

Carbohydrate and Lipid Metabolism in Farm Animals¹

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Abstract

Much research on carbohydrate and lipid metabolism in farm animals conducted over the second half of the 20th century has focused primarily on increasing the production efficiency and improving the quality and acceptability of animal-derived foods. Research was also performed with the express interest in greater understanding of biochemistry and metabolism of livestock species with ultimate application in the food industry. Knowledge about basic nutritional concepts and differences in metabolism among farm animals, however, has been accumulated and has been used successfully to better understand different health problems in humans such as obesity, atherosclerosis, diabetes, and others that are associated with disturbances in metabolism and nutrition. Here we focus on researchers who made major contributions to our understanding of the synthesis and degradation including digestion of carbohydrates and lipids during the past half-century and to our understanding of the growth and development of meat-producing animals (e.g., pigs and cattle) and milk-producing dairy cattle. These findings will serve as the basis for current and future animal biologists to develop newer concepts and methods for use in improving the efficiency of conversion of animal feed to food and the healthfulness of that food for human consumers. J. Nutr. 137: 702–705, 2007.

Carbohydrate metabolism

In farm animals, dietary carbohydrates provide well over one-half of the energy needs for maintenance, growth, and production. Glucose is a primary energy source for certain animal tissues and a precursor for lactose synthesis in the mammary gland. Consequently, understanding carbohydrate digestion and absorption, dietary glucose availability, and the involvement of gluconeogenesis in the regulation of glucose homeostasis is essential for the manipulation of the production and quality of agricultural foods.

Carbohydrate digestion and rumen fermentation. The major sources of carbohydrates in pig diets are feeds rich in starch, whereas in ruminants fibrous feeds containing cellulose and hemicellulose and grains rich in starch are the primary carbohydrate sources. In swine, most dietary carbohydrates (e.g.,

starch) are hydrolyzed to monosaccharides in the small intestine, whereas ruminants have most of their dietary carbohydrates (e.g., starch and cellulose) fermented in the rumen by microorganisms, and only 5 to 20% of consumed dietary carbohydrates are digested in the small intestine (1).

As early as 1883, Tappeiner (2) demonstrated that in cattle dietary cellulose was fermented to volatile fatty acids (VFA),² most of which was acetic acid. Subsequent work of Kellner (2) showed that starch and cellulose have the same energy value in cattle but not in swine. Numerous ruminant nutritionists have confirmed these observations and have shown that the major source of energy to the ruminant is the VFA absorbed from the rumen and other parts of the digestive tract. A major breakthrough in the development of VFA biochemistry in ruminants occurred with the development of gas-liquid chromatographic quantification of VFA by James and Martin in 1952 (3). Later research documented that lesser proportions of VFA are also produced from dietary proteins, pentoses of nucleic acids, and glycerol of glycerophospholipids. Studies on the VFA production rates and metabolism have increased in number and sophistication as a result of the development of an artificial rumen by Hungate with Carroll in 1954 (4).

As summarized by Baldwin (5), numerous scientific pioneers including E. F. Annison, S. R. Elsdon, R. L. Baldwin, C. L. Davis, R. E. Brown, A. T. Phillipson, and M. P. Bryant confirmed acetate as a major endproduct of fermentation, elucidated pathways for synthesis of each VFA and lactate, showed how

¹ Presented as a portion of the History of Nutrition Symposium: Impact of Research with Cattle, Pigs, and Sheep on Nutritional Concepts at the Experimental Biology 2006 meeting, April 1–5, 2006, San Francisco, CA. This symposium was sponsored by the American Society for Nutrition (ASN) and the ASN History Committee. The symposium was partially supported by a National Research Initiative grant from U.S. Department of Agriculture/CSREES (# 2006-35206-16710) and by ASN. The proceedings are published as a supplement to *The Journal of Nutrition*. This supplement is the responsibility of the guest editor to whom the Editor of *The Journal of Nutrition* has delegated supervision of both technical conformity to the published regulations of *The Journal of Nutrition* and general oversight of the scientific merit of each article. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, editor, or editorial board of *The Journal of Nutrition*. Guest Editor for the symposium publication is Harry J. Mersmann, E-mail: mersmann@msn.com.

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² Abbreviations used: bST, bovine somatotropin; CLA, conjugated linoleic acid; TVA, *trans*-vaccenic acid; VFA, volatile fatty acids.

diet composition (e.g., starch and cellulose ratios) influences proportions of each of the endproducts of fermentation, demonstrated that about half of butyrate is converted to β -hydroxybutyrate during absorption of butyrate from the rumen into blood, and showed that branched-chain organic acids are derived from amino acid fermentation. In addition, Baldwin and coworkers (5), using radioactively labeled lactate, showed that high-starch diets increased the flux of lactate to propionate via the acrylate vs. the succinate pathway of pyruvate conversion to propionate. Later, Baldwin's research group published their first (6) of several publications on modeling of metabolic pathways in the rumen and other tissues of dairy cattle that led to the development of the MOLLY program for whole-body metabolism (7).

Gluconeogenesis. Gluconeogenesis is extremely important to neonatal swine and neonatal and adult ruminants because it provides ~70% (8), 75% (9), and 90% (10) of the total glucose needs in those animals, respectively. Pioneers of research on ruminant gluconeogenesis (10–13) showed that glucose production from propionate, valerate, amino acids, lactate, and glycerol is of great importance at all times in ruminants and even more so in lactating ruminants, and the rate of gluconeogenesis increases after feeding. In contrast, the rate of gluconeogenesis in pigs and other nonruminants is lowest after feeding and is highest during energy deficit. Because of rumen fermentation and VFA production, often <10% of the glucose requirement is met by dietary glucose absorption from the digestive tract, as was shown in classic glucose kinetic studies by Bergman et al. (12) and Young et al. (14). To illustrate the significance of gluconeogenesis in a lactating cow, Young (10) calculated that 7.4 kg of glucose is needed daily by a dairy cow producing 90 kg of milk per day and that 6.6 kg of that glucose was derived via gluconeogenesis, hence illustrating the quantitative importance of gluconeogenesis.

Ballard et al. (15) initiated several classic studies to compare gluconeogenesis in ruminants and nonruminants. They and others emphasized the similarity of the pathways and the difference to which the key regulators are “turned on.” Ruminant liver releases glucose into blood during both fed and fasted states, whereas the liver of pigs in the fed state has a net uptake of glucose and a net release of glucose during the fasting state. They showed that both gluconeogenesis and lipogenesis occur at greater rates when ruminants are in positive energy balance, whereas only lipogenesis is accelerated in pigs.

Young (10) was one of the first scientists to relate ruminant gluconeogenesis to several practical situations. First, bovine ketosis and pregnancy toxemia in sheep seem to be caused by a shortage of glucose or gluconeogenic precursors. Second, milk fat depression seems to be associated positively with an overabundance of glucose and/or propionate. Third, milk production by dairy cows seems limited by glucose availability or gluconeogenic capacity of the animal's liver. Fourth, certain feed additives such as monensin promote growth and lactation efficiency by increasing propionate production in the rumen, which probably leads to increased gluconeogenesis and decreased methane production.

Lipid metabolism

Lipogenesis. Research on lipid metabolism in farm animals in the last 35 y has been focused on studying the anatomical sites and main carbon and hydrogen sources for lipogenesis in different animal species. From use of radioactively labeled precursors

with in vivo and in vitro assays, it was found that adipose tissue is the primary anatomical site for fatty acid synthesis in nonlactating ruminants (16) and swine (17). In contrast, in humans and avian species, the liver is the primary site, and in rodents and rabbits, both the liver and adipose tissue are primary sites for fatty acid synthesis (16). In the late 1960s, classic studies by O'Hea and Leveille (18) and Ballard and Hanson (19) established that glucose and acetate are the main carbon sources for fatty acid synthesis in porcine and ruminant adipose tissues, respectively. Smith and Crouse (20) contradicted the “dogma” of Ballard and Hanson by showing that the substrate specificity can differ with depot site, as is the case in intramuscular adipose tissue of beef cattle, where glucose rather than acetate seems to be the primary substrate for fatty acid synthesis.

Several investigators including Ballard, Hanson, Smith, Beitz, Bauman, Prior, and Vernon studied the source of cytosolic acetyl-CoA for de novo fatty acid synthesis. Such information should assist in explaining why ruminant adipose and mammary tissues conserve glucose from fatty acid synthesis for more critical cellular needs. Ballard and Hanson (19) were the first to explain that glucose was a poor precursor for long-chain fatty acids because of very low activities of citrate cleavage enzyme (ATP:citrate lyase) and malic enzyme (NADPH-malate dehydrogenase) in ruminant lipogenic tissues in comparison to those in rats. Therefore, acetate and not glucose was considered the principal generator of cytosolic acetyl-CoA for de novo fatty acid synthesis, which occurs in the cytosol. Later, data by Whitehurst et al. (21) and Smith and Crouse (20) suggested that low rates of glycolysis (glucose $\rightarrow$ pyruvate) explain the low rates of glucose use for lipogenesis in ruminant tissues because lactate conversion to cytosolic acetyl-CoA, which requires citrate cleavage enzyme activity, is greater than glucose use and similar to that for acetate. The precise explanation for low glucose incorporation into lipids in ruminants awaits future studies.

Next, the same investigators mentioned in the previous paragraph studied the source of NADPH for fatty acid synthesis. Three major pathways can generate cytosolic NADPH for fatty acid synthesis: the pentose phosphate, malate dehydrogenase, and isocitrate dehydrogenase pathways. Vernon summarized data from several of these investigators and stated that, in ruminants, as much as 50–80% of NADPH needed for fatty acid synthesis in adipose tissue is produced by glucose oxidation via the pentose phosphate pathway (16). The rest of the NADPH is generated via the isocitrate dehydrogenase pathway, which can provide up to 50% of NADPH needed for fatty acid synthesis in the mammary gland (16). The significance of the isocitrate dehydrogenase pathway is that it can provide reducing equivalents for fatty acid synthesis from acetate in the absence of glucose oxidation (16). The contribution of the malate dehydrogenase pathway to NADPH production in ruminants is insignificant because of very low malic enzyme activity in ruminants (19). In porcine adipose tissue, the pentose phosphate pathway generates 60–90% of NADPH needed for fatty acid synthesis (22), with the rest of the NADPH possibly produced via the malate dehydrogenase pathway as evidenced in rat adipose tissue (19,23).

Metabolic modifiers. Since the mid-1980s, there has been much effort toward practical manipulation of animal production using different metabolic modifiers. Etherton and colleagues (22) demonstrated that porcine somatotropin, when injected, stimulates muscle growth while concurrently decreasing adipose tissue accretion and improving feed efficiency in growing pigs. Moreover, Pursel and Rexroad (24) demonstrated that

increasing the copy number of the porcine somatotropin gene also causes increased ratios of skeletal muscle to adipose tissue. The hormone causes a repartitioning of nutrients toward skeletal muscle and away from adipose tissue. This technology has not been approved by the FDA in the United States but has been used extensively in Australia.

Similar effects were attributed to the use of β -adrenergic agonists to manipulate the carcass composition in food animals (25). Ricks at American Cyanamid initiated studies in the 1980s on the potential use of β -agonists on food animal productivity (26). Increased skeletal muscle accretion and decreased adipose tissue accretion were observed in cattle, sheep, chickens, and pigs. Her research and that of others including Beerman (27), Anderson et al. (28), Dunshea (29), and Mersmann (22) investigated effects of clenbuterol and other β -adrenergic agonists including ractopamine, cimaterol, L-644-969, and salbutamol on animal growth. In general, these compounds repartition nutrients toward muscle and away from adipose tissue to improve feed efficiency via actions on β -adrenergic receptors, as shown by several investigators including Bergen, Mersmann, and Mills (27,28,30). Only 1 of the tested β -adrenergic receptor agonists, ractopamine, is used commercially today by the swine industry.

Over 20 y ago, Dale Bauman with colleagues promoted the concept that exogenous bovine growth hormone could be used to stimulate milk production and improve efficiency of milk production (31). Numerous laboratories around the world confirmed the initial results of Bauman and Vernon (32). Today, Monsanto has commercialized a slow-release preparation of recombinant bovine somatotropin (bST) that is used extensively in the United States and numerous other countries. Administration of bST to lactating dairy cows causes a dramatic increase in the uptake and utilization of nutrients for the synthesis of milk. Thus, treatment with bST increases the activities of acetyl-CoA carboxylase, acetyl-CoA synthetase, fatty acid synthase, and other enzymes for milk synthesis in the mammary gland (33). The effect of somatotropin on mammary gland seems indirect and mediated through the insulin-like growth hormone system (32,33).

Lipid digestion. Lipid digestion in ruminants is unique in that after ingestion feed lipids are placed into a hydrolytic and reductive environment. The result is that glycerol from triacylglycerols and phospholipids is fermented to VFA and that unsaturated fatty acids are hydrogenated to mostly saturated fatty acids before absorption. The early contributions of Shorland et al. (34) and then Tove and colleagues (35) added to our understanding of the biohydrogenation process, and its control and extent are notable. The research of Jenkins, Palmquist, and Ferkins merits mentioning as well because these researchers demonstrated that the fatty acid composition of ruminant meats and milks is affected little by fatty acid composition of the diet because of the ruminal biohydrogenation phenomenon (16). These workers elucidated the pathway by which dietary linoleic and linolenic acids are sequentially reduced primarily to stearic acid. Jenkins and Palmquist (36) developed the technology of forming calcium salts of fatty acids for, in addition to ease of feeding lipids, partial protection against biohydrogenation. Tove and colleagues (35) developed an assay for biohydrogenation and then used it to show that several species of bacteria interact to convert, for example, linoleic acid to 9-*cis*, 11-*trans* conjugated linoleic acid (CLA) to *trans*-vaccenic acid (TVA) to stearic acid. Some of the CLA and TVA become absorbed as such. The TVA may be desaturated by tissue Δ^9 -fatty acyl desaturase to form CLA (37). Both of these sources of CLA contribute to the CLA in ruminant meats and milk.

Pig as a model for biomedical research in humans

Because much intense physiological and pharmacological research cannot ethically be conducted with human subjects, pigs have become highly popular experimental animal models during the past half-century. Bustad and McClellan (38) summarized much research 40 y ago to inform investigators of the many reasons that human nutritional and disease problems can be studied effectively in pigs. Subsequently, Pond and Houpt in 1978 (39), Tumbleson in 1986 (40), and Miller and Ullrey in 1987 (41) confirmed the conclusion of Bustad and McClellan. Hundreds of publications on research with pigs as human models have reported scientific information on cardiovascular physiology, obesity, stress, dermatology, teratology, toxicology, immunology, behavior, hemodynamics, renal physiology, experimental surgery, gastroenteritis, diabetes, drug metabolism, and perinatology as well as many aspects of nutrition (38–41). Dental characteristics, renal morphology and physiology, eye structure and visual acuity, skin morphology and physiology, cardiovascular anatomy and physiology, and digestive anatomy and physiology of the pig and human are similar (38–41), as well as lipoprotein and cholesterol metabolism (42). Many researchers have chosen the miniature pig originally developed at the Hormel Institute of the University of Minnesota (Bustad and McClellan) and other strains (40) because of more convenient adult size and thus handleability.

During the past half-century, we have seen an increase in sophistication of experiments with pigs. Today, pigs are genetically modified with a variety of gene constructs that improve the effectiveness of the pig as a model for many human diseases such as Alzheimer's, breast cancer, atherosclerosis, cellular stress, and psoriasis and other skin diseases. Genetically modified pigs are even being developed so that pig organs can be transplanted into humans with minimal rejection potential. What does the future hold in this regard?

Research with farm animals conducted over the second half of the 20th century has revealed striking differences among different animal species and humans in terms of carbohydrate and lipid metabolism. It was discovered that, unlike in humans and rodents, where the liver is the main site for lipogenesis, ruminants and swine synthesize their fatty acids primarily in adipose tissue. Also, swine, rodents, and humans utilize glucose as the main carbon source for fatty acid synthesis, but ruminants primarily rely on rumen-derived acetate for lipogenesis because of the low dietary glucose availability. The regulation of glucose homeostasis differs among species as well. Adult swine, for example, obtain most of their glucose from different dietary sources, whereas ruminants rely on hepatic gluconeogenesis from propionate to meet their glucose needs. These fundamental differences in metabolism are reflected in how different animal species use diverse regulatory strategies to meet their physiological needs for maintenance and production. Studying those strategies in detail can help us better understand general regulatory principles employed in metabolism and develop strategies to improve animal production and well-being and to find better cures for some diseases in humans.

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