionic	Butyric	Reference
Sheep fed hay				
Rumen production, mol/day*	3.3	0.9	0.6	51, 191
Portal absorption, mol/day	2.3	0.44	0.05	52, 53
Difference, %	30	50	90	
In vitro rumen epithelium†				
Metabolism, %	45	65	85	277

* Measured by isotope dilution in rumen. † Amounts metabolized by isolated sheets of rumen epithelium as a percentage of that removed from medium.

Experiments on VFA absorption into the portal blood of cattle have yielded results qualitatively similar to those obtained in sheep. The cattle, however, were lactating and were fed a highly concentrated grain diet (60:40 hay-to-grain ratio). For a 500 kg cow on this high-grain diet, typical portal VFA absorption rates were 31, 17, and 3 mol/day for acetate, propionate, and butyrate, respectively, and these would account for 16, 16, and 3.5%, respectively (total of 36%), of the cow's total digestible energy intake (245). Other values obtained from both lactating and nonlactating dairy and beef cattle have varied from 35 to 50% of the cow's digestible energy intake (26, 28, 156, 245). These portal absorption rates thus are lower than rates that would be expected for production within the rumen; undoubtedly this is largely due to rumen epithelial metabolism, which again emphasizes the active metabolism of the portal-drained viscera. Other sources of energy available to the animal, besides VFA, would of course include absorbed lactate, ketone bodies, longer chain fatty acids, amino acids, and peptides (47, 171, 287, 309).

C. Rumen Epithelial Transport and Metabolism

As discussed, and as noted in Table 2, large amounts of VFA are metabolized by the rumen epithelium during the process of absorption and transport to the bloodstream. It was the studies of Barcroft et al. (36) that first showed that the major portion of the VFA produced in the sheep rumen actually was directly absorbed from the rumen itself rather than being passed along for later absorption from the abomasum and small intestine. This may seem surprising in view of the fact that the rumen wall consists of stratified squamous epithelium backed by a smooth muscle coat (97). The rumen epithelium also is nonglandular, comparatively simple, and with no secretory function, although numerous folds and papillae greatly increase the epithelial surface area. In at least two studies, rumen outflow to the omasum has been quantitated, and it was calculated that ~88% of the rumen VFA was directly absorbed from the rumen and only ~12% flowed into the omasum (285, 286).

A considerable amount of effort has since been devoted to the study of VFA absorption, metabolism, and transport from the rumen. Because the VFA are weak acids with a pK of ≤4.8 and because the pH of the rumen contents seldom falls below 5.8, most of each VFA is present in the dissociated or ionized state. At the same time, absorption of VFA from the rumen is enhanced by a decrease in the pH of its contents (86), indicating greater permeability of the epithelium to the undissociated or acid form of the VFA. In fact, the epithelium

appears to be almost impervious to passive diffusion of the dissociated or anionic form. However, despite the fact that the VFA are mostly present in their dissociated form at the usual pH of the rumen contents, the VFA are rapidly absorbed from the rumen. Nearly equimolar amounts of hydrogen ions thus must be available to protonate the VFA. In earlier studies, Ash and Dobson (25) concluded that hydration of CO_2 in the sheep rumen provided a source of hydrogen ions for the production of undissociated VFA. This would then favor absorption of the VFA and also explain the accumulation of bicarbonate within the rumen contents, as observed by others (96, 206). Substantial amounts of carbonic anhydrase have been found in rumen epithelial cells, and this could be involved in a subsequent release of bicarbonate into the rumen (283). Most of the CO_2 seems to be produced by intracellular epithelial metabolism, although CO_2 also could be absorbed from the lumen side of the epithelium to provide the carbonic acid for the donation of hydrogen and bicarbonate ions (96, 278).

Subsequent studies by Stevens (278, 280) and by Stevens et al. (281) also showed that transport of VFA across isolated sheets of rumen epithelium could not be explained by an electrochemical gradient for either the dissociated or undissociated forms of the VFA. They proposed, instead, that the lumen and blood surfaces of the epithelium differed in relative permeabilities to the two forms of the VFA and that transport of VFA can be explained by maintenance of an electrochemical gradient for hydrogen ions between the contents of epithelial cells and the solutions bathing their lumen- and blood-facing membranes. Present evidence therefore indicates that transport of VFA from the rumen into the blood can be explained by diffusion alone but that this is affected by the pH of lumen and cell contents as well as by intracellular metabolism of VFA.

For individual VFA, the rate of absorption from the rumen increases with increasing chain length of the acid (86, 126, 231, 282) or acetate < propionate < butyrate, and this is in keeping with their relative lipid solubilities. In contrast, the amounts transported or appearing in the venous effluent are in the reverse order or butyrate < propionate < acetate (52, 206). Thus the proportion metabolized has to increase markedly with chain length, and this is particularly true of butyrate. About 90% of butyrate is metabolized by the rumen epithelium regardless of whether it is measured in vivo or in vitro (Table 2). It is of interest that although anoxia suppresses rumen epithelial VFA metabolism and absorption from the lumen side of epithelial sheets, anoxia can actually increase the amount of VFA transported to the blood side of the epithelium (140, 282). Thus this demonstrates the interdependence of epithelial absorption and transport with that of metabolism.

Formation of ketone bodies or oxidation to CO_2 accounts for most of the butyrate that is metabolized by rumen epithelium (225, 250, 274). Also, ketone bodies have been shown to contain, on an energy basis, ~15% of the VFA found in the portal blood of fed sheep; no ketone bodies are produced by the gastrointestinal tract of starved sheep (171, 250). This process of ruminal epithelial metabolism of butyrate to ketone bodies has been termed an alimentary ketogenesis to distinguish it from the more usually recognized hepatic ketogenesis. Previous work has estimated alimentary ketogenesis to be in the range of 1–2 g/h in fed sheep (43).

Propionate metabolism by rumen epithelium gives rise to lactate and CO_2 (226) but also probably to alanine (50, 219, 319, 321) and other amino acids. Calculations on intact sheep indicate ruminal propionate metabolism to approximate 50% of the total propionate produced in the rumen (44, 46, 166, 310; Table 2). It is of significance, however, that most of the data showing this extensive a metabolism of propionate by rumen epithelium have been derived from sheep. Studies on cattle do not give such high estimates of propionate loss during rumen absorption. In experiments on calves (311) and adult cows (78), only 3–15% of rumen propionate was converted to lactate. Thus the metabolic machinery for the production of lactate from propionate undoubtedly is always present, but species differences in its quantitative importance probably exist (103). The extent of propionate oxidation by rumen epithelium or conversion to other products, such as alanine, also seems to differ with animal species. Large total losses (30–65%) of propionate occur during rumen absorption in sheep (44, 46, 166, 310), but only small reductions in propionate availability in portal blood (relative to acetate) have been noted in cattle (104, 311). Biochemical studies also have shown that propionyl-CoA synthetase activity in mitochondrial preparations from sheep is about equal in liver and rumen epithelium (78). In cattle, however, propionyl-CoA synthetase activity in liver homogenates is 14–28 times that of rumen epithelium (24). Thus these findings are consistent with the concept that rumen epithelium of cattle metabolizes propionate to a considerably lesser extent than in the case of sheep (103). The liver, nevertheless, is an important site of propionate metabolism in both species.

IV. CECAL AND LARGE INTESTINAL VOLATILE FATTY ACIDS

A. Concentrations and Rates of Production of Volatile Fatty Acids

The VFA have been identified in the lower digestive tract or feces of humans and all mammalian species studied so far. As in the case of the rumen, VFA production is primarily the result of anaerobic microbial fermentation of otherwise indigestible carbohydrates, such as cellulose, hemicellulose, pectins, and oligosaccharides. Digestible carbohydrates, such as starch and glucose, however, also are readily fermented should they escape digestion or absorption in the small intestine, and this can occur if unusually large amounts of simple carbohydrates are eaten or if they are malabsorbed. Additionally, sloughed cells, mucus, and endogenous secretions provide some fermentable substances, especially proteins and polysaccharides.

Acetate, propionate, and butyrate are the major VFA produced just as they are in the rumen. Total concentrations of VFA in the cecum, large colon, rectum, and feces of all animals have been measured in the range of 30–240 mM but more commonly average 70–120 mM. Their concentrations in pigs have been shown to increase as the proportion of fiber reaching the hindgut increases (169). A high-fiber diet in rats (91, 293) also has been shown to increase VFA fecal production or absorption into the blood. The amount of soluble carbohydrate as well as fiber reaching the large intestine thus obviously varies with diet as well as with species of animal. As summarized by others (143, 243, 280, 281), from 8 to 26% of total dietary carbohydrate reaches the hindgut in pigs and sheep and as much as 70% has been calculated for ponies. Comparable values for humans on European diets (149, 209) suggest that 50–60 g of carbohydrate are commonly fermented per day, yielding 0.5–0.6 mol VFA with a total energy value of 140–180 kcal.

The molar proportions of acetate to propionate to butyrate in the cecum, large colon, or rectum of animals, such as horses, sheep, pigs, and various wild species, have been found to approximate 70:20:10 (104, 109, 110, 123, 144, 164, 279, 330), although in the rabbit the amount of butyrate is greater than propionate so that the ratio is closer to 70:10:20 (139, 222, 302, 304). Mean values approximating 60:20:20 have been found in the feces of normal humans on American or Western European diets (56, 150, 254, 324). Again, although not as highly variable as in the case of the rumen, highly fermentable carbohydrates and sugars tend to result in a high propionate-to-acetate ratio and a decrease in the pH of the large intestinal contents. Conversely, high-fiber diets increase the proportion of acetate (113, 114, 273). Studies conducted on pigs as well as on cattle and sheep have produced similar findings (6, 19, 173, 220).

Gases also are produced from fermentation in the large intestine and cecum (68, 324) and, as in the rumen, consist mainly of CO_2, CH_4, and H_2. Murray et al. (215) estimated that intestinal fermentation in sheep provides ~13% of the CH_4 produced in the entire gastrointestinal tract. In humans, however, the average percentage of CO_2 and CH_4 is considerably lower than in ruminants and, in fact, CH_4 is produced in only about one-third of the adult human population (192, 324). Some individuals produced ~20% of the CH_4 per day that a sheep produces, but individuals who do not form CH_4 form H_2 gas. The reason for this difference is unknown, although it may be related to the transit time of digesta and thus growth of specific species of slow-growing methanogenic bacteria (151, 213, 324).

Rates of production of VFA in the cecum and large colon have been more difficult to measure than in the case of the rumen, and this principally has been because of the relative inaccessibility of the lower digestive tract for sampling and measurement of flow. Most experimental data on rates of VFA production in the lower digestive tracts of animals have been obtained by the use of cecal or colonic fistulas or by the use of cannulas. The rate of passage of digesta has been calculated in many instances (e.g., see Refs. 16, 125, 279, 281) and, importantly, isotope dilution studies have been performed in a variety of animal species similar to that described for the rumen (110, 115, 123, 221, 330). In some cases, in vitro incubation of large bowel or cecal contents have been carried out (111, 144, 145, 160, 164). Measurements of VFA in blood draining the cecum (36) or in intestinal lymph (62) and in the portal vein of nonruminants (158, 161, 302) and humans (85, 87) also have been made. In all species studied, VFA are readily absorbed into the blood from the lower digestive tract just as in the case of the rumen. Only little VFA appears in the lymph.

TABLE 3. *Estimates of contributions of VFA produced in different segments of digestive tract of various species to energy requirements of whole body*

Species	Organ	% of Energy Requirements	Reference
Sheep	Rumen*	70	51, 128
	Cecum*	5	110
	Total hindgut†	8	143, 294
Cattle	Rumen*	63	269
	Total hindgut†	9	269
Rat	Cecum*	5	330
Porcupine	Cecum‡	16	164
Beaver	Large intestine‡	19	144
Rabbit	Cecum‡	12	145
	Total hindgut*	30	203, 221
Pony	Cecum*	30	123
Pig	Large intestine‡	11	160, 175
	Total hindgut§	25	244
Human	Large intestine†	6–10	209

* In vivo isotope dilution. † Calculations based on amount of fiber and carbohydrate leaving ileum. ‡ In vitro incubation of gut contents. § Absorption into portal blood.

Hoverstad (149), McNeil (209), and Wrong et al. (328) recently reviewed methods used to study VFA absorption or production in the digestive tract of humans. Briefly, these have involved *1*) instillation of a bolus solution of VFA into the colon, *2*) instilling [^{14}C]VFA into the colon and measuring $^{14}CO_2$ in the breath, *3*) in vivo intestinal perfusion of VFA, *4*) dialysis bag techniques, *5*) in vitro perfusion of colonic segments obtained postoperatively, *6*) rough estimates of the amounts of carbohydrate entering the large intestine, and *7*) estimates of growth requirements of bacteria recovered in the feces. Although these methods are subject to considerable assumptions and errors, it has become obvious that all that enters the human large intestine is not lost. In humans, VFA had once been considered to be poorly absorbed, if at all, and instead VFA from carbohydrate fermentation produced diarrhea because of their osmotic properties (70, 317). Thus the role of the large intestine as a potential energy source in humans had been discounted. As stated by McNeil (209), however, humans would be unique members of the animal kingdom if VFA were not absorbed from the large intestine.

Table 3 summarizes estimates obtained in various

species for the contribution of VFA to the energy requirements of the whole body. Considerable variation is present, and errors undoubtedly have arisen because of methodology or assumptions by the authors. In general, in vitro incubation techniques tend to underestimate VFA production, and in vivo techniques tend to be the most reliable. Also in most cases only the cecum or the large colon was used for calculation. Despite these uncertainties, however, considerable energy must be available from the VFA produced in the lower gut; values from 5 to 30% were obtained, and these are in keeping with the differences in diet and digestive tract morphology. All values were, of course, lower than that obtained from the rumen. The highest figures of 30% were obtained from rabbits and ponies; this is expected, since they are entirely herbivorous and are hindgut fermenters. Pigs and humans seemed roughly comparable, and this also is expected in view of their similarities in digestive tract morphology. The value of 6-10% for humans (Table 3) was calculated on the basis of a typical British diet where 50-60 g of carbohydrate (15 g fiber and 35-50 g sugar and starch) are fermented per day (209). It is pointed out, however, that dietary fiber intakes in Africa or the Third World are up to seven times higher than in the United Kingdom (55). It is likely, therefore, that much of this increased fiber intake is fermented to VFA and even greater amounts of energy are made available by large intestinal fermentation. More accurate studies need to be designed for the contribution of the large intestine to VFA production and nutrition in general.

B. Absorption and Metabolism of Volatile Fatty Acids

Each of the VFA is readily absorbed from all segments of the lower digestive tract, and this VFA intestinal absorption has similarities to that occurring in the rumen. The VFA absorption appears to be mostly passive and increases linearly with corresponding decreases in pH or increases in concentration (142). However, unlike the rumen, the individual VFA probably are absorbed at comparable rates rather than in the ascending order of acetate < propionate < butyrate (21, 208, 255, 295, 330). Total VFA absorption from the lumen side of isolated sheets of gut epithelium in general showed remarkable similarities among animal species. Overall rates found for the cecum and colon were 8-10 $\mu mol \cdot cm^{-2} \cdot h^{-1}$ for pigs, 7-10 $\mu mol \cdot cm^{-2} \cdot h^{-1}$ for ponies, and 9 $\mu mol \cdot cm^{-2} \cdot h^{-1}$ for dogs (19, 21, 281). Furthermore, these absorption rates were similar not only to the rate obtained for rumen epithelium (10 $\mu mol \cdot cm^{-2} \cdot h^{-1}$) but also to absorption rates calculated from dialysis bags (6-12 $\mu mol \cdot cm^{-2} \cdot h^{-1}$) in the human colon (209, 210, 281).

The mechanism of VFA absorption from the colon has been the subject of several reviews (84, 149, 255, 280, 281). Briefly, two different patterns of VFA absorption seem to be involved. First, as in the case of the rumen, absorption of the unionized or acid form of the VFA can occur with luminal accumulation of bicarbonate and an increase in pH. A second pattern involves absorption of the ionized form of the VFA, since absorption of sodium occurs at a similar rate to that of VFA but with no associated appearance of bicarbonate in the lumen. Both mechanisms have been elucidated in the colon of ponies, pigs, and humans as well as in the rumen of sheep, with each mechanism accounting for roughly one-half of the total VFA absorbed. In the colon and rectum of goats and dogs, however, only the second mechanism presumably occurs, since VFA and sodium were absorbed at a similar rate and no bicarbonate appeared in the lumen (280, 281). Also, different segments of the pony colon vary as to which mechanism predominates (20); both mechanisms occur in the proximal colon, but the second mechanism was found to predominate in the distal colon. Thus, aside from its energy value, VFA absorption must have a significant role to play in sodium and water conservation by the body.

The VFA also are metabolized by the colon and cecum during the process of absorption and transport to the bloodstream. Although in vitro metabolism of mixed solutions of acetate, propionate, and butyrate can account for as much as 50-80% of that initially absorbed (19, 281), the amounts actually metabolized in vivo most probably are considerably less than these amounts. Less information is available about VFA metabolism by cecal and colonic epithelium, but, qualitatively at least, the metabolism of individual VFA resembles that occurring in rumen epithelium.

Table 4 summarizes total and individual VFA concentrations obtained simultaneously from various blood vessels and in the hindgut of rabbits, pigs, and humans compared with concentrations obtained from

TABLE 4. *VFA molar proportions and concentrations in digestive tract and blood of different mammalian species*

	Total VFA, mM	Molar Proportions of VFA, %			Reference
		Acetic	Propionic	Butyric	
Sheep rumen	106	68	19	13	51
Portal vein	1.60	86	12	2	53
Hepatic vein	1.39	98	1.4	0.4	53
Artery	0.77	98	1.5	0.5	53
Rabbit cecum*	74	73	9	18	302
Portal vein	5.31	74	10	16	302
Hepatic vein	2.51	91	4	5	302
Artery	1.77	88	6	6	302
Pig colon	210	55	34	11	19
Portal vein	0.75	63	29	8	244
Artery	0.17	90	6	4	244
Human colon†	124	60	19	21	85
Portal vein	0.36	69	23	8	85
Hepatic vein	0.15	78	14	8	85
Arm vein	0.08	89	6	5	85
Human portal vein‡	0.16	73	20	7	87
Arm vein	0.04	89	5	6	87

* Anesthetized and during phase of formation of hard feces. † Accident victims. ‡ Fasted before gall bladder surgery.

the blood and rumen of sheep. Clearly total VFA concentrations as well as individual molar proportions in the cecum and colon are close to those found in the rumen. The concentrations and proportions of VFA in the blood also show rough resemblances among the several species. Portal blood, of course, has a higher total VFA concentration than hepatic or arterial blood because of direct absorption of VFA through the gut epithelium and because hepatic and peripheral metabolism has not yet had a chance to occur. Importantly, however, the molar proportions of the individual VFA in blood do not parallel those found in the rumen or gut contents. The reasons for this clearly mean that each of the individual VFA is metabolized to different extents by the gut epithelium. Except for rabbits, propionate and especially butyrate are considerably lower in portal blood than in the gut or rumen, and this must mean propionate and butyrate are metabolized to a greater extent during absorption than is acetate. Similar metabolic patterns occur in the liver; much lower amounts of propionate and butyrate are found in hepatic, arterial, or peripheral venous blood than in portal blood. Thus the liver must remove a large proportion of the remaining propionate and butyrate and a smaller proportion of the acetate. In fact, in all species, acetate comprises ≥90% of the VFA in arterial or peripheral blood and is the principal VFA made available for use by muscle and adipose tissue (Table 4).

In the cecum of rabbits (135, 301, 304) and rats (241), ~12% of the butyrate has been found to be converted to ketone bodies and free amino acids. Furthermore, small amounts of ketone bodies can even diffuse back into the intestinal lumen (135, 255). In addition to ketone bodies, butyrate is readily oxidized to CO_2 in the colonic wall of pigs (160), rabbits (304), rats (252), and humans (251) and thus acts as an important respiratory fuel or energy source for the colon. Glutamine also is used as a respiratory fuel for the colon of most animal species (47, 50, 319), but the above studies indicate that butyrate probably is preferentially utilized over glutamine and all other metabolites as an energy source for the colonic epithelial cells. The oxidation of butyrate to CO_2 by the colon apparently is greatly increased under the influence of aldosterone (301).

Acetate metabolism by the hindgut also can yield some ketone bodies and, in rabbits (204), acetate metabolism varied with the segment studied; the distal portion of the gut showed by far the highest acetate uptake. At least in rabbits, acetate was mainly converted to aspartate and glutamate, which were considered to be stock forms that could then be diverted either toward oxidation or toward protein synthesis (204). For propionate, the rate of absorption as well as of metabolism in the rabbit gut seems to be greater in the proximal colon than in the cecum (303). In addition, propionate was found to be an efficient respiratory fuel for the colonic mucosa, as well as forming substantial amounts of lactate and free amino acids (214, 303).

V. METABOLISM OF VOLATILE FATTY ACIDS BY LIVER AND PERIPHERAL TISSUES

A. *Overall Metabolism of Volatile Fatty Acids by Body Tissues*

It is now well established that microbial fermentation in the gastrointestinal tract contributes to the energy balance of all mammalian species. Carbohydrates or endogenous secretions that are otherwise indigestible are fermented and generate VFA, which are directly absorbed at their site of production. The VFA are then metabolized either locally, by the liver, or by peripheral tissues. Hungate (152) estimated that ~75% of the initial energy is retained in VFA arising from the ruminal fermentation of carbohydrate. Other estimates, based on glucose fermentation in the large colon and its potential contribution to ATP, suggest that the theoretical energy yield is ~60% (113, 212). In either case, the remaining 25–40% of the potential energy is used by the microbes for growth or is lost as hydrogen and methane.

As discussed and as indicated in Table 4, some species differences in VFA metabolism do exist. More importantly, however, the metabolism of VFA differs with each individual compound. Most of the butyrate usually is oxidized to CO_2 or to ketone bodies in the rumen or colonic mucosa during its transport to the bloodstream. Lesser, although still substantial, amounts (probably 10–50%) of propionate also usually are metabolized by the rumen or gut wall. The remaining butyrate and propionate along with most of the acetate are then transported to the liver via the portal vein. The liver then usually and almost quantitatively removes the remaining propionate and butyrate with the result that acetate comprises 90–98% of the VFA present in both arterial and peripheral venous blood. The enzymatic activation of VFA by formation of acetyl-CoA compounds seems to be the important mechanism for regulating the different rates of uptake of the individual VFA by various tissues. The relative activities of acetyl-CoA, propionyl-CoA, and butyryl-CoA synthetases in different tissues (15, 24, 78, 274) thus appear to ensure that, in most species, butyrate is metabolized mainly in rumen and gut epithelium, propionate in liver, and acetate in peripheral tissues.

All of the VFA are readily and effectively used as energy sources for maintenance, growth, and lipogenesis. Considerable research has been performed in ruminants in this regard, since the efficiency of utilization is of nutritional and economic importance. Calculations have shown that for acetate and butyrate theoretical efficiencies for lipogenesis are high (78–80%) provided that sufficient reducing power in the form of NADPH is available (10, 61). The NADPH apparently is largely produced by metabolism of glucose through the pentose phosphate pathway. In ruminants, much of the body's supply of glucose is from propionate, and thus, although propionate availability may not be

called critical (103), propionate does have some effect on the efficiency of acetate utilization. Annison and Armstrong (10) have reviewed relevant data and concluded that the overall experimentally measurable efficiency of VFA utilization for lipogenesis, growth, and milk synthesis is in the range of 60–70%, which is not far below the theoretical value of 78–80%. Interestingly, mathematical models simulating the metabolism of absorbed nutrients have been used to examine the efficiency of acetate utilization in sheep (59). The predicted efficiency of acetate utilization was 58–70% at near maintenance, but at very high levels of absorbed energy the efficiency for acetate utilization ranged from 16 to 50%. Addition of glucose or propionate increased the efficiency as expected from in vivo derived data.

B. Acetate Metabolism

Because of the site and extent of fermentation, ruminants absorb more acetate but far less glucose into the blood than do nonruminants. A major difference between ruminant and nonruminant metabolism thus stems from the availability and roles of acetate and glucose as precursors of acetyl-CoA for later use in oxidation or for synthetic processes, such as lipogenesis. Also, although the biochemical pathways for acetate metabolism in mammals have long been known, quantitative differences in acetate metabolism do exist among tissues as well as among animal species.

Research on acetate metabolism in body tissues has been much more extensive in forestomach than in hindgut fermenters or in humans. A useful approach in studies on ruminants has been the use of the isotope dilution method to measure acetate turnover (or entry) rates in the whole body (9, 15, 44, 53). This method consists of using a continuous intravenous infusion of [^{14}C]acetate, and the calculated turnover represents both inflow and outflow from the body pool of blood acetate. Acetate metabolism is rapid, and it is cleared from sheep blood with a half-time of 2 min (13). Pethick and Lindsay (229) have reported that acetate turnover in sheep is closely related to blood acetate concentration and have derived the equation $Y = 2.06X - 0.10$, where Y is acetate turnover in millimoles per hour times kilogram body weight and X is arterial acetate concentration in millimoles per liter. The oxidation of acetate accounts for at least 30% of the total CO_2 exhaled in the fed ruminant and 10–20% during fasting (9).

When the above isotope dilution procedure is combined with measuring venoarterial concentration differences and rates of blood flow, the production and utilization of acetate by specific tissues can be examined (9, 44). Figure 2 summarizes data obtained by these two methods on the flow and metabolism of acetate in the portal-drained viscera (digestive tract, pancreas, and spleen), liver, and peripheral (or remaining) tissues of fed and fasted sheep. Between 25 and 35% of the [^{14}C]acetate was removed from the arterial blood in passage through the portal-drained viscera, and this corresponded to mean utilization rates of 23 and 7 mmol/h in the fed and fasted sheep, respectively. The actual absorption or rate of appearance of acetate in the blood during feeding (97 mmol/h) thus was larger than its net absorption (157 − 83 = 74 mmol/h). Also of importance is the fact that acetate absorption (97 mmol/h) accounted for only ~75% of total acetate turnover (133 mmol/h), and thus a continuous endogenous production of acetate must have been occurring in peripheral tissues (Fig. 2).

The fact that there is substantial gut utilization of acetate from the blood has been confirmed by others (230), but the acetate probably is used mostly by smooth muscle in the gut wall and adipose tissue in the omentum rather than by epithelial tissues. From 15 to 20% of the total acetate turnover in the blood of sheep thus seems to be used by the portal-drained viscera. Furthermore, gut acetate utilization in sheep has been calculated to be related to arterial concentration by the relationship $Y = 33.58X - 1.1$, where Y is acetate utilization in millimoles per hour and X is arterial acetate concentration in millimoles per liter (9).

In ruminants, only a small proportion of absorbed acetate is utilized by the liver. This is exemplified in Figure 2 and also has been shown by a wide range of in vitro (78, 189, 207) and in vivo studies (28, 53, 79, 141, 292). In this regard, acetyl-CoA synthetase activity is low in ruminant liver compared with adipose tissue or muscle, and similarly lipogenesis in ruminants is known to occur almost entirely in adipose tissue rather than in liver (9, 78, 162, 292). Thus, in ruminants, it is adipose tissue rather than liver that clearly seems to be geared for acetate utilization.

Although acetate uptake is low in ruminant liver, acetate production by liver seems to be slightly more variable. In normally fed or fasted sheep (Fig. 2), liver acetate production was low and accounted for only ~20% of the endogenous acetate production. Furthermore, no significant net liver acetate production existed. The livers of lactating cows and sheep, however, have been reported to produce small but significant net amounts of acetate (27, 28, 80, 122, 196), although further confirmation of these data is needed. If present, acetyl-CoA production in the liver from endogenous sources other than acetate has to be high as well as the relative activity of acetyl-CoA hydrolase to that of acetyl-CoA synthetase (66, 271).

Acetate metabolism by the liver of most nonruminant species shows substantial differences from that described for ruminants. It is known, for example, that lipogenesis occurs mainly in the liver of humans and birds, but in ruminants and pigs, lipogenesis occurs almost exclusively in adipose tissue (39, 185, 224). In rodents, fat synthesis occurs in both tissues. These species differences in lipogenesis definitely seem related to the metabolism of acetate, since acetyl-CoA readily is used for fatty acid synthesis. In rats, it has been shown that hepatic acetate uptake is directly proportional to the concentration of acetate in the portal vein (66, 242), and in fed adult rats, hepatic uptake of acetate averages >60% of that absorbed from the gut. Importantly, also, rat liver puts out acetate into the blood when the portal

concentration falls below a minimum value of ~0.2 mM (66, 136), which is close to the Michaelis constant (K_m) for acetate of acetyl-CoA synthetase (66). Antibiotic treatment of rats can stop gut microbial fermentation and thereby lower blood acetate concentrations sufficiently to bring about an hepatic acetate output.

Also of interest is that diabetic rats (66, 179, 267), sheep (179), humans (268), and ketotic cows (1) all have elevated peripheral blood acetate concentrations, and, at least in rats, this has been shown to be because of increased production and release of acetate by the liver (267, 271). The activity of acetyl-CoA synthetase in diabetic rat liver definitely seems to be decreased (180, 217, 218), and this clearly could alter the characteristics of acetate exchange between blood and liver. Along with the increased hepatic acetate output in diabetes, however, there also seems to be an increased acetate uptake in peripheral tissues apparently simply because of the increased circulating acetate concentrations.

As indicated (Fig. 2), peripheral tissues of ruminants account for a substantial proportion of the acetate produced endogenously. Even more striking, however, is the fact that, even though acetate uptake by the gut is large, peripheral tissues utilize ~80% of the total acetate entering the blood. Thus the major tissues involved in this large acetate metabolism must be adipose tissue and skeletal muscle. The importance of acetate in lipogenesis was just discussed. In ruminants, acetate carbon is incorporated into fatty acids either by adipose tissue or by the mammary gland many times more rapidly than glucose carbon (33, 34, 306). In the rat, the opposite situation exists (34), whereby glucose is the preferred substrate, and thus this demonstrates a major difference in lipogenesis between ruminant and nonruminant species. Short- to medium-chain fatty acids up to palmitate are all readily synthesized from acetate in ruminants (236, 237). Annison (9) recently has summarized the data on acetate metabolism by the lactating mammary gland, and it is clear that there is a release of endogenous acetate presumably from free fatty acids (FFA) as well as an extensive acetate uptake. It is interesting that >25% of the acetate taken up by the mammary gland is oxidized to CO_2 (9, 14, 54).

Skeletal muscle metabolism of acetate has been studied in the hindlimb of both sheep (162, 229) and cattle (40, 41). These animal preparations consist of mostly skeletal muscle, although some adipose tissue is present. In fed sheep at rest, for example, acetate extraction from arterial blood was large and accounted for at least 20% of the oxygen uptake by the hindlimb (162). During exercise, however, acetate uptake sharply fell and accounted for <5% of the oxygen uptake; glucose and FFA were the principal nutrients utilized in this instance.

C. *Propionate and Butyrate Metabolism*

As discussed in section IV*B*, propionate and butyrate are metabolized by both rumen and gut epithelium and by liver. Butyrate, however, is largely removed by the rumen or gut epithelium, whereas most of the propionate is taken up by liver. For both VFA, only little escapes to the general circulation, and thus acetate accounts for 90–100% of the total VFA in arterial blood.

Butyrate metabolism by liver involves conversion to butyryl-CoA by the enzyme butyryl-CoA synthetase (24, 78, 92). After this initial reaction, it is rapidly converted to acetyl-CoA, longer chain fatty acids, or to ketone bodies. At least one-fifth of intravenously injected butyrate has been reported to be used for hepatic ketogenesis in sheep, with the remainder presumably oxidized or used as the primer compound for long-chain fatty acid synthesis (49, 171). Although nearly all the

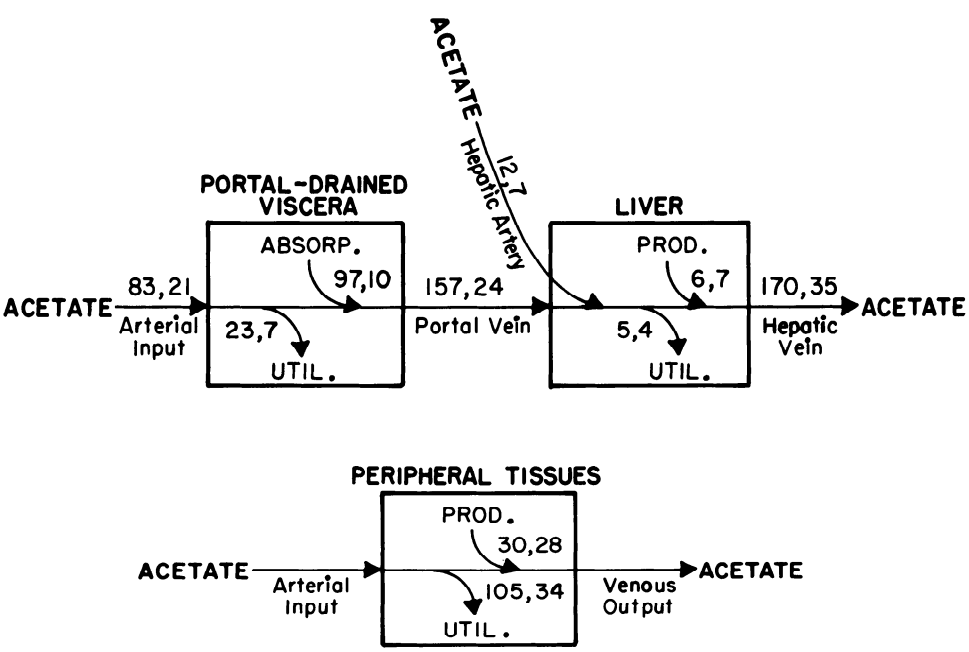

FIG. 2. Diagram of flow of acetate (mmol/h) in sheep tissues. First number for each rate is mean value for sheep fed alfalfa pellets at a constant rate of 33 g/h, and second number is for sheep fasted 3 days. Difference between absorption (absorp) [or production (prod)] and utilization (util) is equal to net production or appearance in blood. Total blood acetate turnover was 133 and 45 mmol/h in fed and fasted sheep, respectively. [Calculated and redrawn from Wolff and Bergman (53) and Bergman (44).]

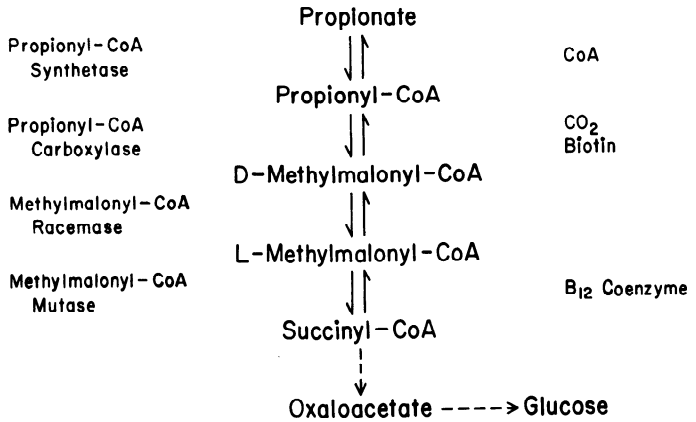

FIG. 3. Major pathway for propionate metabolism in liver.

butyrate is taken up by epithelial tissues of the digestive tract and by the liver, trace amounts can enter the general blood circulation, particularly after large meals and extensive fermentation in the digestive tract. Nearly all tissues of the body have the ability to metabolize butyrate, and metabolic pathways of butyrate metabolism in ruminants seem similar to those known to occur in nonruminants. In peripheral tissues, butyrate is rapidly oxidized or used in lipogenesis; it also is removed by the mammary gland mainly for milk fat synthesis (11, 58).

The major biochemical pathways of propionate metabolism are shown in Figure 3. Propionyl-CoA synthetase activity of liver is high in rats as well as ruminants and greatly exceeds that of acetyl-CoA synthetase (24, 92). As a result, most of the propionate is removed from the portal blood by the liver, and arterial levels of propionate are elevated only if propionate availability is experimentally increased (53, 300, 310, 311) or if specific disorders exist in propionate metabolism (7, 320). Propionyl-CoA carboxylase activity in liver, at least in ruminants, is responsive to starvation and dietary changes; starvation reduces its activity, whereas feeding high-grain diets, which increase the amount of propionate absorbed, increases its activity (29). Interestingly, butyrate tends to inhibit hepatic propionate utilization and conversion to glucose, as demonstrated in sheep, goats, and calves (2).

Biotin is essential for the action of propionyl-CoA carboxylase, but, even more importantly, vitamin B_{12} (and thus cobalt) deficiency results in the methylmalonyl-CoA mutase step (Fig. 3) becoming limiting (103, 200). At moderately low levels (250 ng/g liver) of vitamin B_{12} in sheep, the ability of the liver to extract propionate is not affected (227), but when the animal is stressed with an intravenous load of propionate the half-time of propionate disappearance increases from ~6 to >10 min (103). In severe B_{12} deficiency in sheep, a reduction in feed intake and an elevation of peripheral blood propionate concentrations occurs along with the reduced rate of clearance of injected propionate (201). Interestingly the propionate-loading test also has been used for diagnosis of liver dysfunction as a result of ketosis or liver necrosis (129, 130).

The usual pathway for propionate metabolism thus is to enter the tricarboxylic acid (TCA) cycle as oxaloacetate, and, in liver, large amounts are converted to glucose (Fig. 3). In fact, propionate is the only VFA that can be a major source of glucose. Acetate, butyrate, and longer chain VFA with even numbers of carbon atoms cannot contribute to a net synthesis of carbohydrate. This is because the only pathway for these VFA to be converted to glucose is through acetyl-CoA and the TCA cycle. When an acetyl-CoA molecule enters the cycle, two carbon atoms are lost as CO_2, no net gain of oxaloacetate occurs, and a net synthesis of glucose is impossible (313).

Although propionate is a potent glucogenic compound, it is difficult to assess its precise contribution to glucose production in the whole animal (45, 46, 331). In ruminants, propionate production in the rumen usually is high but also is variable. As summarized in earlier reviews (45, 56, 51, 52, 188, 190, 193, 227), studies on well-fed sheep indicate that ~1 mol/day of propionate is produced in the rumen, and if all were converted to glucose, this would form ~0.5 mol (90 g) of glucose, which is just enough to meet the glucose needs of the animal. However, some of the ruminally produced propionate is metabolized to CO_2, lactate, and amino acids by the rumen epithelium during absorption. Also, all of the propionate taken up by the liver probably does not form glucose; some may be oxidized or form other compounds. On the basis of ^{14}C labeling and use of the isotopic transfer quotient, only ~50-60% of the propionate carbon actually formed glucose (52, 275). Furthermore, by using these methods of calculation, only 25-60% of the glucose could be shown to be derived from propionate (52, 188, 193, 331).

Use of the above isotopic transfer quotient has been criticized, since on theoretical grounds it could underestimate propionate conversion to glucose by as much as 50% (65, 124, 137, 313, 318). The reasons for this underestimation are that oxaloacetate can not only form glucose, it can also go around the TCA cycle and, second, around the reaction sequence of forming phospho*enol*pyruvate and then back to oxaloacetate. The ^{14}C atoms thus can exchange with nonlabeled (or ^{12}C) atoms and be diluted out. Attempts have been made to correct for these underestimations, and at least one mathematical model has suggested that 95% of the propionate taken up by the liver is converted to glucose (275). With the use of this latter approach and, on the basis of net hepatic propionate uptake (45, 46, 53, 227), propionate in ruminants must form, as a minimum, 50% or possibly as much as 75% of the glucose requirements of the animal. Amino acids, glycerol, and lactate would then make up most of the remaining glucose needs.

The glucogenicity of propionate in nonruminant animals is less clear. One study in ponies using the isotope dilution principle and transfer quotient calculation concluded that ~7% of total glucose production was derived from propionate produced in the cecum (121). Further studies on other nonruminant animals

need to be made, although these species absorb far more glucose from their digestive tracts than do ruminants and thus do not need to rely as continuously on gluconeogenesis.

Any propionate that does escape liver metabolism is readily metabolized by other tissues and most prominently by adipose tissue and the mammary gland. Two studies have reported that propionate uptake by peripheral tissues could possibly be as much as 5–10% of that of acetate (54, 103). Also, propionyl-CoA synthetase activity in the ruminant lactating mammary gland is nearly as great as that of acetyl-CoA synthetase (202). Thus small amounts of propionate must be incorporated into odd-carbon fatty acids of adipose tissue and of milk fat. This has been shown to be the case in rats (68, 174) as well as ruminants (99, 100, 106, 120).

VI. INDIRECT EFFECTS OF VOLATILE FATTY ACIDS ON METABOLISM

A. Role of Volatile Fatty Acids in Insulin and Glucagon Secretion

It has become clear that the regulation of insulin secretion in ruminants differs from that in nonruminants. In ruminants, intravascularly administered propionate, butyrate, and valerate, but not acetate, are more potent stimulators of insulin secretion than glucose (146, 198, 199). This is not the case in humans and in animals, such as horses, rats, rabbits, and pigs (18, 146, 163); in these nonruminant species, glucose is the most potent regulator of insulin secretion. Blood glucose concentrations and glucagon secretion in ruminants also are enhanced by injection of propionate and butyrate (38, 64, 168, 228). However, although the increases in insulin and glucagon are almost instantaneous, changes in the insulin-to-glucagon ratio can be erratic or increase slowly after VFA injection. Thus the degree of hyperglycemia that is elicited probably secondarily affects the secretion of insulin and glucagon. In this regard, high blood glucose concentrations would tend to increase insulin but decrease glucagon secretion.

Despite the above clear-cut effects of VFA on insulin and glucagon secretion in ruminants, there is still uncertainty about the physiological importance of propionate and butyrate as regulators of hormone release. When propionate or butyrate are administered into the rumen or portal vein in physiological amounts, they are far less effective than when given into a peripheral vein (38, 64, 90, 276). This is because most of the propionate and butyrate are removed from the blood in a single passage through the liver (53, 228), and only small amounts are available in arterial blood for pancreatic stimulation. Thus, although some propionate and butyrate can escape hepatic uptake, particularly after a large meal, propionate and butyrate may help to influence insulin and glucagon secretion but probably are not the main regulators of their pancreatic secretion.

B. Volatile Fatty Acids and Cholesterol Metabolism

Another possible effect of VFA in both humans and animals is that of lowering blood cholesterol. Ingestion of certain fermentable plant fibers, such as pectins and some brans, has been shown to decrease concentrations of cholesterol in the plasma of humans (178) and also in the plasma and liver of rats and pigs (72, 165). Furthermore, it has been suggested that propionate, in particular, may be the product that mediates the hypocholesterolemic effect of the plant fibers. Concentrations of cholesterol in both serum and liver were significantly lower in rats fed diets containing 0.5% sodium propionate and 0.3% cholesterol than in rats fed diets with the cholesterol but no propionate (72). Also, diets supplemented with propionic acid exhibited hypocholesterolemic effects in pigs (290, 291).

Although propionate is as readily converted to cholesterol as is acetate, the net effect of propionate on cholesterol metabolism most likely is its regulatory effect on cholesterol synthesis. In fact, dietary propionate seems to have an inhibitory effect on the rate of hepatic cholesterol synthesis, and concentrations of 15 and 30 mM propionate inhibited 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthetase activity by 30 and 58%, respectively, in bovine liver. Because HMG-CoA synthetase is the enzyme responsible for synthesizing cholesterol from acetyl-CoA, concentrations of cholesterol in blood and liver obviously could decrease if the enzyme were inhibited. Still another possible effect of propionate is that short-chain fatty acids, in general, tend to decrease HMG-CoA reductase, which probably is the rate-limiting enzyme for cholesterol synthesis in animal tissues (159). Further research obviously is necessary to decide whether or not these effects of propionate on cholesterol metabolism are physiologically significant.

C. Volatile Fatty Acids and Gastrointestinal Blood Flow

Digestion and absorption, particularly of carbohydrates and lipids, have long been known to increase blood flow to the gastrointestinal tract of all animal species. Blood flow thus varies systematically with the feeding cycle, and, since VFA represent the major product of microbial fermentation, the VFA have been implicated as at least one factor responsible for the vasodilation occurring in the large intestine and in the rumen. In dogs and primates, the postfeeding hyperemia is located mainly in the small intestine and pancreas (73, 199, 182, 299), but increases in colonic mucosal blood flow also have been observed after a meal. With the use of the perfused dog colon, infusion of VFA solutions at physiological concentrations (75 mM acetate, 30 mM propionate, and 30 mM butyrate) brought about a >20% increase in blood flow (183). Infusion of individual VFA, however, produced a significant increase in blood flow only for acetate, suggesting that acetate is the primary VFA responsible for the hyperemia occurring in the large intestine. Similarly, cecal blood flow in

rats has been shown to increase when the cecal volume and cecal VFA concentrations are increased by a high-fiber diet (91).

Early studies with cattle clearly showed that an increase in right ruminal and omasal arterial flow occurs on feeding (266). Furthermore, increasing the CO_2 tension within the rumen or intraruminal infusions of VFA also stimulated ruminal arterial flow. Butyrate appeared to be the most effective VFA, and at physiological concentrations of 5–20 mM a quantitative response was seen with arterial blood flow increasing with increasing concentrations of butyrate. At concentrations >40 mM, however, rumen motility tended to be inhibited. Rumen arterial flow thus must be at least partially regulated by the CO_2 and butyrate concentrations available in the postfeeding period.

With the vasodilation occurring after feeding, rumen epithelial blood flow in sheep increases nearly threefold and rises to $\sim 3\ ml \cdot min^{-1} \cdot g^{-1}$ (37, 94, 270). In fact, studies using intravascularly injected microspheres together with the transit time flowmeter (37, 94) have ranked the vascularity of rumen epithelium just below that of the kidney and the thyroid gland but above that of the heart (132). Although the sheep rumen has similar weights of muscle and epithelium, ~90% of the blood flow goes to the epithelium (37, 107). Any increased blood flow to the muscle layers of the rumen corresponds with the increased rate of contraction during ingestion of food. Flow to the epithelium peaks later and depends on increased concentrations of fermentation products, principally CO_2 and VFA (94, 95). On the other hand, omental and mesenteric fat experience a marked fall in blood flow within minutes of feeding, and the vasoconstriction is maintained for several hours (94).

The exact mechanism by which VFA stimulate gastrointestinal epithelial blood flow has not been determined. An increase in oxygen uptake by the colon has not been observed on addition of the VFA to the perfusate (183), and thus the increase in blood flow probably does not arise as a result of VFA stimulation of epithelial metabolism and absorption. One promising explanation for the effects of VFA on blood flow is that the VFA directly act as vasodilators on the epithelial vasculature (113). It is known that functional changes within an organ can result in changes in blood flow. Increased glandular secretion, for example, will increase blood flow, and the reduced blood flow in mesenteric fat after feeding possibly is an expression of the functional change in the metabolism of fat, from lipolysis in the prefeeding to lipogenesis in the postfeeding state (94).

D. Effects of Volatile Fatty Acids on Gastrointestinal Epithelium

Readily fermentable dietary fiber is known to stimulate epithelial cell proliferation of the large intestine and cecum of animals, such as rats and hamsters (257, 258). The effects of fiber on the gut epithelium have been ascribed to the presence of fermentation products, since stimulation occurs only in the presence of gut microbes (258). The VFA seem to be responsible for at least some of the effects of fermentable fiber, since either individual or mixtures of VFA rapidly stimulate DNA synthesis and mitotic indices at physiological concentrations (261). Daily doses of VFA administered into ileal fistulas of rats have been reported to increase crypt cell production three- to fourfold, with the effect appearing within 2 days and lasting at least 14 days (258, 261). Furthermore the effects were dose dependent and with butyrate > propionate > acetate. Also, the effects were independent of lumen pH.

The presence of either fermentable fiber or VFA also stimulates mucosal development and epithelial cell division in the rumen (259, 260, 263, 288). Acetate, propionate, and butyrate all caused the mitotic indices of sheep rumen epithelium to increase within 1-4 days after administration, but, as in the case of the rat colon, the effect of butyrate was quicker and greater than that of acetate or propionate. Interestingly, the VFA, and especially butyrate, have the opposite effect in vitro, whereby they inhibit the proliferation of both large intestinal and ruminal epithelial cells (118, 258, 327). Thus the inhibitory effect in vitro and the stimulatory effect in vivo suggest that the in vivo effect of VFA must be indirect. In fact, epithelial growth in vivo is accelerated in areas not even in contact with VFA.

A systemic mediatory mechanism that transmits the stimuli of VFA to the epithelial cells has been proposed for the above trophic effects on epithelial cells, and this mechanism would be expected to dominate the direct inhibitory effect of the VFA, as demonstrated in vitro (258). A specific receptor mechanism for VFA has been shown to exist either in or beneath the mucosa of sheep rumens (186) and also in colons of rats (329). A vagal reflex can transmit signals from such receptors, and thus involvement of the autonomic nervous system could be possible. Humoral mediation may be another possibility in that, at least in ruminants, VFA can stimulate the release of insulin. Also, the involvement of other humoral trophic factors, such as enteroglucagon, has yet to be evaluated (258). The effects of VFA on stimulation of blood flow (94, 266) or the fact that VFA provide energy to the epithelial cells (252) cannot explain the effects of VFA on epithelial growth, since these factors seem to be local.

It also has been proposed that butyrate might simultaneously stimulate the growth of normal human colonic epithelial cells but inhibit the growth of malignant cells (113, 177). It thus becomes of interest to explore further the effects of dietary fiber and VFA production on cell proliferation and differentiation. Epidemiological studies have shown correlations between high-fiber diets and a reduced incidence of colorectal cancer.

The large intestine seems to be more efficient than the rumen in its ability to conserve water, sodium, bicarbonate, and chloride, and the VFA appear to play a significant role in this regard (84, 280, 305). The production of VFA appears to stimulate secretion of water and, in some species, the secretion of bicarbonate.

Water absorption then becomes mostly dependent on absorption of VFA and sodium, and absorption of VFA and sodium appear to be interdependent. Thus VFA production and absorption can have a very significant effect on the normal secretory and absorptive functions of the large intestine and, although more limited, an effect on the rumen as well. As discussed in section IV*A*, VFA usually can no longer be considered to be the cause of diarrhea but instead VFA fecal excretion usually is the result of a diarrheal condition. If severe malabsorption is present, however, the quantity of VFA produced may exceed the absorptive capacity of the colon so that excessive water secretion into the lumen will occur and result in diarrhea. This osmotic effect also is known to occur in the rumen when a diet low in fiber and high in starch or sugar is fed (134, 194). This results in an extremely rapid production of VFA and lactate, a fall in pH, and a loss of extracellular fluid into the rumen.

VII. SUMMARY

The VFA, also known as short-chain fatty acids, are produced in the gastrointestinal tract by microbial fermentation of carbohydrates and endogenous substrates, such as mucus. This can be of great advantage to the animal, since no digestive enzymes exist for breaking down cellulose or other complex carbohydrates. The VFA are produced in the largest amounts in herbivorous animal species and especially in the forestomach of ruminants. The VFA, however, also are produced in the lower digestive tract of humans and all animal species, and intestinal fermentation resembles that occurring in the rumen. The principal VFA in either the rumen or large intestine are acetate, propionate, and butyrate and are produced in a ratio varying from ~75:15:10 to 40:40:20. Absorption of VFA at their site of production is rapid, and large quantities are metabolized by the ruminal or large intestinal epithelium before reaching the portal blood. Most of the butyrate is converted to ketone bodies or CO_2 by the epithelial cells, and nearly all of the remainder is removed by the liver. Propionate is similarly removed by the liver but is largely converted to glucose. Although species differences exist, acetate is used principally by peripheral tissues, especially fat and muscle.

Considerable energy is obtained from VFA in herbivorous species, and far more research has been conducted on ruminants than on other species. Significant VFA, however, are now known to be produced in omnivorous species, such as pigs and humans. Current estimates are that VFA contribute ~70% to the caloric requirements of ruminants, such as sheep and cattle, ~10% for humans, and ~20–30% for several other omnivorous or herbivorous animals. The amount of fiber in the diet undoubtedly affects the amount of VFA produced, and thus the contribution of VFA to the energy needs of the body could become considerably greater as the dietary fiber increases. Pigs and some species of monkey most closely resemble humans, and current research should be directed toward examining the fermentation processes and VFA metabolism in those species.

In addition to the energetic or nutritional contributions of VFA to the body, the VFA may indirectly influence cholesterol synthesis and even help regulate insulin or glucagon secretion. In addition, VFA production and absorption have a very significant effect on epithelial cell growth, blood flow, and the normal secretory and absorptive functions of the large intestine, cecum, and rumen. The absorption of VFA and sodium, for example, seem to be interdependent, and release of bicarbonate usually occurs during VFA absorption. More knowledge is yet to be gained on the large intestine of humans and animals and much can be developed by applying information and procedures developed from studies on the ruminant forestomach.

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