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A dynamic, mechanistic model of metabolism in adipose tissue of lactating dairy cattle

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ABSTRACT

Research in dairy cattle biology has resulted in a large body of knowledge on nutrition and metabolism in support of milk production and efficiency. This quantitative knowledge has been compiled in several model systems to balance and evaluate rations and predict requirements. There are also systems models for metabolism and reproduction in the cow that can be used to support research programs. Adipose tissue plays a significant role in the success and efficiency of lactation, and recent research has resulted in several data sets on genomic differences and changes in gene transcription of adipose tissue in dairy cattle. To fully use this knowledge, we need to build and expand mechanistic, dynamic models that integrate control of metabolism and production. Therefore, we constructed a second-generation dynamic, mechanistic model of adipose tissue metabolism of dairy cattle. The model describes the biochemical interconversions of glucose, acetate, β-hydroxybutyrate (BHB), glycerol, C16 fatty acids, and triacylglycerols. Data gathered from our own research and published references were used to set equation forms and parameter values. Acetate, glucose, BHB, and fatty acids are taken up from blood. The fatty acids are activated to the acyl coenzyme A moieties. Enzymatically catalyzed reactions are explicitly described with parameters including maximal velocity and substrate sensitivity. The control of enzyme activity is partially carried out by insulin and norepinephrine, portraying control in the cow. Model behavior was adequate, with sensitive responses to changing substrates and hormones. Increased nutrient uptake and increased insulin stimulate triacylglycerol synthesis, whereas a reduction in nutrient availability or increase in norepinephrine increases triacylglycerol hydrolysis and free fatty acid release to blood. This model can form a basis for more sophisticated integration of existing knowledge and future studies on metabolic efficiency of dairy cattle.
Key words: adipose, metabolism, mechanistic model, lactation

INTRODUCTION

The metabolism of the adipose tissues is an essential part of a successful lactation. There is a large body of knowledge on metabolism in the adipose tissues of dairy cattle (Vernon, 1980; Baldwin, 1995; McNamara, 2012; Khan et al., 2013). The adipose tissues support the overall efficiency of milk production and reproduction.

The original studies of Shirley et al. (1973) and Yang and Baldwin (1973) demonstrated changes in enzymes that controlled lipid metabolism in adipose tissues during lactation. These studies were followed up by several others that determined that the metabolic adaptations are controlled by several endocrine and neurocrine systems, including insulin, growth hormone and the sympathetic nervous system (Vernon, 1980; McNamara and Murray, 2001). These studies found, and repeatedly confirmed, that dairy cows of high genetic merit for milk production had greater rates of subcutaneous adipose tissue lipolysis and lower rates of lipogenesis compared with average or lower genetic merit cows (McNamara and Hillers, 1986b, 1989; Sumner-Thomson et al., 2011; Rocco and McNamara., 2013).

Recent studies show that expression of mRNA for most genes controlling lipogenesis decline in a coordinated fashion early in lactation, whereas those coding for lipolytic control do not change in early lactation but do rise during peak lactation in conjunction with increased milk yield (Sumner and McNamara, 2007; Sumner-Thomson et al., 2011). The body of knowledge demonstrates that several proteins and enzymes are involved in control of adipose metabolism including acetyl CoA carboxylase, fatty acid synthetase, adipose tissue triacylglycerol lipase (**ATGL**), hormone-sensitive

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Table 1. Sources of data for construction of equations and setting parameter values and for evaluation of model behavior

Reference
Yang and Baldwin (1973)
Shirley et al. (1973)
Vernon (1980)
McNamara and Hillers (1986a,b)
McNamara and Hillers (1989)
McNamara and Murray (2001)
McNamara and Baldwin (2000)
Baldwin et al. (1987b)
Baldwin et al. (1987b)
Baldwin (1995)
Kenéz et al. (2014b)

lipase (**HSL**), perilipin, and caveolar proteins (CAV1, CAV2; Koltes and Spurlock, 2011; Elkins and Spurlock, 2009; Khan et al., 2013; Kenéz et al., 2014).

Recently, research has resulted in several data sets on genomic differences and changes in gene transcription and control proteins in dairy cattle (Loor, 2010; Koltes and Spurlock, 2011; Rocco and McNamara, 2013). This knowledge can be helpful in a more complete description of adipose metabolism that supports productive efficiency. Research in genomic and transcriptomic control of efficiency is ongoing in many research laboratories and is a major funding priority in many countries. However, to utilize this knowledge fully, we need to build new and expanded mechanistic, dynamic models that integrate control of metabolism and production across all levels of cellular, organ, and animal metabolism.

Research models have already been extremely useful in many areas of systems biology, agriculture, and dairy cattle nutrition, metabolism, and reproduction (Baldwin, 1995; Cornish-Bowden et al., 2007; Boer et al., 2011, 2012; McNamara and Shields, 2013). Such models form a framework for systems biology research and integration of genomic information, gene transcription, enzyme amount and activity, metabolic flux, and integration of adipose tissue metabolism with productive and reproductive efficiency in the dairy cow. There have been at least 2 versions of a model of adipose tissue metabolism in the dairy cow, one embedded as part of a whole-cow metabolic mode as originally published in 1987 (Baldwin et al., 1987a,b,c) and as an updated version, named "Molly" by the author in 1995 (Baldwin, 1995). Second, an extremely detailed carbon-balance model was also published by this group (Baldwin and Miller, 1995) which traced specific carbon and had a major set of objectives to interpret the existing data available at that time and to identify key data and concepts that required further study and refinement (Baldwin and Miller, 1995). That research program and model inspired much of the work conducted in our laboratory as cited above. For many reasons, that highly detailed model was not widely distributed and used. Therefore, our objective was to construct a dynamic, mechanistic model of control of metabolism in adipose tissue that is suitable for analysis of data and concepts on regulation of adipose tissue metabolism, which contributes to overall metabolic efficiency of dairy cattle—a model meant to be intermediate in detail between "Molly" and the model of adipose tissue in Baldwin and Miller (1995) and approachable for use in a wide variety of research and teaching applications.

METHODS

Model Construction

The model was constructed based on data from experiments conducted in our laboratories, published literature (Table 1), and previously published equations in a model of metabolism in the dairy cow aggregated at the pathway level (Baldwin et al., 1987a,b,c; Baldwin, 1995). The flowchart of model pools and fluxes demonstrates the aggregated nature; it is built at the pathway level within the adipocyte, not for individual reactions (Figure 1). The adipose elements of the Molly model were aggregated at the whole-organ level; thus, the present model is at one level of biological organization lower. Components and definitions are provided in Table 2, and the general flux equation forms and parameter values are in Table 3. Model equations are presented in the model description below. The full model in ACSLX code is available upon request.

Modeling principles were followed in the construction: parsimony, that is, equations that were the simplest and most defendable were included, and others that might be defensible but added more complexity than needed were avoided; and defensibility: if there is some indication other processes are involved but could not be strongly supported, they were not included. More detail can be added as necessary in future iterations, this being a major facet of systems research and modeling. The model is scaled to represent the total adipocyte volume and triacylglycerol (**TAG**) content of a dairy cow. The reactions are aggregated at the pathway level within adipocytes but include some explicit intermediate reactions.

Concentrations of blood and cellular nutrients were set to be model mean observed values for a cow at energy balance (regardless of stage of lactation). Blood nutrient concentrations can be modeled explicitly by changing the initial values to model any given situation. To provide a connection to the needs of lactation,