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Predicting extraction and uptake of arterial energy metabolites by the mammary glands of lactating cows when blood flow is perturbed

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ABSTRACT

Previous work shows that mammary uptake of milk precursors from blood can be affected by the rate of blood flow (F) to the glands. The purpose of the current work was to test the ability of compartmental and cylindrical capillary models to account for the variation in mammary extraction and net uptake of plasma metabolites produced by perturbation of mammary F. The data for model fitting were obtained from a previous experiment in which mammary arteriovenous differences of acetate + β-hydroxybutyrate (2C), glucose, triacylglycerol (TAG), and long-chain fatty acids (LCFA) were measured in 4 cows before, during, and after intraarterial infusion of inhibitors of endothelial nitric oxide synthase and cyclooxygenase, which are 2 major systems of F control in the mammary glands. The 4 models tested were (1) constant extraction within each cow, (2) clearance from an extracellular compartment is a linear function of F with an intercept, (3) total capillary volume in a cylindrical representation is a linear function of F with an intercept, and (4) uptake from an extracellular compartment obeys Henri-Michaelis-Menten kinetics, where maximum velocity (V_{max}) is a linear function of F with an intercept. According to prediction errors, model 4 fitted 2C extraction data best, accounting for 82% of the observed variation. The estimated K_m (Henri-Michaelis-Menten constant) for venous 2C was 0.4 m*M*. For glucose clearance, a variant of model 2 with a positive effect of 2C uptake on clearance was identified as best, producing a coefficient of determination (R^2) of 0.31. For TAG, model 2 with a positive effect of arterial TAG concentration on TAG clearance was best, with an R^2 of 0.22. For LCFA, model 2 with a positive effect of arterial LCFA on LCFA clearance was best, with an R^2 of 0.29. Models 2 and 3 fitted the extraction data with the same R^2-values and prediction errors, so both compartmental and cylindrical approaches to describing the vascular bed were equally capable of describing the effect of F on mammary uptakes. A combined fit of all best-fit models to extraction data for all 4 metabolites at once explained 52, 42, 73, and 77% of variation in net uptakes of 2C, glucose, TAG, and LCFA, respectively. According to the fitted model, each 1 L/min increase in F increased the mammary volumes of distribution of 2C, glucose, TAG, and LCFA by 13, 14, 18, and 7%, respectively.

Key words: mammary blood flow, dairy cow, mammary uptake, modeling

INTRODUCTION

Nutrient utilization by the mammary glands of lactating ruminants is particularly suited to study by arteriovenous difference methodology because of venous drainage through an easily accessible vein, and secretion of biosynthetic products through a separate network of epithelial ducts (Linzell, 1974). The difference between arterial ($[\mathbf{S}]_\mathbf{A}$) and venous ($[\mathbf{S}]_\mathbf{V}$) concentrations of a metabolite (substrate S) gives rise to an estimate of net uptake when plasma flow rate ($\mathbf{F}$) is taken into account, according to the Fick equation:

$$\text{uptake} = ([\text{S}]_\text{A} - [\text{S}]_\text{V})\text{F}. \quad [1]$$

The balance between net uptakes of milk precursors and their outputs in milk products is assumed to indicate utilization in catabolic pathways. Quantifying net anabolic and catabolic utilization of each milk precursor from one set of blood and milk samples produces a relatively complete view of mammary metabolite fluxes, and the technique has been widely used to explain how perturbations in diet and physiological state elicit changes in production and composition of milk from dairy ruminants (e.g., Linzell and Mepham, 1974; Cant et al., 1993; Mackle et al., 2000; Delgado-Elorduy et al., 2002; Lemosquet et al., 2009; Safayi and Nielsen, 2013).

Decades of measurement of mammary arteriovenous differences have spawned attempts to accurately predict rates of net uptake of milk precursors from blood as a test of understanding of the underlying mechanisms.

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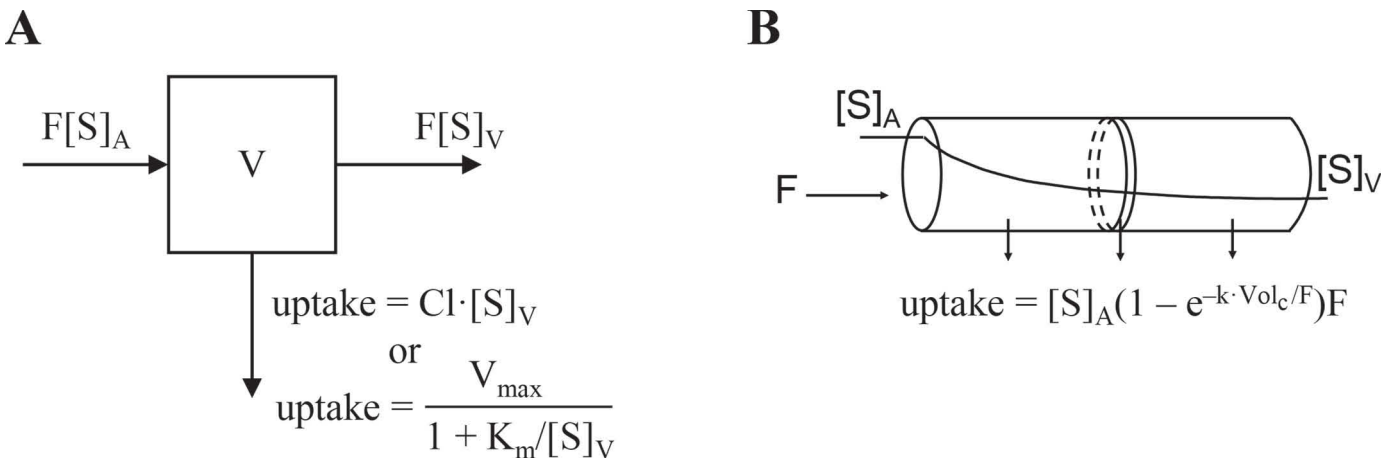

Figure 1. Flow diagrams for (A) compartmental, and (B) cylindrical capillary models. Cl = clearance, F = flow, K_m = Henri-Michaelis-Menten constant, $[S]_A$ = arterial concentration of substrate, $[S]_V$ = venous concentration of substrate, V_{max} = maximum velocity, Vol_c = total capillary volume.

One of the questions that has arisen is how to accommodate a change in mammary blood flow (**MBF**) in the prediction of nutrient uptake from blood. Mammary blood flow is affected by changes in hormonal or nutritional state (Linzell, 1974; Davis and Collier, 1985; Cant et al., 1993; Bequette et al., 2000; Mackle et al., 2000; Rigout et al., 2002) because of local vasodilator release from cells of the mammary glands (Nielsen et al., 1995, 2004; Cieslar et al., 2014). Recently, Madsen et al. (2014) showed that inhibition of mammary vasodilatory systems to decrease blood flow through the glands caused decreases in mammary uptakes of acetate, glucose, and long-chain fatty acids (**LCFA**). A compartmental model of the uptake process provides a framework to accommodate this effect of MBF. If the extracellular fluid of the mammary glands is considered to be a well-mixed compartment (Figure 1A), according to Hanigan et al. (1998), then

$$\text{uptake} = Cl\cdot[S]_V, \qquad [2]$$

where clearance (**Cl**) is a product of first-order transport efficiency (**k**) and volume of the compartment ($\mathbf{Vol_e}$):

$$Cl = k\cdot Vol_e. \qquad [3]$$

In addition to decreased nutrient uptakes when MBF is depressed, Madsen et al. (2014) also reported that Cl values decreased, and it was proposed that closing capillaries to flow, due to vasodilator inhibition, decreased the apparent volume of distribution of arterially delivered nutrients into the extracellular fluid of the mammary glands. Thus, the effect of MBF on uptake could be accommodated by setting Vol_e as a function of F, and calculating uptake according to Eq. [3] and [2].

An alternative to the well-mixed compartmental model is the Krogh cylinder model, in which each capillary is considered a cylinder through which blood flows and along the length of which net uptake occurs (Figure 1B). Among many parallel capillaries, the average transit time of blood from arterial to venous end is equal to the ratio of total capillary volume ($\mathbf{Vol_c}$) to F. Thus, as derived in Cant and McBride (1995),

$$[S]_V = [S]_A e^{-k\cdot Vol_c/F}, \qquad [4]$$

and, substituting Eq. [4] into Eq. [1],

$$\text{uptake} = [S]_A\left(1 - e^{-k\cdot Vol_c/F}\right)F. \qquad [5]$$

Again, Vol_c could be set as a function of F, and Eq. [5] could be used to describe a positive relationship between MBF and uptake of milk precursors.

The purpose of the current work was to test the ability of compartmental and cylindrical models to account for the variation in mammary uptake of plasma metabolites produced by MBF perturbation in the experiment of Madsen et al. (2014) and to parameterize deterministic equations that describe effects of $[S]_A$ and F on net mammary uptakes. Inputs to the models are $[S]_A$ and F. However, uptake and clearance are both estimated from F and would thus be expected to exhibit correlations with F unrelated to the accuracy and precision of predictive equations using F as an input. Similarly, $[S]_V$ and arteriovenous difference are both highly related to