Comparative Aspects of Lipid Metabolism: Impact on Contemporary Research and Use of Animal Models

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ABSTRACT The emerging obesity crisis and consequent concerns for corrective measures and appropriate public policy have stimulated research into causes, prevention, remediation, and health consequences of obesity and associated maladies. Such research areas include eating behavior, appetite control, and food intake regulation as well as the regulation of lipid metabolism, cardiovascular function, endocrine function, and dyslipidemia states utilizing various animal models and cell culture systems. Although the liver has a central role in lipid/fatty acid synthesis and glucose is the precursor for de novo fatty acid synthesis in rodents and humans, in many other species, adipose tissues are the primary sites of lipogenesis. In addition, many species utilize acetic acid as a precursor for fatty acid synthesis. This fundamental difference in the site of fatty acid synthesis and the pattern of consequent lipid trafficking influences overall animal lipid metabolism and the role of regulatory hormones and transcription factors. Researchers utilizing various animal species in targeted biomedical research should be aware of these species differences when interpreting their data. In addition, many animal species are used for food production, recreational, and companion purposes. Understanding the lipid metabolism regulatory mechanisms of such species from a comparative perspective is important for the proper nutrition and health of these animals.

KEY WORDS: lipogenesis • lipolysis • lipoproteins • species comparisons • transcription factors

In the early 21st century, humanity finds itself facing burgeoning medical problems related to overconsumption of highly available, energy-rich foods. This human culinary behavior contributes to the onset of obesity, type 2 diabetes, and related cardiovascular maladies. Although there are emerging data pointing to increased longevity upon energy restriction in eukaryotic cell, insect, and animal models (1), unfortunately for most overweight individuals, voluntary reductions in dietary energy intake and needed lifestyle changes are difficult to maintain for sustained periods of time. This emerging or present obesity crisis has prompted initiation of extensive research efforts in areas such as eating behavior, appetite control, and food intake regulation as well as in regulation of lipid metabolism, cardiovascular function, endocrine function, and dyslipidemia states utilizing various animal models and cell culture systems. This review will summarize various interspecies differences in lipid metabolism that may have to be considered when evaluating research findings from various animal models for application to human biology.

Comparative Lipid Biology: an Overview. Various animal species have been used to exploit their physiological uniqueness in addressing biomedical research issues, but too often differences in lipid biology between animal species and humans are not adequately considered in experimental designs. The availability of various animal models, in particular gene knockout and transgenic rodents, can make explorations of the role or function of a given or set of genes experimentally relatively straightforward and extremely useful in identifying gene level relations between atherosclerosis and associated maladies (2). The question that is often not addressed, however, is how data obtained with the “rodent model” apply to actual physiological/clinical settings in humans? In addition, there are numerous animal species that provide recreation or food to humans. Many key aspects of lipid metabolism in these species are not identical to rodents, but their lipid biology has been studied not only from a biomedical perspective but also to apply such knowledge to agricultural production and animal health. For example, domestic pigs, because of their similarity to humans in body size and other physiological/anatomical features, including their innate tendency to overconsume food, have been used to study multiple aspects of atherosclerosis and cardiovascular disease (CVD) (3). In humans, obesity and CVD are typically associated with chronic, high-fat, excess energy consumption but domesticated pigs, although omnivores (4) in wild settings, consume a very carbohydrate-rich diet. In pigs, feeding a high-fat cholesterol diet results in the onset of atherosclerosis-like symptoms, which is of real benefit in experimental protocols in which the emphasis is on disease progression and pathogenesis (3,6).

Sites of De Novo Synthesis of Fatty Acids and Principal Carbon Source in Animal Species. Although liver, adipose tissue, mammary gland, and intramuscular fat depots have the capacity for de novo lipogenesis (DNL) (7–9), lipogenesis, cholesterol synthesis, lipoprotein synthesis and export, and fatty acid oxidation have been investigated pri-
Table 1: Organ/tissue sites of de novo fatty acid synthesis or lipogenesis (DNL) and primary carbon precursor sources in various species

<table>
<thead>
<tr>
<th>Species</th>
<th>Item</th>
<th>Humans (Primates)</th>
<th>Rodents (Rats, Mice)</th>
<th>Rabbits</th>
<th>Pigs</th>
<th>Dogs</th>
<th>Cats</th>
<th>Avian species</th>
<th>Cattle</th>
<th>Sheep/Goats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary DNL-site</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Liver</td>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td>Secondary DNL-site</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Adipose</td>
<td>Liver</td>
<td>Liver</td>
<td>Mammary¹</td>
</tr>
<tr>
<td>Other Precursor for DNL</td>
<td>Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
<td>Mammary; Muscle/glucose</td>
</tr>
<tr>
<td>Type of digestive system</td>
<td>Simple intestine</td>
<td>Simple intestine</td>
<td>Simple intestine</td>
<td>Simple intestine</td>
<td>Simple intestine</td>
<td>Simple intestine</td>
<td>Simple intestine</td>
<td>Ruminant fermentor</td>
<td>Ruminant fermentor</td>
<td></td>
</tr>
</tbody>
</table>

¹ In lactating ruminants (especially dairy cows and goats), the mammary gland is a major site of DNL. All mammalian species exhibit mammary DNL during lactation.

² Preferred carbon source in dogs and cats for adipose tissue DNL (13, 14).

³ In species with foregut or hindgut fermentation, acetic acid is the principal (or only) precursor for DNL.

Compared in rodent liver (8–10). Except in avian species in which DNL occurs in the liver (7,11), DNL in many other animals is centered in the adipose tissues. In addition, although glucose is the principal carbon source for DNL in some species, acetic acid serves as the precursor for DNL in many other species. Use of acetate as substrate eliminates or modifies the role of glucose transporters and carbohydrate-specific transacting factors, such as carbohydrate responsive element binding protein (12) in the regulation of lipid metabolism. Table 1 presents a comparison of site of de novo lipogenesis (DNL) and carbon precursor sources in humans, rodents, and various other species. For dogs, cats, pigs, cattle, sheep, and goats, DNL is centered in adipose tissues (13–16), whereas in humans and rodents, the liver is the primary site for DNL (7–9). Significantly, in animals with extensive forestomach and hindgut fermentations such as rabbits, cattle, sheep, and goats, a digestive tract fermentation end product, acetic acid, is the principal precursor for DNL (16). In addition, in species that do not metabolize glucose particularly well, e.g., cats, which are carnivores (17), acetate appears to be the principal precursor for DNL (14). Figure 1 depicts the pathways for DNL in utilizers of glucose and acetate irrespective of tissue specificity. A principal difference between glucose utilizers and acetate utilizers is the path for fatty acid precursor carbon flow; in glucose utilizers, carbon flow is routed through the mitochondria, whereas in acetate utilizers, acetate is activated directly in the cytosol (Fig 1). There appear to be no other differences in the process of fatty acid synthesis, e.g., the roles of cytosolic acetyl CoA carboxylase and fatty acid synthase are similar among all species.

Comparative Regulation of Lipid Metabolism in Adipocytes. Adipocyte lipid metabolism is modulated by a number of endocrine, paracrine, and autocrine substances. The rodent adipocyte is unusually responsive to a wide variety of endocrine entities including insulin, adrenergic hormones, thyrotrophin, somatotrophin, adrenocorticotrophin, thyroid hormones, and glucocorticoids. Adipocytes from other mammalian species exhibit less breadth of endocrine control with meager or no demonstrable response to many of these hormones (18). Regardless of species, insulin and the adrenergic hormones are the primary acute controllers for mammalian adipocyte anabolic and catabolic lipid metabolism; other hormones have lesser effects, or more subtle chronic effects. Generally, insulin stimulates anabolic and inhibits catabolic lipid metabolism, whereas β-adrenergic receptor (βAR) agonists have the opposite effects (9,19). The physiological βAR agonists are the adrenal medullary hormones, epinephrine, and the neurotransmitter norepinephrine. In addition, there are many synthetic βAR agonists and antagonists used as pharmacological agents and in clinical settings (20). The rodent adipocyte responds dramatically to insulin with stimulation of anabolic and inhibition of catabolic lipid metabolism. Smaller adipocytes, present to a large extent in young rats, have greater fatty acid synthesis rates and insulin responsiveness than larger adipocytes, present to a greater extent in older rats (21). In general, ruminants are not very responsive to insulin, perhaps because glucose is only a minor substrate for fatty acid synthesis.
sis in these species (16). Under certain experimental conditions, however, bovine adipocytes may exhibit expected responses to insulin (22).

Adipocytes from most mammalian species respond to βAR agonists quite well, with the most profound effects demonstrable on stimulation of catabolic lipid metabolism, i.e., lipolysis; the anabolic pathways are generally inhibited (19,23). Three subtypes of β-adrenergic receptors (β1 AR, β2 AR, and β3 AR) are usually observed in adipocytes. However, the subtype distribution in various tissues, including the adipocyte, is species specific; the predominant rodent adipocyte receptor is the β3 AR (~90%), whereas in most other species, this subtype is present in very small numbers in adipocytes (usually ≤10%). Thus, the rodent adipocyte is controlled primarily by β3 AR, whereas this is not true in most other mammals (24). Furthermore, the primary structure of the βAR subtypes varies with the species, potentially imparting species specificity for responses to synthetic βAR agonists and antagonists. For example, there is considerable stringency for the agonists and antagonists to stimulate or inhibit βAR in pigs, whereas the rodent βARs are stimulated or inhibited by a broad range of agonists and antagonists (24). The α-adrenergic receptors, particularly the α2-receptors, work in opposition to the βAR, e.g., they inhibit lipolysis. In some species such as rats and pigs, the α2-adrenergic receptor function is difficult to demonstrate; in adipose tissue from other species, including humans, α2-adrenergic inhibition is marked (25).

**Effects of Dietary Fatty Acids on Fatty Acid Synthesis.** De novo fatty acid synthesis is inhibited by nonesterified long-chain fatty acids [NEFA (26,27)] and cytosolic acetyl-CoA carboxylase activity is sensitive to feedback inhibition from long-chain fatty acyl CoA in rodent liver (28). PUFA are particularly effective inhibitors of rodent hepatic fatty acid synthesis, whereas saturated NEFA have a lesser effect (26,27); a somewhat similar pattern is observed in rodent adipose tissue (26,29). These effects of PUFA are due largely to a reduction of mRNA for lipogenic enzymes at the transcription level (26,27). In contrast, in pigs with little hepatic DNL, adipose tissue DNL is inhibited by feeding fats containing predominately saturated or unsaturated fatty acids (30); in one study (31), palmitic acid was 2–3 times as effective as linoleic acid. Ruminants do not respond well to supplemental dietary lipids in excess of 5% dietary dry matter because fatty acids interfere with reticulo- rumen anaerobic microbial digestive activity. Dietary fatty acids may be shunted to the small intestine in ruminants by feeding rumen-protected lipids such as whole cottonseeds and fatty acid-calcium salts (32,33). Under such conditions, supplemental fatty acids reduced DNL in adipose tissues and mammary glands of dairy cows (32,33).

During the last decade, there has been considerable interest in conjugated linoleic acids (CLAs), 18-carbon fatty acid analogs of linoleic acid (34). The 2 double bonds in linoleic acid are cis-9, cis-12, whereas the common CLA isomers studied are cis-9, trans-11, and trans-10, cis-12. Feeding of large amounts of CLA to various species decreases adipose deposition of fat, but in mice, this may be accompanied by increased lipid accumulation in the liver; the 10,12-CLA isomer is the active form for most of these effects (34). In mice or in rodent clonal adipocytes in culture, CLA increases metabolic rate and fatty acid oxidation, and decreases adipocyte hyperplasia and differentiation, fatty acid synthesis, lipoprotein lipase, and stearoyl CoA desaturase (34,35). Decreased fat deposition is observed in other species, but the effects, including those in rats, are not as striking as in mice (35,36). Also, many of the potential mechanisms for decreased fat deposition observed in mice are difficult to demonstrate in other species or are inconsistent (35). In ruminant species, the 9,11- and, to a lesser extent, 10,12-CLA isomers are produced during ruminal biohydrogenation of dietary PUFA and subsequent desaturation in various tissues, resulting in some deposition of CLA isomers in meat and milk from ruminant species (37). The 10,12-CLA isomer was causally linked with the milk fat depression syndrome in lactating cows fed low-fiber, high-cereal grain diets (37). The 10,12-CLA isomer has now been shown to suppress expression of mammary fatty acid synthase by attenuating sterol regulatory element binding protein-1c (SREBP-1c) expression and proteolytic processing (38). The effects of CLA in humans are marginal and difficult to demonstrate, perhaps because much lower levels were fed than in experimental animals.

**Role of Transcription Factors in Lipid Metabolism.** The transcription factor SREBP-1c (or ADD1) has an important role in the control of fatty acid synthase expression (10). The most definitive data on the regulatory role of SREBP-1c in lipogenesis arise from SREBP-1c null mice, SREBP-1c overexpression, and negative-dominant SREBP-1c expression studies in rodents (10), but such data are lacking for most species (11). Typically SREBP-1c and fatty acid synthase (FAS) genes are both expressed and correlated in tissues that synthesize fatty acids de novo (11). Thus, in chicken liver, SREBP-1c and FAS transcripts and proteins are elevated coordinately (7), whereas in pigs, SREBP-1c and FAS transcripts and DNL are elevated in adipose tissue (11). In pigs, after feeding a commercial β-adrenergic agonist for >2 wk, adipose expression of both FAS and SREBP-1 were attenuated in parallel (39). In contrast, other findings, indicated that although adipocyte lipogenesis is highly correlated with insulin status (9), SREBP-1c mRNA abundance does not always coincide with lipogenic activity (40).

It is generally considered that the transcription factor, peroxisomal proliferator-activated receptor α (PPARα) controls the expression of fatty acid oxidative metabolism by modulating the expression of peroxisomal acyl CoA oxidase and mitochondrial carnitine palmitoyltransferase (41). This transcription factor and these enzymes are highly expressed in rodent liver and to only a modest extent in adipose tissue, giving rise to the concept that adipose tissue does not oxidize fatty acids to any extent. In pigs, there appears to be greater expression of PPARα transcripts in adipose tissue than in liver (42,43), suggesting that in this species, and perhaps in other mammals as well, adipose tissue may oxidize sizeable quantities of fatty acids. Sundvold et al. (44), however, could not demonstrate PPARα expression in porcine adipose tissues in their extensive work. PPARα is expressed in skeletal muscle; when activated, for example, by a fatty acid ligand, it promotes fatty acid oxidation, ketone body synthesis, and glucose sparing (41).

**Comparative Aspects of Lipoproteins and Lipid Trafficking.** Lipids are transported in the blood plasma as lipoproteins, complexes of various lipid materials with specific proteins. The large chylomicron and VLDL contain considerable amounts of triacylglycerol with small amounts of cholesterol. Chylomicrons are synthesized in the intestine and are found in lymph and in plasma after a meal containing fat (45,46). Ruminant species have few or no chylomicron particles because consumption of fats > 5% diet dry matter interferes with the rumen microbial feed digestion; under such circumstances, few long-chain fatty acids are absorbed (45). The LDL and HDL are the predominant carriers of cholesterol.
Species differ in the proportion of the plasma cholesterol-containing lipoprotein, LDL and HDL (46,47). Guinea pigs, pigs, rabbits, and sheep transport most of the cholesterol in LDL, as do humans. Many potential animal models, in particular rodents, carry the majority of cholesterol in HDL rather than LDL, making them less than desirable as models. Pigs have been a useful model for human atherogenesis, not only because of many similarities in the lipoproteins, but also because it is an omnivorous species, as are humans (4).

**Coda.** This short review provides evidence from the rich literature on comparative lipid metabolism that many differences in lipid biology exist among species. Workers must be cognizant of such differences whenever applying their results from various animal models to humans. This point is amplified in a recent report on novel mechanisms of PPARα activation (48) in which the authors state, “In mammals, the liver integrates nutrient intake and delivery of carbohydrate and lipids to peripheral tissues.” Clearly this is not correct for all mammals.

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**LITERATURE CITED**


