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Short communication: Parameters of abomasal emptying and glucose-insulin dynamics in Holstein-Friesian calves at 2 ages and 2 levels of milk replacer intake

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ABSTRACT

Elevated planes of nutrition in the preweaning period of dairy calf management can increase average daily gain, shorten age at puberty, and increase milk yield. In a previous study, 12 Holstein calves were fed 2 meals/d of 4 or 2 L milk replacer up to 7 wk of age. The objective of the current study was to estimate parameters of abomasal emptying and glucose-insulin dynamics in these calves by fitting a mechanistic model to postprandial appearances of plasma glucose, insulin, and the abomasal emptying marker acetaminophen measured at 4 and 7 wk of age. Higher intake of milk replacer resulted in longer bouts of abomasal emptying at a slower rate. Parameters of glucose and insulin dynamics were not affected by milk replacer intake. However, older calves had decreased insulin-stimulated glucose utilization indicating impaired insulin sensitivity, as well as increased pancreatic responsiveness. Neither of these effects were apparent from i.v. glucose tolerance tests on the calves and may have been related to postprandial gut hormone release. Effects of age on parameters of glucose-insulin dynamics were larger than effects of milk replacer intake. Conversely, effects of milk replacer intake on abomasal emptying were larger than effects of age.

Key words: milk replacer, abomasal emptying, insulin sensitivity, pancreatic responsiveness, mechanistic model

Short Communication

The anabolic hormone insulin, secreted from the endocrine pancreas, exerts effects on glucose metabolism pathways in tissues to a degree that reflects the sensitivity of those tissues to the hormone. Plasma glucose and insulin concentrations following an i.v. bolus of glucose can be used to estimate parameters describing pancreatic responsiveness to glucose, insulin sensitivity at target tissues, and the ability of glucose to stimulate its own disposal, called glucose effectiveness (Pacini and Bergman, 1986). These 3 parameters are good indicators of the anabolic state of animals and their ability to respond to dietary nutrients (Wolever and Mehling, 2002; Short et al., 2003). An oral glucose dose is much easier to deliver and more nutritionally relevant than an i.v. bolus, but estimation of glucose-insulin parameters from postprandial curves is complicated by an unknown rate of appearance of glucose into the circulation. Recently, we developed a mathematical model of the mixed-meal tolerance test (Stahel et al., 2016), in which gastric emptying dynamics are fit from appearance of a marker such as acetaminophen (**Ac**) in plasma (Marshall et al., 2005), and gastric emptying informs glucose appearance rates to solve the oral appearance dilemma. The purpose of the current work was to fit the Stahel et al. (2016) model to postprandial plasma glucose, insulin, and Ac curves in female Holstein-Friesian calves at 4 and 7 wk of age, fed either low (4 L/d) or high (8 L/d) volumes of milk replacer (**MR**), from MacPherson et al. (2016), to assess treatment effects on parameters of abomasal emptying and glucose-insulin dynamics during feeding. Analyses before development of the model were limited to estimates of peak concentrations, times to peak concentration, and areas under the curve (**AUC**). The modeling analysis permits biologically meaningful parameters of pancreatic responsiveness, insulin sensitivity, and glucose effectiveness to be estimated in the postprandial period, as opposed to the fasted state of an i.v. glucose tolerance test. Insulin sensitivity indices for the fasted state, calculated from glucose and insulin concentrations during the first 30 min of an i.v. test, were not different between calf ages or MR allowances (MacPherson et al., 2016). We hypothesized that glucose-insulin dynamics following a meal could differ

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from those in the fasted state because of the role of gut peptides, such as incretins, in the postprandial response (D'Alessio et al., 2007; Woerle et al., 2012).

Postprandial glucose, insulin, and Ac time-course data were obtained from MacPherson et al. (2016). Briefly, 12 Holstein-Friesian calves were blocked in pairs with a similar parity of dam and given 4 L of the same previously-frozen colostrum within 6 h of birth. Calves were fed either low (4 L/d) or high (8 L/d) volumes of MR (150 g/L of DM; 24% CP, 18% crude fat, and 45.2% lactose on a DM basis; Trouw Nutrition, Deventer, the Netherlands) given in 2 equal meals per day from 1 to 7 wk of age (MacPherson et al., 2016). At 4 and 7 wk of age, blood samples were taken from a jugular vein catheter at −30, 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, and 420 min relative to a meal containing 150 mg/kg of metabolic BW ($BW^{0.75}$) of Ac as an abomasal emptying marker. All animal procedures complied with the Dutch Law on Experimental Animals, and the ETS123 (Council of Europe, 1986) and were approved by the Animal Care and Use Committee at Utrecht University. Plasma was analyzed for concentrations of Ac (**cAc_P**), glucose (**cGl_P**), and insulin (**cIn_P**).

The Stahel et al. (2016) model describes masses of glucose, insulin, and Ac in plasma as differential equations of input minus output. Input to the plasma Ac pool is based on fast, slow, or zero abomasal emptying according to first-order rate constants (**$k_{SP,3}$**, **$k_{SP,2}$**) and 0, respectively, assigned to successive 30-min blood sampling intervals. Output is due to first-order elimination according to rate constant $k_{Ac,UAc}$. Concentrations of Ac in plasma are calculated by dividing plasma Ac mass by 0.9 BW, accounting for volume of distribution (0.67 BW; Janus et al., 2003) and first-pass splanchnic metabolism of the oral dose (Cant et al., 2005). Abomasal emptying of carbohydrate proceeds according to the Ac rate constants but, because of additional time for intestinal carbohydrate hydrolysis and absorption, appearance of exogenous glucose in plasma lags behind Ac appearance by the time lag between stomach and plasma (**$T_{lag,sp}$**) in minutes. A fixed 50% of the consumed glucose + galactose is assumed to appear as glucose in plasma, with the remainder lost to first-pass splanchnic metabolism. Endogenous glucose production (**PGl_{end}**) is maintained at a constant, zero-order flux, and irreversible loss of glucose is a function of cGl_P and the insulin signal (**Is**) according to a glucose effectiveness constant (**$k_{Gl,UGl}$**) and an insulin sensitivity constant (**$k_{Is,UGl}$**). Insulin is released from the pancreas according to a sigmoidal Hill equation of 3 parameters, where V_{PIn} is the maximum rate of insulin release, $K_{Gl,PIn}$ is a Michaelis-Menten parameter describing dependence on cGl_P, and the exponent (**exp**) for the production (**P**) of insulin (**In**) is the Hill coefficient that sets the maximum acceleration of insulin release (i.e., at the inflection point). This inflection-point slope represents pancreatic responsiveness. Elimination of insulin from plasma follows first-order kinetics according to rate constant $k_{In,UIn}$. The Is lags behind cIn_P by $T_{lag,IS}$ minutes, representing a time delay for insulin signaling to occur.

Although the model accounts for variation in cAc_P, cGl_P, and cIn_P due to several sources, it does not also consider variation due to differences between calves and weeks in volumes of distribution and first-pass extraction percentages. The model was written in ACSLX (Aegis Technologies Group Inc., Orlando, FL) and solved with a 4th-order Runge-Kutta algorithm using an integration step size of 0.002 min. For each calf at each week, the parameters of Ac kinetics ($k_{SP,2}$, $k_{SP,3}$, and $k_{Ac,UAc}$) were estimated using Microsoft Excel Solver (Microsoft Corp., Redmond, WA), and the parameters of glucose-insulin dynamics (PGl_{end}, $k_{Gl,UGl}$, $k_{Is,UGl}$, $T_{lag,SP}$, V_{PIn}, $K_{Gl,PIn}$, exp_{PIn}, initial Is, $T_{lag,IS}$, and $k_{In,UIn}$) were estimated with a differential evolution algorithm, as previously described (Stahel et al., 2016). Both procedures minimized residual sums of squares between predicted and observed cGl_P, cIn_P and cAc_P. A root mean square prediction error was calculated to represent goodness of fit. The number of sampling intervals during which abomasal emptying was fast, slow, or off was used to estimate total time spent in each abomasal emptying state during the 420-min time-course.

Statistical analysis of treatment effects on parameter values was performed in PROC MIXED of SAS (version 9.4, SAS Institute Inc., Cary, NC), with age as a repeated measure, where block, treatment, age, and a treatment × age interaction were considered fixed effects. Compound symmetry was assumed for the covariance structure and means were separated using the PDIFF option of SAS. Significance was declared at $P \leq 0.05$, trends at $0.05 < P \leq 0.1$.

The high treatment significantly decreased Ac clearance rate from plasma ($k_{Ac,UAc}$; Table 1) whereas age tended to increase its clearance, an effect that has also been demonstrated in human infants (Anderson et al., 2000). The slow abomasal emptying rate tended to be slower on high, whereas the fast emptying rate was significantly slower on high. With slower abomasal emptying rates, the high treatment resulted in less time spent with abomasal outflow completely off and a tendency for more time where emptying occurred, either slow or fast. Therefore, the high treatment resulted in longer bouts of slower abomasal emptying. This effect of meal size on gastric emptying has been reported in several species (Delgado-Aros et al., 2004; Jackson et al., 2004; Métayer et al., 2004) and is attributed to intestinal release of glucagon-like peptide-1 (**GLP-1**) in response